Suitability of haematopoietic cell donors: updated consensus recommendations from the WBMT standing committee on donor issues

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The contribution of related donors to the globally rising number of allogeneic haematopoietic stem cell transplantations (HSCT) remains increasingly important, particularly because of the growing use of haploidentical HSCT. Compared with the strict recommendations on the suitability for unrelated donors, criteria for related donors allow for more discretion and vary between centres. In 2015, the donor outcome committee of the Worldwide Network for Blood and Marrow Transplantation (WBMT) proposed consensus recommendations of suitability criteria for paediatric and adult related donors. This Review provides updates and additions to these recommendations from a panel of experts with global representation, including the WBMT, the European Society for Blood and Marrow Transplantation donor outcome committee, the Center for International Blood and Marrow Transplant Research donor health and safety committee, the US National Marrow Donor Program, and the World Marrow Donor Association, after review of the current literature and guidelines. Sections on the suitability of related donors who would not qualify as unrelated donors have been updated. Sections on communicable diseases, clonal haematopoiesis of indeterminate potential, paediatric aspects including psychological issues, and reporting on serious adverse events have been added. The intention of this Review is to support decision making, with the goal of minimising the medical risk to the donor and protecting the recipient from transmissible diseases.

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Introduction

Between the first haematopoietic stem cell transplantation (HSCT) in 1957 and 2019, more than 1·5 million HSCTs have been reported worldwide.[1,2] Currently 90 000 HSCTs are done annually, of which approximately 46% are allogeneic ones. Although the proportion of HSCTs using HLA-identical sibling donors has declined since 2014, more HLA-mismatched related-donor HSCTs have been done due to novel graft-versus-host disease (GVHD) prophylaxis with post-transplant cyclophosphamide in HSCTs with haploidentical donors.[2,3]

The age of patients receiving HSCT has substantially increased since the late 1990s, due to the use of reduced intensity and non-myeloablative conditioning protocols in this patient population.[4] As a consequence, older patients can also have older HLA-identical sibling donors.[4]

With increasing donor age, the risk of comorbidity and the potential of transmitting age-related disorders including malignant diseases (eg leukaemia, myelodysplastic syndrome, and other oncological diseases) from donor to recipient might increase.[5] In addition, use of older donors is associated with increased GVHD risk and significant reductions in disease-free survival and overall survival both in HSCTs of unrelated donors and related haploidentical donors.[6–9] Therefore, the increase of haploidentical donor HSCTs has been associated with an increase of underage donors, as children and other relatives are readily available, which potentially raises ethical issues. Recommendations for standardised donor assessment, haematopoietic progenitor cell (HPC) collection, and follow-up for HSCT donors already exist. However, these guidelines need to be updated to consider these changes in HSCT practice.[10,11]

Considering the differences in legal regulations between countries, recommendations should be based on published reports from quality databases, reports of adverse events in paediatric and adult donations, and consensus-based recommendations from worldwide experts in the field to ensure the best donor protection.[4,10,12–14] Furthermore, an ongoing, standardised reporting system of adverse events in all donors is strongly recommended to define donor risk groups and to monitor medium-term and long-term adverse events.[4] Finally, we provide a list of general considerations that should be considered when arranging and clearing HPC donors for allogeneic HSCT (panel 1).

Review aims

This Review intends to support decision making in donor suitability and donor counselling. We acknowledge that although many recommendations are data driven, others are expert opinions that still need to be validated. For this reason, the registration of donors in an outcome database is strongly recommended to improve risk assessment for HPC donation in accordance with WHO guiding principles on human cell, tissue, and organ transplantation.[15] This recommendation is especially relevant for related donors for whom, unlike unrelated donors, comprehensive registries do not exist yet.

This consensus document presents updated recommendations for donor testing and final acceptance of family donors, including those who would not fit the eligibility criteria of unrelated donor registries because of

Panel 1: **Important considerations when arranging for HPC donation for allogeneic HCT**

