Selection Criteria to Protect the Blood Donor in North America and Europe: Past (Dogma), Present (Evidence), and Future (Hemovigilance)

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The safety of the blood supply depends on measures to protect not only the transfusion recipient but also the blood donor. Donor selection criteria have been voluntarily adopted or enforced through regulation in different countries, but review of practices in different blood centers reveals wide disparity in the current approaches. Such variability in practice suggests that the criteria for the protection of donor are often arbitrary or reflect deeply engrained precautionary practices and exposes the inherent uncertainty about the best way to minimize risk to the donor. Certain selection criteria introduced years ago have become dogma in some countries but were never subjected to systematic study and persist despite available evidence that the measures do not measurably improve donor safety. Current efforts to define a rational, evidence-based approach are crucial to eliminate practices that lead to the unnecessary deferral of large numbers of blood donors without improving the safety of the donation process. Future prospects to improve the safety of the donation process rest with hemovigilance initiatives to monitor the effectiveness of interventions to minimize the risks to blood donors.

A SAFE AND adequate blood supply depends on healthy, volunteer blood donors. Blood centers have an obligation to minimize the risk of harm to not only the transfusion recipient but also the blood donor.[1-4] This review focuses on the donor selection criteria that have been voluntarily adopted, or enforced through regulation, in different countries that are intended to protect the safety of the blood donor. Although blood donation is well tolerated by most donors, approximately 3% to 10% will experience an adverse reaction or injury after the donation.[5-7] Most reactions are minor symptoms, such as dizziness, lightheadedness, or bruises, but on occasion, serious complications can occur such as phlebotomy-related nerve damage or physical injury resulting from loss of consciousness. In addition, some donors may be susceptible to potential long-term consequences of whole blood donation, most notably iron depletion and anemia.[8] Consequently, blood centers must inform donors of the risks and take reasonable measures to minimize the potential for adverse reactions.

The past several decades have seen efforts to define criteria to ensure selection of healthy donors. Unlike the codified federal regulations to protect the transfusion recipient, such as infectious disease testing of each donation, the criteria intended to protect the donor are often widely open for interpretation and left to medical discretion. Consequently, substantial variability is apparent in the approaches taken by blood centers within a given country and throughout the world.[2,4] Such variability in practices suggests that the criteria for the protection of donors are arbitrary or deeply engrained precautionary practices based on poorly understood risks and reveal the inherent uncertainty about the best approach. Several donor eligibility criteria were selected to exclude groups or individuals at "greater risk" of untoward effects of donation, yet few, if any, have been subjected to meaningful analysis to determine their predictive value for future reactions, their ability to identify occult health issues, or the effectiveness of screening measures to protect donors. Some degree of risk cannot be eliminated with such a nonspecific approach because it would be inappropriate to eliminate large groups of donors (eg, first-time or female donors) with the highest predisposition to reactions. Paradoxically, other deferral criteria have been promulgated in regulations despite the demonstration they do not correlate with an increased risk of donor reactions (eg, limits on blood pressure) or may be normal for the individual (eg, hemoglobin concentration). Similarly, some criteria designed primarily to protect the donor, such as minimum hemoglobin levels, have major impact on deferral rates and therefore affect blood availability. An adverse reaction or even a temporary deferral

reduces the probability that a donor will return for a subsequent blood donation leading to substantial donor attrition.[9-12] The pronounced, dampening effect of deferrals on future donation affects the behavior of both first-time and repeat donors. Because regular, repeat donors have the lowest rates of infectious disease markers, as well as the lowest rates of reactions, ensuring the return of loyal donors improves both donor and recipient safety.

The impact of donor deferral policies on the blood supply necessitates critical examination of the selection criteria intended to protect blood donors. Hopefully, benchmarking practices and highlighting the discrepancies in donor deferral criteria in different countries may prompt blood centers and regulators to reevaluate their policies and to eliminate practices that lead to unnecessary deferral of blood donors without improving the safety of the donation process. Precautionary measures are often implemented without subsequent evaluation of their effectiveness, but proposals to eliminate or modify such practices receive close scrutiny and are often met with an unwillingness to change without definitive proof of equivalent safety. Future hemovigilance efforts and ongoing surveillance of adverse reactions after blood donation may allow refinement of donor selection criteria. This review explores the past, present, and projected future state of the approaches used to protect the donor and prevent donation-related complications.

PAST: DOGMA AND TRADITION

Development of the Donor History Questionnaire in the United States

In 1953, AABB (formerly known as the American Association of Blood Banks) provided the first clear and practical donor screening recommendations in the first edition of Technical Methods and Procedures of the American Association of Blood Banks.[13] The document contained a list of 21 "diseases and conditions about which the donor must read and be questioned," including heart disease, diabetes, allergies, and convulsions. The questions were the only means to improve donor and recipient safety before the availability of donor screening tests. The questionnaire was refined in subsequent years but took on a renewed purpose during the 1980s with the emergence of AIDS. Incontrovertibly, the introduction of educational

materials and direct questioning about HIV risk factors were effective in decreasing the risk of transfusion-transmission before a specific test for HIV infection became available.[14] However, the length and complexity of the donor questionnaire grew exponentially in the 1990s, to the point that health history questionnaires used by blood centers included compound or multi-item questions covering more than 60 different topics.[13] The questions were not standardized, and their specificity, sensitivity, and predictive value for their intended purpose were never determined. In 2000, an industry-wide effort was launched to redesign the Donor History Questionnaire (DHQ) to make it clear and understandable and to ensure that the questions elicited the expected information from donors. The newly designed Uniform DHQ and accompanying materials were released in a final Food and Drug Administration (FDA) guidance in 2006.[15] The DHQ documents are currently in use in most blood centers in the United States.[16]

