Evaluation of Hematopoietic Stem Cell Donors

Mary M. Horowitz and Dennis L. Confer

Donation of hematopoietic stem cells, either through bone marrow or peripheral blood collection, is a generally safe procedure for healthy donors. Serious adverse events are uncommon and death is exceedingly rare. Nevertheless, all donors must be carefully evaluated and fully informed prior to donation. This should be done by clinicians having good understanding of the potential physical and psychological complications of donation and the factors that may increase these risks. Additionally, donors and graft products must be evaluated for the potential to transmit infections and other diseases to the recipient and to satisfy an increasing number of national and international regulatory requirements. Donors must be able to provide informed consent without coercion or pressure. Special attention to the clinical, psychological and social needs of pediatric donors is necessary.

Hematopoietic stem cell (HSC) donors provide grafts for >15,000 allogeneic hematopoietic stem cell transplants (HCT) annually, about 70% for related and 30% for unrelated recipients. Until recently, bone marrow was the most common graft source, but the use of cells collected from peripheral blood has increased dramatically. Data from the Center for International Blood and Marrow Transplant Research (CIBMTR) indicate that peripheral blood collections accounted for 75% of related and 50% of unrelated donor donations in North America in 2003. Prospective donors must be evaluated to ensure that: 1) their cells are suitable for transplantation in the recipient, 2) the donation process will be safe for them, and 3) they understand fully what they are being asked to do.

Assessing the Donor for Risks to the Recipient

There are numerous infectious agents that, if present in the donor, pose definite or theoretical risk to the transplant recipient. HSC can transmit the same infectious agents transmissible by blood transfusion including hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV). Additionally, some congenital or acquired conditions, such as genetic defects or immune deficiencies, are potentially transmissible. Assessing the risk of disease transmission requires a targeted screening history, a search for physical signs of disease and laboratory testing for specific pathogens or traits. HSC donors should complete a questionnaire to elicit medical history and to identify behaviors associated with risk of disease transmission. Topics should include sexual behaviors, non-prescription drug use, skin-breaching procedures, e.g., tattooing, and residence in regions where exposure to malaria or the agent of bovine spongiform encephalopathy (BSE) may occur. Standardized questionnaires for assessing a prospective donor’s health history are freely available. The National Marrow Donor Program (NMDP) maintains such a questionnaire, which is based upon a uniform donor questionnaire utilized in the blood banking field. The NMDP questionnaire, comprised of 57 relevant questions for prospective donor, is available in English and Spanish. Companion documents provide rationale for the questioning and recommendations for evaluation of responses. Copies of the NMDP forms are available at no charge from the NMDP (www.marrow.org or 1-800-marrow2 in the US and 1-612-627-5800 outside the US). A Uniform Donor History Ques-
tionnaire for Hematopoietic Progenitor Cells, Apheresis or Marrow was recently drafted by an inter-organizational task force to include requirements of the US Food and Drug Administration (FDA), the Foundation for the Accreditation of Cellular Therapy (FACT) and the American Association of Blood Banks (AABB). It can be viewed by visiting www.factwebsite.org.

Testing the donor’s blood, while important, cannot substitute for questioning because tests may be falsely negative and available tests do not detect all potentially transmissible diseases. Positive responses on a screening questionnaire may lead to donor disqualification or, at a minimum, careful donor evaluation and a thorough assessment of risk versus benefit.

The donor physical examination should detect behavioral and experiential stigmata, such as recent tattoos, piercings, or signs of intravenous drug use, as well as signs of significant illnesses. Blood must be tested for, at least, the following infectious disease agents: human immunodeficiency virus 1 and 2 (HIV 1/2), HBV, HCV, *Treponema pallidum*, human T-cell lymphotropic virus I and II (HTLV I/II) and cytomegalovirus (CMV). Recent FDA regulations require that these tests be done in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory. Results must be reviewed prior to initiating preparative conditioning therapy in the recipient. If the time between initial donor evaluation and collection is delayed, repeat testing may be necessary. It is also desirable to perform testing for prior infections with varicella-zoster virus (VZV) and Epstein-Barr virus (EBV) and possibly others, such as toxoplasmosis. Positive tests for exposure to these agents may not preclude donation but may modify the transplant approach or posttransplant surveillance strategies.