- Start donor search, selection, and health assessment early to avoid delay of haematopoietic cell transplantation (HCT). For decision making, consider the risks for both donors and recipients (including risks for the recipient if HCT is canceled or delayed)
- The donor's written informed consent is a prerequisite for donor assessment and haematopoietic progenitor cell (HPC) donation; informed consent must be voluntary; emotional relationships and dependencies (in underage individuals or individuals who are disabled that are potential related donors) need to be considered carefully; an underage individual could be a sibling donor at almost any age, but could also be considered for haploidentical family donation as they get older depending upon their degree of maturity and provided that they do not object to the donation; underage donors must be supported by a donor advocate;[24] donor advocates must understand the requirements of the national and local regulations relevant to the donation process and not be personally known to the potential donor or recipient
- Medical assessment in related donors is recommended by a short questionnaire to evaluate donor fitness and willingness to donate before human leukocyte antigen (HLA)-typing; if potential donors are found to be hesitant or potentially unwilling to donate, they should not undergo HLA typing
- In related donors HCT, it is essential to know the exact diagnosis of the recipient and, if indicated, to search specifically for inherited predispositions to haematopoietic malignancies or other inherited disorders to make sure that the donor does not carry the genetic disorder
- If a donor is not suitable either due to medical reasons or unwillingness, the only information that should be shared with the transplantation physician (or the recipient and the family) is a statement that the donor is ineligible for donation without communicating further details
- Health issues in donors that are associated with an increased risk for the recipient (eg, food allergies or hepatitis B), require an informed consent of both the recipient and the donor (to share this information); otherwise, the donor is ineligible
- An HLA-identical related donor with health disorders should be deferred if an alternative suitable donor is available
- If the potential donor has a history of serious adverse reactions to mobilising or other agents administered for donation, previous apheresis or anaesthesia, the donor shall not be exposed to this risk again; for example, for granulocyte-colony stimulating factor, these conditions are capillary leak syndrome, acute febrile neutrophilic dermatitis, spleen laceration, and any allergic reaction to growth factors; therefore, physicians must check regularly for updates of the respective drug safety sheets

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their age (ie, younger than 18 years or older than 60 years) or pre-existing health conditions. In addition, important topics missing in the Vienna workshop's publication,[14] have been addressed in this Review (eg, paediatric concerns including psychological issues; clonal haematopoiesis of indeterminate potential [CHIP], and germline predisposition; communicable disease and emerging infections; central venous catheter-specific issues; and Serious [Product] Events and Adverse Reactions [S(P)EAR] reporting).

Methods

A working group consisting of experts from the Worldwide Network for Blood and Marrow Transplantation (WBMT), European Society for Blood and Marrow Transplantation (EBMT) donor outcome committee, Center for International Blood and Marrow Transplant Research (known as CIBMTR) donor health and safety committee, the US National Marrow Donor Program (NMDP), and World Marrow Donor Association (WMDA), participated in several online meetings to discuss and harmonise decision making for the final acceptance of related donors with respect to existing medical issues and potential infectious risks. From the Vienna Workshop in 2013, the suitability criteria for related donors were published, which were used to update recommendations for related donors and to discuss specific paediatric issues.[14]

Update for related donors

All transplantation, collection, and donor centres must have procedures in place for donor testing including obtaining written informed consent, and HPC collection procedures to ensure donor safety. Guidance is given in several documents.[16,17,20] The European Directorate for Quality in Medicine has published a guide for the quality and safety of tissues and cells for human application, which includes chapters on Donor Evaluation and Biovigilance for HPC collections from bone marrow and peripheral blood that are updated biannually.[21] In addition, recommendations to ensure the physical and psychological health and safety of related HPC donors have been established.[22]

Usually, the entire process from search to selection of a family member is done in the transplantation centre where the recipient is receiving the HSCT. It is accepted that donor health assessments should be done according to standardised medical suitability criteria under the supervision of a physician who is not involved in the recipient's care (ie, divided responsibility) but who is experienced in donation procedures.[13,23,24] These stipulations are listed in Foundation for the Accreditation of Cellular Therapy (FACT)-Joint Accreditation Committee of ISCT and EBMT (JACIE) international standards for Haematopoietic Cellular Therapy, which have been widely accepted by HSCT centres worldwide.[20,25]

Unrelated donor registries have become increasingly involved with the evaluation of related donors. This involvement separates donor counselling from the physicians involved in recipient care, and is also due to the practical, financial, and logistical concerns that might preclude the travel of some related donors to the recipient's transplantation centre.[23] Moreover, there are certain countries and regions that prefer an unrelated donor registry does this assessment as it is unbiased and objective. This preference has been particularly true during the COVID-19 pandemic. Although most related donor evaluations are straightforward and can be done using the current donor evaluation tools that were developed for unrelated donors, a growing number of donors with concomitant comorbidities, elderly donors, or paediatric donors can be challenging. Some registries, such as the NMDP, have adopted the WBMT recommendation to do

related donor evaluations, with some notable exceptions (ie, rejecting donors with dementia, diabetes with a HbA_{1C} of at least 8% regardless of the medication regimen, body mass index (BMI) of at least 45 kg/m², and lymphoedema). Other donor issues have been considered on a case-by-case basis, including disability, recurrent infections, hypertension, or history of concussion. In these situations, where unrelated donors would have been automatically deferred per registry criteria, the medical team might allow donation to occur on the basis of related donor test results and other indications that the specific donor is medically cleared for donation.