The DHQ incorporates all necessary FDA requirements for health history screening that are contained in the Code of Federal Regulations [21 CFR 640.3(a) and 640.63(a)] and the AABB Standards.[15,16] In addition, the DHQ covers donor eligibility topics for which FDA has no current requirements, such as cancer, organ, tissue, or bone marrow transplant; bone or skin graft; and pregnancy. In 2007, FDA released for public comment a Proposed Rule on Requirements for Human Blood and Blood Components Intended for Transfusion (hereafter referred to as the "Proposed Rule"), which introduced new requirements or recommended changes to the federal regulations related to donor medical history assessment and consolidated donor eligibility requirements for blood and blood components as well as source plasma.[17] Public comment to the Proposed Rule was extensive, with many organizations and individuals challenging some of the current and proposed criteria as arbitrary and poorly supported, or not supported, by available evidence.[18] At the time of this writing, a final rule has not been issued. However, both the current regulations and the Proposed Rule require assessment of donors' health history to determine whether the donor is free of disease, and the decision is still largely left to the discretion of the medical directors of blood-collecting facilities. Not surprisingly, donor center physicians often use different criteria and make different decisions leading to considerable

variability in policies and procedures among blood centers.[2,4] Although meant to protect the health of individuals, these disparate donor deferral policies often cause confusion, disenchantment, and anger among blood donors, who are puzzled by the relevance of certain questions to their health or the ability to donate blood, particularly when their personal physicians have a different perspective about the same medical condition.

Evolution of Donor Criteria in Canada

In 1989, blood became regulated under the Canadian Food and Drug Act. Changes to donor criteria must be submitted by both of the Canadian blood centers, Héma-Québec and Canadian Blood Services, to Health Canada before implementation. Many criteria designed primarily to protect the donor, such as blood pressure and pulse requirements, were adopted from the AABB or FDA requirements at that time. Some of these criteria have subsequently been incorporated into the Canadian Standards Association Standard Z902-04, Blood and blood products. Ironically, there was little evaluation of actual benefits to donor safety when these criteria were adopted, but the conservative nature of such a regulated system places the onus on blood centers to provide evidence that there will be no increased risk if the criteria are modified or eliminated.[19] This double standard of imposing measures based on theoretical, anecdotal, or precautionary concerns while requiring definitive evidence of equivalent safety when considering changes to donor selection criteria is a formidable challenge to those wanting to improve the process.

History of the European Union Blood Directive

The establishment of blood donor eligibility criteria for the 27 member states of the European Union (EU) was the result of decades of international collaborations occurring at the same time as the political process of formation of the EU in 1993. A detailed review of European blood regulations has recently been published.[20] Distinct from the EU is the Council of Europe (CoE), which is a voluntary organization of 47 European countries founded in 1949 "to improve the quality of life for all Europeans."[20] Some non-European countries (Canada, the Holy See, Japan, Mexico, and the United States of America) have observer status. The CoE preceded the formation of the EU by 4 decades, and its activities mostly focused on ethics

and public health through the establishment of binding agreements between countries and statements of policy labeled as Recommendations. In contrast, the EU is a political organization of member states with the European Parliament representing the people of Europe, the Council of the EU representing national governments, and the European Commission representing the common EU interest. Treaties between member states focus on trade and economics.

Since 1995, the CoE described requirements for donor selection and the preparation of blood and components in Recommendation No. R (95) 15. Work on this recommendation started in 1986 and was based on decisions made by a Select Committee of Experts; the final report was published as the first CoE "Guide to the preparation, use and quality assurance of blood components" in 1995. New editions are published on an annual basis.[21] In 2002, the European Commission of the EU, issued a "blood directive" establishing overall requirements for the preparation of blood components that was 2002/98/EC.[22] An expanded blood directive supplementing the earlier one was issued in March 2004 as the Commission Directive 2004/33/EC.[23] This new one incorporated the voluntary donor eligibility criteria recommended by the CoE Guide, making them a legal requirement. This directive lists in detail the donor history elements that define donor eligibility (eg, age, weight, hemoglobin, history of cancer, exposure to infectious diseases) and establishes specific permanent and temporary deferral criteria. Notably, the directive does not list requirements for donor blood pressure or pulse. The directive also lists elements of the donor informed consent and technical specifications for blood components. According to the rules of the EU, directives must be incorporated into the local laws of each of the member states and must be implemented within a specified period. Member states and collecting facilities are allowed to adopt stricter criteria.

The health area of the CoE was reorganized in December 2006, and since that time, the European Directorate for Quality of Medicines and of Health Care (EDQM) became responsible for the CoE activities on quality of blood transfusion and organ transplantation and of the European Pharmacopoeia. The EDQM continues to revise, update, and publish the Guide, as of 2008, in its 14th edition.[21] Both, the Commission Directive 2004/33/EC as a

legal mandate and the CoE Guide as a set of voluntary standards coexist.

It should be noted that blood components are not medicinal products in the EU but can be considered medical services in the realm of public health. However, all plasma, because it can be used for fractionation, fall under the additional oversight of the European Medicines Agency. The European Medicines Agency is a component of the EU equivalent to the US FDA that is responsible for the protection of public and animal health through the evaluation and supervision of medicines for human and veterinary use.[20]

In 2005, Dr Gilles Folléa from France presented the results of a survey of blood donor selection practices in the 25 EU member states and compliance with 2004/33/EC at the International Society of Blood Transfusion Congress in Athens.[24] He concluded that there was substantial compliance with criteria to protect the donor contained in the directive except in age limits for donation (specified as between 18 and 65 years and ranging from 17 to >70 years) and considerable variability in the minimum interval between whole blood donations (not specified in the directive with practices ranging from 8 to 16 weeks among countries). He also found discrepancies in deferrals for risk behavior that reflect the ability of member states to adjust questions and deferrals in accordance with the epidemiology of disease in the different countries. The overall concordance among European countries was the result of the long history of development of standards for blood and components within the CoE. European recommendations in the past regarding donor history criteria were created by individuals that are part of the Select Group of Experts representing the different member states and were reviewed by the different countries before issuance. The recent change of responsibility for the Guide to the EDQM may result in processes that include more widespread public consultation. This would be similar to the ones customary in the United States where FDA Guidances and Rules, as well as AABB Standards, are published as a draft for public comments before final issuance. At the end of a comment period, submissions are reviewed by these organizations, and not infrequently changes are incorporated into the original documents as a result of good reasoning and evidence. The CoE Guide does not include references supporting the strength of evidence that led to the establishment of the various selection criteria. However, both the CoE and the EU allow updates based on evidence-based reviews.