Emerging infectious diseases present unique problems for donor screening and qualification. Recent examples include the severe acute respiratory syndrome (SARS) and West Nile virus (WNV). In both of these instances, additional screening questions were emergently added to the donor qualification process in the US, based upon recommendations from the FDA. In the case of WNV, the FDA also encouraged industry to develop valid blood screening tests, which could be used to test donors for evidence of active infection. Currently, two blood screening tests for WNV are available for use, but these tests remain under Investigational New Drug (IND) applications.

The situation with WNV is further complicated and illustrates the difficulties that can occur in addressing new diseases. The problem with WNV is that, unlike CMV, HCV and other viruses, the donor’s blood—and by inference, the cellular product—is only infectious during the viremic phase of the illness, which has a rapid onset in the few days following an infected-mosquito bite. Individuals who have developed antibodies to WNV are, for all intents, no longer infectious. What this all means is that, to be informative, the testing for WNV must be performed concomitantly with product collection. For example, a donor who tests negative for WNV weeks before donation has ample opportunity to become infected by the day of donation; while at the same time, a donor who tests positive weeks before donation will likely be recovered by the time of donation. In recognition of this dilemma, the NMDP implemented WNV testing under IND on the actual day of donation, reasoning that while it might not be possible to prevent the infusion of an infected product, knowing that a product was infected with WNV would provide an opportunity to develop a preemptive treatment strategy, such as infusions of immune plasma. Fortunately, after testing well over 1000 products for WNV, the NMDP has not encountered a single positive result. It may be worth noting that this result—no infections after more than 1000 tests—is expected because the point prevalence of WNV viremia among asymptomatic persons, even in the midst of a community epidemic, is far less than 1 in 10,000.

Donors with a confirmed positive test for HIV must not donate. Donors with prior exposure to HBV and HCV may be used when there are no suitable alternatives. Strategies for managing hepatitis exposure in donors and recipients have been reviewed. When antibodies to HCV are detected, polymerase chain reaction (PCR) testing may be performed to detect HCV RNA. Failure to detect RNA, however, does not preclude HCV transmission. Pretreatment of the donor with interferon-α may be beneficial. Donors who have recovered from HBV infection can safely donate; HCT recipients with active HBV infections may even benefit from having a donor with hepatitis B immunity. Transplant recipients whose donors are positive for hepatitis B surface Ag, however, are at high risk for post-transplant hepatic complications and transplant-related mortality. CMV seronegative recipients may benefit from having CMV seropositive donors, though this is controversial and donor CMV status correlates less strongly with recipient outcome than other donor characteristics like HLA-match and age. It has been suggested that CMV seropositive recipients may benefit from CMV seropositive donors.

**Regulatory issues**

On May 25, 2005, the FDA implemented new regulations governing the manufacture of human products for transplantation and immune modulation, as well as a variety of other cellular- and tissue-based human products. These regulations are similar in some respects, but quite different in others, to regulations emerging in the European Union, Canada, Australia and elsewhere. The US regulations are founded on the FDA’s responsibility to limit the transmission of infectious diseases through the administration of human or human-derived products. From the transplant physician’s perspective, they apply to peripheral blood stem cells, cord blood and donor lymphocytes; responsibility for bone marrow regulations has been assigned by the US Congress to the Health Resources and Services Administration. The FDA regulations are comprehensive in their scope. They require that all facilities engaged in the “manu-
Adverse Events after HSC Donation

While HSC donation is a reasonably safe procedure, adverse events do occur. It is essential that donors are assessed to detect conditions that might increase risk of donation to unacceptable levels. In order to perform an adequate pre-donation assessment, and to adequately inform prospective donors about risks, it is necessary to understand the most common and the most serious potential adverse events. These differ for marrow and peripheral blood collections.