There are an increasing number of studies that have evaluated the risks associated with HPC collection in related donors. The Related Donor Safety Study,[26] a prospective clinical trial, addressed the effect of age on several variables including cell counts, pain, donation-related symptoms, and recovery in 1680 related donors. Donors aged between 18 years and 79 years who were enrolled in this prospective observational study donated peripheral blood stem cell (PBSC) (n=1211) and bone marrow (n=469). Related donors older than 60 years had a lower median $CD34^+$ cell count before apheresis compared with related donors younger than 60 years. Older donors also underwent more apheresis procedures, had higher collection volumes, and had postcollection thrombocytopenia more often, along with more frequently persistent pain at 1 month, 6 months, and 12 months. Donors reporting comorbidities were significantly older, and those with comorbidities that would have led to deferral by NMDP standards for unrelated donors had an increased risk for persistent grade 2–4 pain and failure to recover to their predonation baseline for the symptoms of their comorbidities. Similar outcomes were reported in another study, in which related donors had more severe symptoms and less complete recovery at one year after donation compared to unrelated donors and had significant decreases in their Health-Related Quality of Life scores at 1 month and 1 year postdonation.[27]

A Dutch study[28] evaluated short-term and long-term adverse reactions in 268 related donors who underwent PBSC mobilisation. 15% (of 268) of donors would have been deferred on the basis of NMDP criteria for unrelated donors due to age (older than 60 years), BMI (at least >40 kg/m²), and hypertension (higher than 160/95 mmHg); and medical contraindications which included clotting issues, diabetes, or heart issues.[16] There was no increase in cardiovascular events, autoimmune diseases, or malignancy in those donors that would not have been eligible due to NMDP criteria.

When assessing a related donor's suitability to donate, it is important to consider the psychosocial component of donation. There is a growing body of literature on the psychosocial experiences of paediatric HPC donors;[29–33] less is known so far on the psychosocial experiences of adult related donors.[34,35]

Specific updates of suitability criteria in donors with pulmonary diseases

For donors with chronic obstructive pulmonary disease up to the severity level of GOLD II we recommend considering PBSC donation only. Individuals with obstructive sleep apnoea are suitable for PBSC donation in the absence of cardiorespiratory complications. Donations from individuals with cystic fibrosis are generally not recommended (appendix p 1).

Specific updates of suitability criteria in donors with non-infectious eye disease

Individuals with retinal detachment due to trauma are suitable donors if they have a history of a single episode that has resolved or if they have a stable visual defect after careful ophthalmological re-evaluation. In the case of retinal detachment without trauma only bone marrow donation should be considered (appendix p 4).

Specific updates of suitability criteria in donors with haematological diseases and coagulation disorders

Donors with secondary polyglobulia are suitable if the underlying condition is no contraindication and if their haematocrit concentration is at most 52% for males and at most 48% for females. Individuals with haemophilia A or B are not suitable for unrelated donations, but they are suitable for related donation after careful assessment and if the risk of bleeding is controlled (eg, after replacement therapy). Individuals with secondary immune thrombocytopaenia (platelets $\leq 130 \times 10^9$cells/L), hereditary thrombophilia without venous thromboembolism, and homozygote factor V Leiden mutation are considered suitable as related donors but are not eligible to be unrelated donors (appendix pp 4–6).

Specific updates of suitability criteria in donors with malignancies

Individuals with a history of noninvasive papillomatous bladder cancer are suitable as donors if an absence of invasive disease is histologically confirmed. Donors with a history of invasive cancer that are in remission for between 2 years and 5 years could be considered after careful assessment if no other donor is available and only if there is a low risk of tumour transmission.[36,37]

Women who carry *BRCA1* or *BRCA2* mutations who do not have a history of cancer on antihormonal medication are suitable donors in the absence of other contraindications without suspending their medication (appendix pp 6–7).

Specific updates of suitability criteria in donors with autoimmune disorders and musculoskeletal diseases

Individuals with Behçet disease and mild symptoms, a history of antinuclear antibodies positivity with no diagnosis (ie, no symptoms) after careful evaluation, coeliac disease in the absence of acute bleeding that is stable under treatment, and eosinophilic gastrointestinal

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See **Online** for appendix

conditions if well controlled might be suitable for bone marrow donation only. Donation by individuals with fibromyalgia is not recommended in unrelated donors but can be assessed individually in related donors, where bone marrow should be preferred if the risk of long-term pain symptomatology is considered acceptable (appendix pp 7–8).

Specific updates of suitability criteria in donors with metabolic disease

Donors with obesity are suitable for PBSC and bone marrow donation if their BMI is less than 35 kg per m². Individuals with a BMI of 35–40 kg per m² are acceptable for PBSC and bone marrow donation if no technical difficulties are anticipated. Individuals with a BMI more than 40–45 are only acceptable for PBSC and provided that no alternative donor is available and no other disease that would be a contraindication is present (appendix pp 9–10).