PRESENT: AN EVIDENCE-BASED APPROACH

The evidence-based imperative has permeated the field of blood banking and transfusion medicine as in other areas of health care. With more transparency and public involvement in decision making, blood centers must also be able to explain the rationale for deferral criteria to both donors and the general public.[25] Within this framework, the strength and relevance of the available data to inform deferral criteria are reviewed and in some cases contrasted against the current regulations or variable practices in donor centers. Benchmarking practices intended to protect the donor among different countries, and the highlighting of discrepancies in donor deferral criteria may prompt blood centers and regulators to reevaluate their policies and to eliminate practices that lead to unnecessary deferral of blood donors without improving the safety of the donation process. With this goal, surveys of donor screening practices in the United States, Canada, Australia, the United Kingdom, and France were conducted by the Alliance of Medical Operator's Medical Group in 2008 (Tables 1 and 2).[4] Data for health history deferrals in the United States and Canada combined results from an America's Blood Centers (ABC) survey of 74 members and the 36 regions of the American Red Cross (ARC).

Donor Age, Weight, and Collection Volume

The changing demographics of the donor base has increased the dependence of blood centers on young (<18 years old) donors in the United States; however, other countries maintain the minimum donation age at 17 or 18 years. The effect of donors' age, first-time donation status, and weight on syncopal-type (eg, vasovagal) reactions have been well-described since the 1940s, and the studies clearly identify donor characteristics associated with a greater risk of reactions.[26-31] Younger donors and first-time donors are more likely to experience donation-related vasovagal reactions after whole blood donation when compared with older and more experienced donors. Both age and donation status are strong and independent contributors to the risk of vasovagal complications after whole blood donation.[27-30] Other donor characteristics that correlate with higher syncopal complication

Table 1. International Deferral Policies for Allogeneic Whole Blood Donors: Age, Hemoglobin, Vital Signs

	ABC/ARC	CBS	Australia	UK	EU Directive 2004/33/EC
Age, y					
First time donors					
Usual procedures	16*, no upper limit	17-60[†]	16*-70	17-65	17-60
Extra medical assessment	No[‡]	No	No	No	≥61
Repeat regular donors					
Usual procedures	16*, no upper limit	17-70	16-70	17, no upper limit	17-65
Extra medical assessment	No	≥71	71-80	No	≥66
Hemoglobin, g/L					
Female	125	125	120	125	125
Male	125	125	130	135	135
Donation interval (WB), wk	8	8	12	12-16[§]	Not specified
Blood pressure, mm Hg					
Systolic	90-180	90-180	90-180	Not taken	Not specified/ Optional[‖]
Diastolic	50-100	50-100	60-100 or <60 with systolic 90 to 140		
Pulse, beat/min	50-100	50-100	50-100	Not measured	Not specified/ Optional[‖]

Abbreviations: CBS, Canadian Blood Services; WB, whole blood.

*Minimum age may be 16 or 17, depending on state laws, and may require parental consent.

†All ages include the last year that the donor is eligible, in this case, up until 61st birthday.

‡Unless required by state law (eg, New York State requires the medical director or designee to approve donation by an individual >76 years old).

§Donors encouraged to return after 16 weeks but may be accepted after 12 weeks; they may donate a maximum of 3 donations/y.

‖Not specified in the EU Directive (); optional in the CoE Guide[21], which states, "if pulse and blood pressure is tested then the pulse should be regular and between 50 and 100 beats per minute….as a guide the systolic blood pressure should not exceed 180 mm Hg and the diastolic pressure 100 mm."

rates include low weight, low blood volume, female sex, and white race.[27,28,30]

Most donors in all age groups do not experience complications after donation, but the risk of donation-related complications, including the rare but more medically serious injuries, steeply increases with younger age. The rate of physical injury from syncopal-related falls at the donation site among 16- to 17-year-old donors was twice that observed among 18- to 19-year-old donors and 14-fold greater than the rate observed among adults older than 20 years.[29] Even after controlling for weight or total blood volume, young age is still a strong and independent predictor of reactions.[30,31] The US FDA has no age requirements for donation in guidance or regulation; AABB allows collection from 16-year-olds or as allowed by state laws.[32] Most states allow blood collection from 17-year-old donors without parental consent, although a few states maintain this requirement. At the time of this writing, 26 states or US territories allow donation by 16-year-olds typically with parental consent, either through adoption of legislation or the granting of variances. California also allows donation by 15-year-olds with written permission

of a parent or guardian and the written authorization of a physician or surgeon. Practices vary at American blood centers and internationally, with the minimum donation age varying from 15 to 18 years, with or without parental permission. The ARC requires parental consent for all 16-year-old donors, does not collect from 15-year-olds, and follows state regulations or variances applicable to parental consent, or drive sponsor preferences, for collection from 17-year-old donors.

The relationship between age and donation complications is likely a continuous function, and the differences between successive age groups are relatively small but statistically significant and more pronounced for younger donors.[29] Consequently, the youngest donors collected by any blood center will always be the group at the greatest risk, and it is not feasible to set the limit to the age (eg, >30 years) at which reactions rates level off or fall below a given arbitrary cutoff value (eg, 3% reaction rate). Recognizing the possible effect of increasing recruitment of young donors, blood centers have recently focused on more selective strategies to mitigate risk at high-school drives. The current eligibility requirement in the United States for

Table 2. International Selection Practices for Blood Donors With Medical Conditions