Specific updates of suitability criteria in donors with neurological, psychological, and psychiatric disorders

Individuals with fainting, dizziness, Ménière syndrome, and vertigo might be suitable if constant medical care is ensured. Bone marrow donation should be preferred.

Use of recreational drugs (eg, alcohol or cannabis) is no reason for deferral but donors should not donate if under a substances' influence. In individuals who abuse substances or have a history of substance use (eg, cocaine, amphetamines, barbiturates, or hallucinogens) a careful assessment (ie, medical history, clinical, psychiatric) is necessary. Donation is not recommended if the individual is addicted to a substance (appendix pp 10–12).

A summary of conditions, suitability of the donor, and individuals at risk is given in the appendix (pp 1–16). Considerations for HPC donor evaluation are given (table 1). The American Society of Anesthesiologists physical status (ASA PS) Classification is also available (appendix pp 17–19).

Paediatric donors

Ethical issues and donor advocacy

Beyond being donors for sick siblings, children are increasingly considered eligible for haploidentical donation to their parents. Although ethical issues remain, it is generally accepted that the potential benefits to an underage donor who is unable to give true informed consent—including the survival of their sibling or parent—might justify the small risk related to HPC donation.[38]

In 2010, the Bioethics Committee of the American Academy of Pediatrics published recommendations about what conditions are acceptable for an underage sibling to donate for HSCT.[39] When considering whether HPC donation from an underage is appropriate, the most important issue is if the donor feels forced or has substantial animosity toward the recipient. In such situations, donation might be psychologically problematic for the donor and alternative donors should be considered. Some countries require legal approaches or have other rules surrounding such donations, including adjudication in court.

Despite the strong recommendation for donor advocates, many US-based and European-based transplantation centres still do not have a donor advocate regularly available.[22,39,40] A large 2019 study[41] of transplantation centre practices in the USA and Europe found that just over half of centres consistently use a donor advocate to ensure that a potential donor is willing to donate. Reported barriers to using an advocate included cost and uncertainty about the need for an advocate. Furthermore, this investigation also found that 22% (of 52) of centres have no process in place to assess donor assent, 30% do not regularly perform psychosocial screening or assessment, 70% do not have written policies for donor psychosocial screening or assessment, and 44% always or often have the same physician managing both the donor and the recipient.[41]

Safety data in children: approaches to minimise toxicity

Since it began in the 1960s, bone marrow donation by infants, children, and adolescents to treat siblings has become an acceptable practice.[42] To date, however, the scientific literature on paediatric bone marrow donation is scarce. Factors associated with increased risk include donation at very young age (eg, less than 1 year) and donations of high volumes of bone marrow compared to donor body size.[42] In general, restricting the volume of bone marrow collected to less than 15–20 mL/kg donor weight can avoid a need for red blood cell transfusion during or after donation.[42–44] Girls older than 13 years have the highest risk compared with others for short term side effects and pain, along with mild chronic pain at 1 year.[44] Pain not related to recombinant granulocyte-colony stimulating factor (G-CSF) was the most common adverse event reported by 453 paediatric donors, mainly in older children after bone marrow harvest and central venous catheter placement for PBSC collection (62·3%, 195/313 in bone marrow donors; 15%, 21/140 in PBSC donors). Only one patient experienced a serious adverse event (0·7%; 1/140), developing a hydropneumothorax after central venous catheter placement.[42]

PBSC collection in children is considered standard in many countries and has a good safety profile.[42] The major risks of collection are associated with central venous catheter placement, which is needed universally in donors younger than 10 years. PBSC collection of young donors (younger than 12 years) should be limited to centres with substantial expertise in line placement and apheresis in small children. Although concern has been raised about G-CSF use in healthy children, there is currently no evidence that it increases the risk for serious adverse events in either paediatric or adult donors.[45,46] In children with small total blood volumes (ie, donors <20–30 kg body weight), priming of cell separators before apheresis is