Medical Condition	ABC/ARC Centers (% US centers or ARC)	Canadian Blood Services	Australian Red Cross Blood Services	EU Directive 2004/33/EC
Pregnancy, term delivery	100% centers, accept 6 wk postdelivery	Accept 6 mo postdelivery	Accept 9 mo postdelivery	Accept 6 mo postdelivery
Treated cancer				
Skin (except melanoma)	99% centers, accept	Accept if successfully treated	Accept if excised and healed	In situ, accept after complete recovery
	1% centers, permanent deferral			
In situ (eg, cervical, breast, colon)	1%-4% centers, permanent deferral	Cervical intraepithelial neoplasia, accept	Cervical intraepithelial neoplasia, accept	Cervical intraepithelial neoplasia, accept
	96%-99% centers, accept after recovery	Other in situ, permanent deferral	Other in situ, accept after 5 y if relapse free	
Other non hematologic	9%-34% centers, permanent deferral	Permanent deferral	Accept after 5 y if relapse free	Permanent deferral
	66%-93% centers, accept after 1-5 y if relapse free			
Hematologic (leukemia, lymphoma)	90% centers, permanent deferral	Permanent deferral	Permanent deferral	Permanent deferral
	4% centers, variable acceptance criteria			
Myocardial infarction	• 50% centers, accept after 6 mo or less	Permanent deferral	Permanent deferral	Permanent deferral
	• 30% centers, accept after 1 y			
	• 6% centers, permanent deferral			
Central nervous system disease	Accept after 6 mo if medically treated and if no new symptoms (ARC)	Permanent deferral, unless reversible underlying condition	Permanent deferral	Permanent deferral
Diabetes	Accept if healthy and well (ARC)	Defer if on insulin	• Well controlled on diet/ oral medications, accept	Defer if on insulin
			• Well controlled on insulin, accept with physician approval	
Minor surgery	Accept when fully recovered (ARC)	Accept when fully recovered	Minor surgery, eg, arthroscopy, defer until recovered	Accept after 1 wk if fully recovered
			Minor surgery, eg, laparoscopy, tubal ligation, hernia repair, defer 2 mo	

Abbreviation: WB, whole blood.

minimum weight of 110 lb (50 kg) and to limit collection to 10.5 mL/kg is sufficient to protect most, but not all, donors from reactions resulting from an acute blood loss. This requirement was based on the assumption that blood volume can be estimated as 70 mL/kg so the limitation would prohibit drawing more than 15% of a donor's blood volume or 525 mL of whole blood. Interestingly, the CoE and the UK Blood Services promulgate the "13% rule," which is that no more than 13% of the donor's estimated blood volume (455 mL in a donor who weighs 50 kg) may be collected at each donation.[1]

Recent data suggest that such assumptions about estimated blood volume are not accurate,[30] and a new standard approach may be needed to limit whole blood collection to no more than 15% of the total blood volume for all donors. Wiltbank et al[30] estimated blood volume from self-reported height and weight using standard formulae and found that donors with estimated blood volume less than 4000 mL were considerably more likely to have a reaction (adjusted hazard ratio 2.88 for blood volume <3500 mL and 2.09 for blood volume 3500-4000 mL, vs reference blood volume of

>4775 mL). Five percent of donors in this study had blood volumes of less than 3500 mL, which guarantees that a 525-mL whole blood donation will be more than 15% of their blood volume. A policy of excluding donors less than 23 years of age with blood volume less than 3500 mL (about 9% of presenting donors in this age group; 1.6% overall) is estimated to eliminate 20% of moderate and severe reactions among this age group (9% of all reactions).[33] Although the expected reduction in reaction rates for a given change in selection criteria can be estimated by multivariate analysis, it is not known if implementation in the field will achieve the predicted results, especially when there are many other factors that influence reaction rates.

Similarly, some blood centers have advocated increasing the donor weight requirement for young donors.[34] Multivariate analysis has been used to model the possible reduction in reactions that could be achieved with such a policy against the expected donor loss and suggests such exclusionary practices would achieve modest benefit and would be most noticeable among female donors.[31] Even so, most (22/32, 69%) injured 16- and 17-year-old donors who received outside medical care for donation-related injuries in one study weighed 130 lb or more.[29] Selection criteria based on donor-reported weight, therefore, would be expected to prevent some but not all of the injuries sustained by adolescent donors.

Overall, the published data provide little guidance in setting a "safe" lower weight limit, minimum age limit, or acceptable blood volume for donors. Of concern is the observation that more than 15% of a donor's total blood volume may be collected under current standards from a significant percentage of donors.[30] Further study and continued hemovigilance are necessary to evaluate the various donor selection strategies being tested, especially among the youngest donors at greatest risk for donation-related complications.

Practice varies greatly between regulatory authorities and blood centers on the upper age limit for whole blood donation in different countries. The upper age limit may be different for first-time donors, lapsed donors who have not donated in the past 2 years, or regular repeat donors.[35] The FDA does not specify an upper age limit or stipulate the need for any extra medical assessment for older donors, regardless of their first-time or repeat status. However, both the EU blood directive and Health

Canada regulations require an extra medical assessment for first-time donors 61 years and older and regular repeat donors 66 or 71 years old, respectively. As shown in Table 1, blood centers differ in their criteria, in part due to regulatory restrictions in their country.

Data from the United States and Canada demonstrate that reaction rates are low in donors older than 30 years and do not appreciably increase with age.[7,36] Although reaction rates are higher in first-time donors as compared with repeat donors in all age groups, the incidence of moderate to severe reactions does not increase in older age groups.[7,36] There is therefore little evidence to justify a different permissible age requirement for first-time donors compared with repeat donors. Similarly, because the DHQ and routine donor health assessment questionnaires in use in all countries query donors about their overall health status and the presence of cardiovascular or neurologic disease that may increase their risk with donation, any additional value of an external medical assessment has not been demonstrated. On the contrary, a Canadian study demonstrated its lack of utility because most donors deferred by their family physicians on a medical enquiry would have been deferred based on routine evaluation using the donor health assessment questionnaire alone.[35]