	Method	Topics to consider	Specific for this stage
Recruitment or registration for unrelated donors	Medical history and questionnaire	Malignancy; autoimmune disease; cardiovascular disease (or a combination of risk factors for cardiovascular disease); chronic disease (eg, pulmonary, neurological, or haematological diseases or serious allergies); relevant medical history (eg, malignancy, or thromboembolic disease); behavioural risk factors for infections; and inherited or genetic diseases	Look for permanent diseases or behaviours that have a clear donor risk or unacceptable recipient risk and that are relatively easy to assess
Before HLA-typing for related donors	Medical history and questionnaire (including age)	Malignancy; autoimmune disease; cardiovascular disease (or a combination of risk factors for cardiovascular disease); chronic disease (eg, pulmonary, neurological, or haematological diseases or serious allergies); relevant medical history (eg, malignancy, or thromboembolic disease); behavioural risk factors for infections; and inherited or genetic diseases; avoid HLA typing in minors if other adult relatives are available and willing to donate	Identify contraindications before concluding that the related donor is the best one (might save time and psychological distress)
During selection stage for related and unrelated donors	Medical history and questionnaire; blood tests for infectious disease markers (ie, HIV, hepatitis B virus, hepatitis C virus, HTLV, syphilis, and cytomegalovirus); at this stage Epstein-Barr virus and blood group and rhesus could also be assessed in donors; in related donors for patients with: (1) genetic diseases: check for presence of the genetic disease, (2) metabolic disorder: check respective enzyme levels, (3) paediatric myelodysplastic syndrome: document healthy bone marrow (4) haemoglobinopathies: prefer homozygous donors, (5) history of malignancies in the family: check Karyogram or analysis for germ line mutations	Update medical history including tumor history of parents and other relatives (related), behavioural risk factors for infections; history of or planned: invasive medical procedures, vaccinations, travel, and tattoo; planned medical procedures (including blood transfusion, dentist, and vaccination); serious psychosocial or psychiatric disease with an effect on their availability or capacity to go through the donation procedure; medication; non-prescription drug use; height and weight; blood pressure; pregnancy, pregnancy planning, and breastfeeding; back problems; and chronic pain	Identify contraindications for one of the two collection methods; provide information about possible transmittable disease to the transplantation centre; provide information to the transplantation centre about any availability issues for the donor
During testing of related and unrelated donors	Medical history including full tract history; complete physical examination; laboratory tests: infectious disease markers: for HIV-1, HIV-2, hepatitis B virus, and hepatitis C virus, validated serological testing algorithm for syphilis, (3) on indication or per request of the transplantation centre: HTLV-1, HTLV-2, Chagas, West Nile virus, malaria, etc; full blood count; if any are indicated: coagulation screen, blood film, Hb electrophoresis; blood group, and rhesus typing; biochemistry including electrolytes, liver enzymes, LDH, urea, creatinine, ferritin; random glucose; β-HCG (for women younger than 55 years), and protein electrophoresis; chest X-ray, abdomen ultrasound, and electrocardiogram	Behavioural risk factors for infections history of or planned: invasive medical procedures, vaccination travel, and tattoo; planned medical procedures (including blood transfusion, dentist, and vaccination); serious psychosocial or psychiatric disease with an effect on their availability or capacity to go through the donation procedure; medication; non-prescription drug use; height and weight; blood pressure; pregnancy, pregnancy planning, and breastfeeding; back problems; chronic pain; and any signs of undiagnosed disease	Emerging infectious disease: check latest infectious disease epidemiology maps (ie, CDC, ECDC); avoid donors with any active illness or close contact with potentially transmissible diseases

β-HCG=β-human chorionic gonadotropin. CDC=Center for Disease Control and Prevention. ECDC=European Centre for Disease Prevention and Control. HIV=human immunodeficiency virus. HLA=human leukocyte antigen. HTLV= human T-cell-lymphotropic virus. HPC=Haematopoietic progenitor cell. LDH=lactate dehydrogenase.

Table 1: **Recommendations on assessing the medical suitability of HPC donors at different assessment stages**

necessary, which means that these donors will have the risk of requiring allogeneic red blood cell transfusion.

There are very little data concerning the long-term effects of paediatric bone marrow or PBSC donation beyond 1 year of follow-up. Although there are no strong signals indicating the possibility of clinically significant long-term toxicities associated with donation, a mechanism to ensure the collection of long-term data related to adverse reactions would be helpful to confidently show long-term safety. In addition, there are some small studies of quality of life after donation, the largest of which showed significant decreases in health-related quality-of-life after donation, especially in the youngest participants (aged 5–7 years).[29–33] This study also showed that parent proxy reports substantially overestimated donor health-related quality-of-life, suggesting that health-related quality-of-life studies of paediatric donors should obtain responses from donors themselves whenever possible. Large health-related quality-of-life studies of families involved in paediatric HPC donation are needed, along with more long-term follow-up health-related quality-of-life studies.

Clonal haematopoiesis and germline predisposition

Clonal haematopoiesis of indeterminate potential (CHIP) is characterised by one or more somatic mutation that is associated with haematological malignancies in otherwise healthy individuals who do not have detectable haematological diseases. Detection of mutations with a variant allele frequency of at least 2% is rare in people younger than 40 years but increases up to 9·5% in people aged 70–79 years.[47] A consensus on biologically and clinically meaningful variant allele frequencies is still