Hemoglobin Requirement and Interval Between Donations

Minimal hemoglobin requirements for blood donation were introduced by most developed countries in the 1950s. Both the minimum hemoglobin requirement and permissible interval between donations differ between jurisdictions (Table 1). Donor hemoglobin or hematocrit are assessed using a capillary fingerstick sample that is analyzed using one or several methods such as copper sulfate, microhematocrit testing, and hemoglobin measurement with a portable hemoglobinometer. Both capillary sampling and each of these measurement techniques are subject to substantial variability. Ideally, hemoglobin screening should ensure that donors who are already anemic or borderline anemic are deferred from donation. The minimal acceptable hemoglobin for both men and women in the United States is defined by the FDA as 125 g/L; with the essentially equivalent hematocrit requirement of 38% [21 CFR 640.3(b)(3)]. These criteria are identical in Canada, and both

countries have a minimum interval of 56 days between donations of 450 to 500 mL. The minimal hemoglobin requirement for women in Canada was decreased to 115 g/L in the late 1980s, based on statistical analysis performed by Ali et al[37] on the sensitivity and specificity of various cutoff levels in predicting iron deficiency. However, the requirement was increased back to 125 g/L after a study of repeat female blood donors demonstrated that 67% of donors meeting the threshold of 115 g/L were iron deficient, compared to 55% of donors meeting the threshold of 125 g/L.[38] Both the EU blood safety directives and UK and Australian criteria specify different acceptable levels of hemoglobin and hematocrit for men and women. Whether a single acceptance criterion for both men and women is appropriate from a donor safety perspective is debatable because the distribution of normal hemoglobin values for a population depends primarily on sex and race. The lower limit of normal for white men is 137 g/L; for black men, 129 g/L; for white women, 122 g/L; and for black women, 115 g/L.[39] Hemoglobin values that fall below these reference limits would have only a 5% chance of being normal for the population and would most likely be an indication of anemia in an individual, at least if they were performed on a venous sample analyzed in a laboratory.[40] The hemoglobin requirement of 125 g/L is therefore within the reference range for women. Not surprisingly, this requirement results in the deferral of 10% to 20% of female donors, many with a hemoglobin level in the range of 120 to 125 g/L. Slight variations in the accuracy of hemoglobin determination may have marked effects on the deferral rates of female donors. In contrast, men with an acceptable hemoglobin for blood donation (125-136 g/L) are likely anemic. Therefore, the use of a hemoglobin cutoff of 125 g/L in Canada and the United States results in deferral of many nonanemic women and does not necessarily ensure deferral of anemic men. The higher hemoglobin standard in use for men in other jurisdictions is more logical in this regard.

Because the usual whole blood donation of 450 to 500 mL results in the loss of approximately 250 mg of iron, and iron deficiency is a common public health problem in most countries, a possible goal of hemoglobin assessment and definition of donation intervals is to ensure that donation does not result in iron deficiency in individuals with already depleted stores. Low iron stores may impede hematologic recovery after whole blood or red cell donation. The physiologic consequences of low iron stores in the absence of anemia are controversial, with both protective and detrimental effects reported.[41-45] However, hemoglobin screening does not ensure that the donor has an adequate store of iron as many studies have demonstrated that repeat donors frequently have iron stores in the iron-deficiency range.[46] There are no formal recommendations or requirements for iron supplementation after blood donation, but dietary advice including the use of iron-containing multivitamins is relatively widespread practice in donor centers, and even casual use of iron supplementation has been shown to be beneficial.[47] There are ongoing trials in the United States, Australia, and several European countries offering donors oral iron supplementation to replace the iron lost in donation; however, this approach has not been adopted for widespread use by blood centers.

Blood Pressure

Blood pressure and pulse are among the most controversial issues in the focused physical examination of prospective donors. Current FDA regulations state that blood pressure should be "within normal limits" on the day of donation but do not specify the actual values [21 CFR 640.3(2)]. The FDA's Proposed Rule introduces a requirement for a donors' systolic blood pressure to be between 90 and 180 mm Hg and their diastolic blood pressure to be between 50 and 100 mm Hg.[17]

The need to have blood pressure within this range for a blood donation is debatable. Indeed, blood centers in the United Kingdom do not measure a donors' blood pressure before donation. The CoE does not require measurement of blood pressure and recognizes that recording blood pressure is subject to several variables.[21] As a guide, the CoE offers that if blood pressure is measured, an upper limit could be considered (systolic blood pressure should not exceed 180 mm Hg; diastolic should not exceed 100 mm Hg).

There is no evidence that blood pressure within an arbitrarily defined acceptable range (eg, systolic blood pressure 90-180 mm Hg; diastolic blood pressure 50-100 mm Hg) measured before blood donation improves donor safety. From a practical standpoint, measurement of blood pressure, especially in the setting of an anticipated blood

donation, does not necessarily reflect the donors' baseline blood pressure; a single recorded value is not clinically diagnostic in any setting, and white coat hypertension is a well-recognized phenomenon.[48] From a clinical standpoint, the "acceptable" range currently used by the United States and other countries includes donors who are classified as having stage I hypertension (systolic 140-159/90-99 mm Hg) or stage II hypertension (systolic >160/100 mm Hg),[49] as well as donors who may be hypotensive. Low blood pressure values, however, have no clinical significance to donors who are otherwise asymptomatic.

Approximately 45 000 donors are temporarily deferred for blood pressure each year in the ARC; yet, many of these donors subsequently return to donate without incident and have no underlying pathology. Before 2004, the ARC did not define a lower limit for blood pressure to qualify donors. Providing support for this practice was a multivariate analysis of 1778 adverse reactions recorded in 8 geographically distinct ARC regions after 72 059 whole blood donations, which evaluated donor weight, pulse, systolic blood pressure, diastolic blood pressure, age, sex, and first-time donation status. There was no statistical association of adverse reactions with systolic or diastolic blood pressure, but a strong association ($P < .0001$) with each of the remaining variables of low weight, high pulse, low age, being female, and being a first-time donor (unpublished data, ARC). These observations have been corroborated in other published studies that also used multivariate modeling to assess the relationship between vital signs and vasovagal reactions.[27,30] Trouern-Trend demonstrated that predonation systolic blood pressure, diastolic blood pressure, and pulse were not significantly associated with reactions after adjustment for donors' age, sex, first-time donation status, and weight.[27] In the most recent study using a similar analytical approach, lower pulse and higher blood pressure within the current acceptable range was associated with *decreased* risk of a reaction; low blood pressure was not a risk factor for a donor reaction.[30]

The lack of correlation of blood pressure with donor reactions in multivariate analysis and the lack of relevance of a single measurement of blood pressure to a donor's health contradict the need to set arbitrary selection criteria. Informing donors about their blood pressure at each donation may provide a useful public health service by making them aware of the risks of chronic hypertension, but deferral practices based on blood pressure have questionable value in terms of donation safety. Accordingly, a proposal to eliminate the requirement to measure blood pressure to qualify donors is under consideration for the 26th edition of AABB BB/TS Standards. However, blood centers in the United States will not be able to eliminate this requirement because it is mandated by the CFR. In Europe, blood pressure measurement for donor qualification is optional and not mandated by either the CoE or the EU Directive, based on available evidence and accumulated experience.