	Test to be done	Consequence
HIV-type 1 or 2*	HIV-1, HIV-2 antibody, and HIV NAT, (if required, also p24 antigen)	Permanent deferral if positive
Hepatitis B*	Hepatitis B surface antigen, Hepatitis B core antibody, and Hepatitis B NAT	Accept the donor if hepatitis B virus core antibody is positive, hepatitis B virus surface antigen and NAT are negative, and hepatitis B surface antibody >100 IU/l
Hepatitis C*	Hepatitis C antibody and Hepatitis C NAT	Donors who are hepatitis C virus antibody positive but negative for hepatitis C virus NAT might be acceptable at the discretion of the requesting transplantation centre
*Treponema pallidum**	Validated serological test for syphilis	Accept if the donor has a successfully-treated history or is currently receiving treatment
HTLV types 1 and 2 (if the donor is at risk)†‡	HTLV-1 and HTLV-2 antibody	Permanent deferral if positive
Cytomegalovirus‡	Cytomegalovirus IgG and IgM antibody (NAT for cytomegalovirus in selected cases)	If only the IgM for cytomegalovirus is positive, NAT should be done
Epstein-Barr virus‡	VCA-IgG (EBNA-IgG) and VCA-IgM (NAT for Epstein-Barr virus in selected cases)	If only VCA-IgM is positive, PCR for Epstein-Barr virus should be done
Parvovirus-B19,‡ HHV-6‡ and HHV-8,‡ HSV‡ and VZV‡	Optional	Transmission from the donor not yet documented
Toxoplasma gondii‡	Toxoplasmosis IgM and IgG; toxoplasmosis NAT-testing is not relevant, since negative NAT does not exclude relevant infection or parasitemia	If the donor is toxoplasmosis IgM and IgG positive do avidity testing to measure the binding strength of antibodies (allows estimation of the time point of primary infection and differentiation of acute and chronic infection); if the donor is toxoplasmosis IgM positive and IgG negative do further testing (eg, immunoblot or ISAGA) to verify if the result is due to acute infection or non-specific binding

EBNA=Epstein-Barr virus nuclear antigen. HHV=human herpes virus. HSV=herpes simplex virus. HTLV=human T-lymphotropic virus. ISAGA=immunosorbent-agglutination-assay. NAT=nucleic acid test. VCA=viral capsid antigen. VZV=varicella zoster virus. *Mandatory. †Required if donor is at risk for being infected, or if required according to local regulations. ‡Additional testing if required by transplantation centre.

Table 2: **Required and additional pretransplantation donor testing for different pathogens**

unknown and more sensitive techniques detected CHIP in more than 90% of 50–60 year old participants in the Nurses' Health Study.[48] CHIP with a variant allele frequency of at least 2% is associated with increased risk of haematological malignancies, coronary artery disease, myocardial infarction, venous thromboembolic disease, and other cardiovascular and pro-inflammatory complications.[47,49] In the majority of healthy individuals, mutated HPCs are be stable over many years without causing disease, which makes individual predictions of the malignant transformation potential challenging.

CHIP can be transferred from donor to recipient during allogeneic HSCT and might contribute to poor engraftment, unexplained cytopaenias, or donor-derived leukemia.[49] Three recent publications observed that, overall, HSCT from donors with CHIP seem to be safe and result in similar recipient survival.[50–52] Donor CHIP might be associated with an increased risk of chronic graft-versus-host disease and reduced relapse or progression risk.[50–52] However, current evidence does not support the screening of all potential donors, or even donors older than 60 years, for the presence of CHIP before HPC donation.

Regardless of donor age, it is essential to avoid HPC donation by related donors who have an inherited predisposition to haematopoietic malignancies.[53] Familial autosomal dominant mutations in several genes (eg, *CEPBA*, *DDX41*, *RUNX1*, *ANKRD26*, *ETV6*, *GATA2*, or *TP53*) are associated with an increased risk for myeloid malignancies, telomere biology disorders, and lymphoid disorders. The use of HPCs from carriers of the deleterious genes *RUNX1* and *CEBPA* is prohibitive.[55] Phenotypes could vary even within families. A careful family history of haematological disorders, bone marrow failure, organ fibrosis, or primary lymphoedema is important. Further key findings might be mild cytopaenias or unexplained bleeding diathesis.[54] If, during donor evaluation, haematological disorders, excessive bleeding, mild cytopaenias, or health conditions known to cluster with hereditary haematological malignancies, such as primary lymphoedema, are identified, we recommend evaluation by a genetic counsellor or hereditary cancer expert familiar with familial haematopoietic disorders. Targeted investigation in higher risk donors should be done to identify carriers of genetic predispositions for myeloid neoplasms, which would make them unsuitable as donors.

Communicable Diseases

Donor screening for infectious diseases

Recipient outcome can be adversely affected by the transmission of infectious diseases via donor HPCs, or because of bacterial or fungal contamination of the graft during apheresis or cell processing. Therefore, donors should be screened with appropriate serological or molecular methods for relevant blood-bourne or graft-borne communicable diseases or disease agents as is legally required and suggested in specific standards (table 2).[20,55] Eligibility criteria could differ between

unrelated donors and related donor, as certain risks for disease transmission might be tolerated in related donors after careful assessment of the potential benefits and risks.[14]

The risk of communicable infectious diseases can be assessed using standardised questionnaires such as those developed by the American Association of Blood & Biotherapies, NMDP, or WMDA.[56,57] Donor serological status for cytomegalovirus, Epstein-Barr virus, and *Toxoplasma gondii* are often requested from transplantation centres to identify the most suitable potential donor, and to optimise post-transplantation management of the recipient.

Endemic or regionally limited infections and pandemics

A donor's medical history should consider the risk of endemic or regional infections and, therefore, the predonation interview should identify place of residence, travel history, and any prolonged stays in regions with endemic infections that can cause serious disease if transmitted to the recipient. Endemic areas can change rapidly during the year, hence the use of real-time guidelines from blood transfusion services and the US Center for Disease Control or European Centre for Disease Control is recommended to provide updated information for the assessment of disease risk. WBMT has reviewed this topic and recommendations have been issued for both related and unrelated donors (Muhsen IGS, personal communication).

Among the most common tick-borne or mosquito-borne viruses that can be transmitted through blood, and potentially through HPCs, are *Flaviviruses* (including dengue, Zika, yellow fever, West Nile fever and Japanese encephalitis) and *Togaviruses* (eg, chikungunya). Therefore, in the context of a recent infection donation should be deferred for 4 months.

Parasites that can be potentially transmitted through the graft even in asymptomatic donors include *Plasmodium spp*, *Trypanosoma cruzi*, *Leishmania spp*, and *Babesia spp* and zoonotic bacterial infection due to *Brucella spp*. Therefore, donors should be asked about their epidemiological risk or past history and be tested as appropriate.

In general, donors with confirmed active or recent endemic communicable infections should be excluded or deferred according to international and local policies on HPC donation. In unaffected areas it is also preferable to avoid the use of HPC products from areas of epidemiological risk, unless there are no other equivalent or suitable donors available.

During pandemics or disease outbreaks, risk assessments must include the risk of transmission by blood or HPC, the risk for the donor and the collection team by the collection procedure, and possible travel restrictions. These challenges have recently been highlighted in the context of the COVID-19 pandemic by WBMT, EBMT and other scientific organisations.[58–61]

Donor vaccination

Donors should receive routine vaccines, but vaccination should be avoided in the 2–4 weeks before HPC donation, particularly for live agents. Deferral periods could be even longer after passive immunisation. Donor vaccination with the aim of reducing infectious complications in the recipient is generally discouraged due to an absence of evidence of benefit.[62]

Recently, the EBMT published recommendations on HPC donation and COVID-19 vaccination.[63] If a donor has received an unlicensed or unknown vaccine, they should be deferred for 4 weeks. To avoid an increase in side effects in addition to mobilising agents (eg, G-CSF), COVID-19 vaccination should not be given within 1 week before donation.[63]

Central venous catheters in allogeneic HPC donation

Central venous catheters for PBSC collection should only be used with the utmost restraint when peripheral venous access is not deemed feasible after skilled assessment, cannot be obtained, or has failed and there is no other equivalent donor available.[4,64] Several serious adverse reactions have been reported, including fatal outcomes in at least two donors worldwide.

S(P)EAR reporting

The WMDA has set up a central global reporting system for WMDA member organisations to report serious events and adverse reactions: S(P)EAR. The aim of the S(P)EAR system is to gain insight into the occurrence of serious events and adverse reactions for haematopoietic cell donation (ie, collection and processing) from unrelated donors. WMDA can send out a rapid alert in the rare event of a donor fatality, or if the S(P)EAR Committee deems a S(P)EAR report to be expedited. The rapid alerts consist of a brief description of the event and recommendations that can be used as a guideline for best practice.[19]

A second system dedicated to the collection of global adverse events and reactions is NOTIFY Library, a public website in which experts from across the globe collaborate to voluntarily share information on documented adverse outcomes associated with the clinical use of human organs, blood, tissues, and cells. NOTIFY Library is a global vigilance and surveillance database for medical products of human origin organised by WHO, the Italian National Transplant Centre and the European Union, and includes adverse events and reaction reports from both unrelated and related donors. A total of 150 different adverse reaction records of harm to a donor after PBSC (n=98), bone marrow (n=50) and lymphocyte (n=2) donations are currently available in the NOTIFY Library. In PBSC donation, unexpected adverse reactions were predominantly G-CSF-related (46%), of vascular, thromboembolic and infectious origin (35%), or apheresis-related (20%). In contrast, most adverse

For **NMDP** see https://network.bethematchclinical.org/

For the **US Center for Disease Control** see https://www.cdc.gov/

For the **European Centre for Disease Control** see https://www.ecdc.europa.eu/en

reactions reported after bone marrow harvest were procedure (54%) or anaesthesia related (25%). The unexpected adverse reactions (17%) included bleeding, embolic, and cardiovascular complications.