Pulse

Currently, requirements for a donor's pulse rate or rhythm for allogeneic blood donation are not defined in the CFR, although the Proposed Rule would set the requirement at 50 to 100 beat/min and regular, which is consistent with FDA's source plasma requirements [21 CFR 640.63(c)].[17] A rapid heart rate (eg, sinus tachycardia) in the absence of other symptoms most often is a physiologic response to emotion, anxiety, caffeine, or exertion. As an isolated finding, increased pulse rate has poor predictive value in an ambulatory population for making specific diagnoses and cannot differentiate those who have a condition from those who do not.[50] The most commonly encountered cardiac arrhythmias in asymptomatic individuals are benign premature ventricular contractions or atrial fibrillation. Individuals with atrial fibrillation are hemodynamically stable and often asymptomatic—as much as 1% of the US population older than 50 years may have the condition. Although pulse rate and blood pressure are important prognostic indicators in patients under treatment for hypertension, in elderly patients, or after a myocardial infarction,[50] the clinical value of taking a donor's pulse in a donation setting is dubious. Not surprisingly, recording the donors' pulse on the day of donation is not a universal practice, and there is no requirement for donor qualification based on pulse in the United Kingdom or EU (Table 1). In contrast, approximately 27 000 donors each year in the ARC are temporarily deferred for having an "unacceptable" pulse.

There is no clear evidence that pulse rates within arbitrarily defined acceptable ranges (eg, 50-100 beat/min) measured before blood donation improve donor safety. Some have argued that the higher incidence of reactions among donors with a

higher predonation pulse supports the need to define an acceptable range for pulse. It is clear that anxiety before a phlebotomy can frequently be the reason for an elevated pulse rate and a mild reaction. Not surprisingly, some studies have demonstrated that a higher pulse within the currently acceptable limits correlates with the likelihood of reactions. However, the relative difference between donors with pulse 65 to 90 beat/min and higher pulse (90-100 beat/min) was on the same order of magnitude as the increased risk of reactions recognized for female donors when compared to male donors (pulse greater than 90 had adjusted odds ratio 1.25 [1.16-1.34]; for females, adjusted odds ratio 1.20 [1.10-1.31]).[30]

In 1999, the ARC used 110 beat/min as the upper limit of pulse and also observed a statistically significant but relatively small absolute difference in reaction rates for the group of donors with pulse of 100 beat/min or less compared with donors with pulse between 100 and 110 beat/min (unpublished data, ARC). Most reactions in both groups were minor reactions. These data were recently reanalyzed in a statistical model that demonstrated that young age and female sex had the greatest effect on risk of vasovagal reaction,[51] whereas increased pulse made a relatively small contribution to the overall risk. Moreover, individuals may be accepted for autologous donation if their pulse is greater than 100 or irregular or if other medical conditions are present. Regardless, systemic (syncopal-type) reactions were not more likely after autologous whole blood donation compared with allogeneic donation to the ARC (Eder, ARC Hemovigilance Program 2007).

In view of these data and experience, blood centers that do not currently measure donors' pulse have ample justification to continue their practice, which is optional in the CoE Guide and in the EU Directive. Héma-Québec has recently requested that Health Canada eliminate the pulse requirement for donor selection. Similarly, a proposal to eliminate the requirement to measure pulse to qualify donors is under consideration for the 26th edition of AABB BB/TS Standards.

Health History Assessment

Cardiovascular disease. Cardiovascular disease affects an estimated 79.4 million (1 in 3) Americans[52]; not surprisingly, individuals with a cardiac history frequently present to donate whole blood or blood components. Excluding hypertension, the Agency for Healthcare Research and Quality reports that 12.9 million (11.6%) adult women and 11.7 million (11.4%) adult men reported being told by a doctor that they have cardiovascular disease (i.e., coronary heart disease, congestive heart failure, myocardial infarction, or stroke).[53] The concern for blood donors with a cardiac history centers on the possible effect of the acute blood loss and susceptibility to vasovagal-type reactions, or medication effects that may blunt the physiologic compensation to volume reduction. Few research studies and little objective evidence are available that would determine when blood collection from a person with a history of cardiovascular disease is associated with an unacceptable risk of complications.

Consequently, there are no clinical guidelines or regulatory guidance for blood centers regarding donors with cardiovascular disease. The US Code of Federal Regulations requires only that the donor be qualified on the day of donation by a physician or persons trained in determining suitability (21CFR 640.3) but does not specify criteria to use in this qualification. AABB standard 5.4.1A (9)(a) (25th edition) requires that "The prospective donor shall appear to be in good health and shall be free of major organ disease (eg, heart, liver, lungs)...unless determined suitable by the medical director."[32]

Decisions regarding donor acceptance then fall to the donor center physician who must assess the relative safety of donation for an individual with a cardiac history compared with an individual without the condition. Because each donor is an individual, often times the medical director must evaluate the donor's unique circumstances on a case-by-case basis. However, in the absence of evidence, some donor centers still automatically reject all donors with cardiac history,[2] and some countries defer individuals with a history of a myocardial infarction or other cardiovascular history from donating blood (Table 2). Such an approach is problematic and leads to a large number of deferrals because of the prevalence of cardiovascular disease and the wide spectrum of disease severity. However, the accumulated experience with both autologous and allogeneic donors with a history of cardiac conditions favors a more pragmatic approach evaluating the eligibility of these individuals to donate.[54] Generally accepted guidelines for

autologous donors exclude those individuals with aortic stenosis, unstable angina, and myocardial infarction within 6 months of donation.[55] Although selection criteria for allogeneic whole blood donors arguably should be more restrictive than for autologous donation, individuals who are by all reasonable standards in an acceptable state of health should be able to safely donate blood.

A practical, albeit empirical, approach to donors with a history of cardiovascular disease is to accept donors who are asymptomatic on the day of donation, have been medically evaluated, and report no functional impairment or limitations on daily activity for at least 6 months after being diagnosed or treated for cardiac disease. Although this deferral period is arbitrary, the practice has been associated with a low rate of complications in the donor population at risk, with safety comparable to that of allogeneic or autologous donations accepted under less stringent acceptance criteria.[7,34,56-60] Precaution is warranted if individuals have symptoms and have not been medically evaluated or report limitations on activity or functional impairment.