Donor outcome registries

Collecting data on severe adverse events or reactions is important, but we should also place them in context and have appropriate controls—usually not the general population but, for example, siblings or unrelated donors eligible for donation but who did not donate—to understand whether the donation process increases the risk of severe adverse events.[45] Collected severe adverse events might have no relation to the donation process itself or to mobilisation treatment; they might simply be a description of events that would have occurred regardless of the donation procedure.

For the **NOTIFY Library adverse occurrence search** see https://www.notifylibrary.org/notifylibrary/search/incident/16445158577967

Since the late 1990s, several carefully done analyses have been published on donor safety outcomes. Most of these analyses are based on data from unrelated donors registries (WMDA S(P)EAR committee annual report 2020);[65] however, the number of publications on outcomes in related donors including quality of life analyses is also increasing.[45,66,67] These analyses also support the consistency of care between unrelated and related donors.[26,27,33,35,68] In 2022, we have reliable information on the frequent early events and reactions that are associated with donation. Most of the events are of mild-to-moderate intensity.[4,26–28,42,44,45,65–67,69] Information on the type and relative risk of serious adverse events is scarce. In 2020 the WMDA S(P)EAR committee received 474 S(P)EAR incident reports in unrelated donors from 32 different organisations. Reporting these data is mandatory for WMDA members; however, donors are not obliged to report to the registries, therefore, the calculation might underestimate the true incidences. In the 2020 report, 80% (367/458) of these reports were categorised as "harm to the donor"[65] with 41% (151/367) observed within 6 months of donation. The type of harm included development of an autoimmune disease, non-haematological malignancies (mainly breast, testicular, and prostate cancer), and haematological malignancies.[65] Most of these reports are deemed to be unrelated to the donation by the S(P)EAR committee.

Other reports summarise severe adverse events or reactions in related donors and donor outcome data.[4,42,69] The continuation of large datasets collected by a combined international effort are needed to ensure reliable information on donor risks. As a first step, recommendations for a minimum dataset and an extensive dataset for prospective donor follow-up have been developed by the WBMT.[13] On the basis of these recommendations, EBMT established a donor outcome registry for both related donors and unrelated donors in 2013.[70] Currently, reporting is voluntary and consistent data of donors of all age groups (especially underage donors) are scarce. Several initiatives by national and international organisations and authorities might make donor follow-up mandatory in the future.[15,22,71]

Search strategy and selection criteria

We did a thorough review of the literature. Sources of information included English-language articles from PubMed that were published between Jan 1, 2015, and Jan 31, 2022. The search included the following terms: "adverse events allogeneic HPC donation; adult and/or paediatric donor", "disease transmission from HPC donors to the recipient", "HPC mobilization and donation", "G-CSF adverse events in HPC mobilization", and "clonal haematopoiesis HPC donor". After a review of the abstracts, the expert group retrieved the full text of the articles that were considered relevant. Moreover, the NMDP and WMDA recommendations for evaluation of unrelated donors were reviewed.[16–18] Finally, the S(P)EAR Committee Annual Report from 2020 provided by the WMDA and the NOTIFY Library were included.[19]

Conclusions

Safe and standardised assessment and care of both related and unrelated donors is crucial to protect the increasing number of donors involved in allogeneic HSCT worldwide. Although suitability criteria defined by experienced donor registries for unrelated donors remains essentially unchanged; the increasing use of HSCTs in emerging countries using haploidentical HPC donors requires established, standardised donor assessments by independent physicians who are HSCT-experienced and pay strict attention to donor safety. Related PBSC donors with comorbidities are at increased risk for pain, toxicity, and non-recovery within 1 year after donation and need to be considered when counselling related donors for donation. Understanding that related donors are at higher risk could assist physicians in developing practice approaches aimed at improving the related donor experience and mitigating adverse events.

Ensuring the safety of HPC donation remains a central goal for donor protection. Global structural registration of severe adverse events and reactions, and long-term follow-up of donors, which includes health-related quality-of-life assessments, will also aid in optimising related donor care management and should be included globally in clinical routine.

Contributors

NW, JPH, HTG, DN, MAP, and HES contributed to the conceptualisation of the Review. NW, JPH, MC, SG, SMvW, MA, CA, ASB, AMK, MBCK, TM, GES, and HY did the literature review. NW and JPH contributed to data conceptualisation. NW, JPH, HTG, DN, MAP, HES, MC, SG, and SMvW summarised the literature. All authors wrote and edited the draft of this Review.

Declaration of interests

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