Cancer. Neither the FDA nor AABB have specific requirements for evaluation of blood donors with cancer. AABB Standard 5.4.1A (9)(a) (25th edition) requires that "the prospective donor shall appear to be in good health and shall be free of....cancer....unless determined eligible by the medical director."[32] The FDA acknowledges they have no requirement to screen donors for a history of cancer, and the DHQ requires only that blood centers develop a standard operating procedure to determine the eligibility of donors who report having had cancer. Consequently, donor selection is left to the discretion of the medical director, and practice varies at different blood centers.[2,61,62]

Concern about donors with a history of cancer often centers on the potential risk to the recipient rather than the donor. Data are not available to definitively establish transmission, or a lack of transmission, of cancer to a transfusion recipient.[2] To date, however, transfusion of blood from donors with cancer has not been linked to a single case of cancer transmission to a recipient. The available evidence that cancer is not a meaningful transfusion risk is reviewed elsewhere,[61,62] and support for this conclusion comes from experimental data, clinical experience, postdonation information, and most recently a large epidemiologic study.[63]
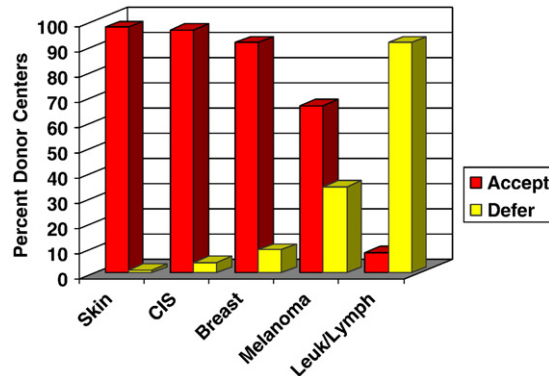

Fig 1. Cancer deferrals, America's Blood Center Donor Survey, 2006. CIS indicates carcinoma in situ (fully excised).

Cancer as a possible donor safety issue deserves careful consideration. Some degree of caution is warranted to allow sufficient time for donors to recover from cancer treatment, but the medical director of the collecting facility has considerable flexibility in determining donor eligibility policies. A theoretical concern may be that a cancer survivor could relapse soon after blood donation, despite qualification, and require cancer treatment before adequate recovery of hemoglobin/hematocrit. All blood donors may become iron deficient or develop anemia with repeated whole blood donation; however, the development of iron-deficiency anemia in a donor with a history of cancer will cause more concern and is likely to trigger an aggressive medical evaluation. Donor centers may suggest to donors who are cancer survivors that they consult with their primary health care providers regarding blood donation.

International practices for accepting donors with a history of cancer share some common ground with practices observed in the United States and Canada for in situ cancer but diverge considerably for other malignancies (Table 2). Most blood centers accept donors who report localized cancers after treatment, with no deferral period. These cancers include skin cancer (eg, basal cell or squamous cell carcinoma) and carcinoma in situ (eg, cervical, others), which have been fully excised and are considered cured. Regardless, 1% of centers still reported permanent deferral for this history in the ABC survey (Fig 1). Most US and Canadian blood centers will defer a donor with a history of a solid organ or nonhematologic malignancy for a defined period after completion of treatment and allow them to donate

if they remain symptom free without relapse. A common deferral period after completion of treatment for nonhematologic cancer is 5 years, although some centers including the ARC have shortened this interval to 1 year after completion of treatment.[64] In contrast, any cancer diagnosis other than an in situ malignancy is a permanent deferral in the EU Directive and several countries (Table 2). Hematologic malignancy typically results in the permanent deferral of the donor, although a few blood centers accept adults who were successfully treated for childhood leukemia or lymphoma after a defined cancer-free interval (eg, 5-10 years) after completion of treatment (Fig 1). Given the available data and accumulated experience, permanent deferral of all cancer survivors is unwarranted, and the various criteria that have been defined by blood centers are currently defensible, but the approach to donors with a history of cancer could be harmonized.

Medication use. Blood donors are asked about medication use, primarily as a precaution to identify substances that potentially affect the safety, purity, or potency of the component (eg, teratogens, coumadin, aspirin, or irreversible inhibitors of platelet function) or identify donors at greater risk of transmitting disease (eg, antibiotics).[15,16] Indirectly, the reason for taking the medication may identify a deferrable, underlying medical condition, although any relevant medical condition is more likely revealed in the donation interview by other direct questioning. Policies on medication use differ markedly between countries, leading to pronounced differences in resultant deferral rates. For example, in a 2005 survey on blood donor deferrals summarizing data from 77 US and Canadian ABC members and the ARC, medication use accounted for approximately 3.7% of all deferrals and resulted in the deferral of 0.3% of donors; in a similar Portuguese study, medication use accounted for approximately 13% of all deferrals and resulted in the deferral of 4.5% of donors.[65] In the United States, some blood centers have implemented locally defined medication deferral policies that are not necessarily evidence based, particularly when donors are otherwise feeling healthy and well. Moreover, a significant proportion of donors (11%) did not fully disclose their recent medication history,[66] revealing the inherent limitations of the donor interview.

Antihypertensives are among the most widely prescribed medications in developed countries. In the United States, hypertension (defined as blood pressure >140/90 mm Hg) affects more than 65 million individuals, and approximately 62.9% of hypertensive adults take a prescription hypertensive medication.[67] Some countries such as the United Kingdom defer donors on all or some classes of hypertensive medications. Presumably, the deferrals reflect concern that compensatory mechanisms to volume loss may be blunted in individuals on antihypertensives, potentially leading to higher reaction rates. Addressing these concerns are studies of both autologous and allogeneic blood donors, which demonstrate that the reaction rates in donor groups taking antihypertensive medications were not increased compared with donors who were not taking medication.[60,68]

Consequently, most blood centers in Canada and the United States do not defer donors taking antihypertensives if the donor is feeling healthy and is well and meets other eligibility criteria. Current criteria for blood pressure do not identify individuals with poorly controlled hypertension that falls within the acceptable range of blood pressure for blood donation.

Some blood centers defer donors for using immunosuppressant medications or disease-modifying antirheumatic drugs such as corticosteroids (eg, prednisone), tumor necrosis factor antagonists (eg, adalimumab, etanercept, infliximab), or antimetabolites (eg, methotrexate).[69] The impact of broad deferral policies for all immunosuppressants as a class would be significant because an estimated 1% of all US adults have rheumatoid arthritis and a significant proportion receive methotrexate.[2,70] The amount of residual drug in an additive red cell unit is inconsequential, and that in a plasma unit is not likely significant for an adult recipient, but concerns are often raised for transfusions to infants. The concern over recipient risk posed by medications is further mitigated when donations occur between doses, at times when donor blood drug levels are negligible.

Although donors taking immunosuppressants have not been extensively characterized as a distinct group, many blood centers allow these individuals to donate, and anecdotal evidence suggests that these individuals are not at greater risk for donation-related complications.

Autoimmune diseases. Autoimmune diseases are a widely diverse group of conditions with protean manifestations, variable severity, and

uncertain etiology. More than 21% of American adults (>46 million people) have arthritis or another rheumatic condition diagnosed by a doctor. Rheumatoid arthritis affects an estimated 1.3 million adults, spondylarthritides affect from 0.6 million to 2.4 million adults, and systemic lupus erythematosus affects from 161 000 to 322 000 adults.[70] Approximately 1 million Americans have type 1 diabetes mellitus, and physicians diagnose 10 000 new cases every year.[71] Individuals with autoimmune diseases (eg, rheumatoid arthritis or insulin-dependent diabetics) are rejected outright by some blood centers (Table 2), presumably out of concern that the disease could be transmitted with transfusion, that the medications pose risk to the recipient, or that their condition may increase the risk of adverse reactions after donation.[2]

Although a theoretical concern, autoimmune disease in a person who feels healthy is not likely to pose a meaningful risk to either the donor or recipient. As with cancer, transmission of autoimmune disease has not been described after blood transfusion but has occurred in the transplant setting.[72] Microchimerism, or the persistence of foreign immune cells for long periods, may play a role in autoimmune diseases and can occur after blood transfusion, pregnancy, or organ transplantation.[73,74] However, the same considerations that make transfusion-transmission of cancer unlikely, if it occurs at all, also apply to autoimmune disease.

The donor selection criteria that are in place to protect all donors are likely sufficient to protect donors with autoimmune disease. Consequently, several large blood centers will accept donors with autoimmune disease, even if they are taking medications. A few centers advise stable patients to schedule blood donation around their medication doses, but from a practical perspective, such a policy is problematic and has questionable value. In contrast, a substantial proportion of blood centers both within the United States and abroad reports various deferral criteria for individuals with autoimmune disease. Depending on the condition and the presence of symptoms, acceptance rates at US blood centers ranged from 30% to 80%, with only 15% requiring that donors not be taking medications. Individuals with autoimmune diseases should be encouraged to discuss blood donation with their primary health care providers, but automatic or universal deferral is not warranted for those who feel healthy and meet all the other selection criteria.

FUTURE: ONGOING HEMOVIGILANCE

Efforts to improve donor and donation safety are the focus of hemovigilance initiatives in several countries. First coined by the French in 1992, the term "haemovigilance" describes various activities related to the surveillance of adverse reactions to blood transfusion and donation.[75] The European imperative for hemovigilance has focused more on recipient complications, although Denmark, the United Kingdom, and other countries have established national donor hemovigilance programs and international collaboration through the International Haemovigilance Network (formerly, the European Hemovigilance Network).[76] The Canadian hemovigilance system has focused on recipient complications, although both blood operators monitor moderate and severe donor reactions. The situation in the United States is more complex, and no national system is in place, but blood centers have developed programs and published extensive data on complications experienced by blood donors.[7,30]

A major obstacle in comparing data on donor complications from various hemovigilance programs is the use of different definitions and coding procedures for adverse events in different countries. Published reports from different countries suggest a 2- to 10-fold difference in the rate of syncopal reactions among blood centers, but comparisons are meaningless when the differences could reflect dissimilar reaction types or severity, or other variables such as donor demographics, donor selection criteria, or collection practices.[7,30,77,78] Even within a large blood system that uses standard procedures and training programs at all collection sites, many factors may contribute to the variance in hemovigilance data at different locations.[7] These factors may include the subjectivity inherent in recognizing and reporting reactions, complexity in the coding scheme, and the fact that a single donor event can have multiple aspects to it.

In 2004, the International Society of Blood Transfusion and the European Haemovigilance Network established the Common Working Group on Complications Related to Blood Donation.[76] The effort focused on creating a set of definitions for donor reactions, which could be used internationally and thereby facilitate international benchmarking. In the United States, the effort to develop a national hemovigilance system is underway by the AABB Interorganizational Task Force on Biovigilance. The

ultimate goal of all of these efforts is to advance the safety of blood donors by collecting, analyzing, and disseminating data on donor reactions. An effective hemovigilance program will likely generate hypotheses about interventions to reduce the risk of reactions that can be tested and validated in practice or prospective studies.

CONCLUSIONS

Blood centers constantly strive to take reasonable measures to mitigate adverse reactions after donation and have an obligation to inform all donors of the potential risks. Donor education and staff preparedness to recognize and treat donation-related complications are crucial components of initiatives designed to protect donors. In the past, the approach to donation safety has often focused on defining criteria for donor selection, which is a blunt and nonspecific tool and leads to the unnecessary deferral of many individuals who could safely donate.

At the present time, many donors are still deferred based on characteristics that have low or no demonstrated predictive value for reactions, and the donor loss through such a nonspecific approach is substantial. If a truly evidence-based approach were to be adopted, blood centers would continue to monitor donor reactions to validate the safety of the current approaches or modify them as appropriate. Ideally, blood centers should develop methods to reduce donor reactions and long-term complications and target them to donor groups at highest risk, based on age, blood volume, or other identified factors. Clearly, current deferral policies could be further refined with careful study while protecting blood donor safety.

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