Adverse events after marrow donation

Almost all marrow donors report some symptoms after donation. Table 1 describes symptoms reported by 9601 individuals donating marrow through the NMDP. Pain and fatigue are the most common. Among the first 493 NMDP marrow donors, when surveyed 2 days after donation, 75% reported fatigue, 68%, pain at the collection site and 52%, low back pain.9 Nausea, vomiting and sore throat are more common following collections done with general rather than regional anesthesia, while fever and fainting are less likely to occur after general anesthesia. Sixty-three percent of 493 NMDP donors interviewed reported complete recovery within 14 days, and 24% between 2 weeks and 1 month after donation. Thirteen percent took more than a month to feel fully recovered. Observations in related donors are similar, though more severe pain symptoms are reported.

Minor complications occur in 6% to 20% of marrow donations. These include transient hypotension, syncope, severe post-spinal headache, excess pain, unexpected hospitalization, and minor infections resolving within a few days of onset. Serious complications occur in 0.1%-0.3% of donations. The NMDP classifies major complications into 5 risk categories: anesthesia, infection, mechanical injury, transfusion and others. Anesthesia risks generally involve reactions to anesthetic agents, including hyper-sensitivity reactions, malignant hyperthermia and arrhythmias. Rarely, there are problems with intubation, such as laryngospasm, or with intravenous catheter insertion. Hypotension may develop from anesthetic-related vasodilatation and/or from volume depletion. Infections may occur at sites of marrow collection or line insertions. Infections at distant sites, e.g., pneumonia, are also reported. Infection requires therapy with antibiotics, which may produce adverse reactions. Mechanical injuries result from direct damage of local tissues during the collection procedure. These may include bone damage, nerve damage or entry of a collection needle into a blood vessel, an organ or the spinal canal. Hemorrhage can create pain from compression of soft tissues. Visceral injuries are very rare. Many but not all marrow donors require post-donation blood

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Women (n = 4106)</th>
<th>Men (n = 5495)</th>
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<tbody>
<tr>
<td>Tired*</td>
<td>85%</td>
<td>76%</td>
</tr>
<tr>
<td>Collection Site Pain*</td>
<td>78%</td>
<td>75%</td>
</tr>
<tr>
<td>Back Pain</td>
<td>67%</td>
<td>68%</td>
</tr>
<tr>
<td>Nausea*</td>
<td>63%</td>
<td>40%</td>
</tr>
<tr>
<td>Sore Throat*</td>
<td>62%</td>
<td>57%</td>
</tr>
<tr>
<td>Pain Sitting*</td>
<td>62%</td>
<td>57%</td>
</tr>
<tr>
<td>Lightheadedness*</td>
<td>53%</td>
<td>42%</td>
</tr>
<tr>
<td>Headache*</td>
<td>40%</td>
<td>32%</td>
</tr>
<tr>
<td>Vomiting*</td>
<td>39%</td>
<td>17%</td>
</tr>
<tr>
<td>IV Site Pain*</td>
<td>37%</td>
<td>23%</td>
</tr>
<tr>
<td>Fever</td>
<td>22%</td>
<td>22%</td>
</tr>
<tr>
<td>Bandage Pain*</td>
<td>19%</td>
<td>26%</td>
</tr>
<tr>
<td>Bleeding at Site*</td>
<td>10%</td>
<td>8%</td>
</tr>
<tr>
<td>Fainting*</td>
<td>7%</td>
<td>5%</td>
</tr>
</tbody>
</table>

* P < 0.05 between men and women
transfusion and many donor complications reported in the 1980s related to infusion of allogeneic blood. These risks are now minimized as autologous blood has largely replaced allogeneic blood for transfusion of both related and unrelated marrow donors. Among 6277 NMDP marrow collections, allogeneic blood was administered in only 16 instances (0.25%). In 7 of these, it was probably avoidable since the donor was asymptomatic and hemoglobin levels were not prohibitively low. It is important to allow adequate time for autologous blood collection when planning the pretransplant evaluation and the transplant procedure.

Adverse events after peripheral blood donation
Like marrow donors, most peripheral blood HSC donors report symptoms. Most are related to hematopoietic growth factors, usually filgrastim (rhG-CSF, r-metHUG-CSF), lenograstim (a glycosylated rhG-CSF formulation, not marketed in the US) or sargramostim (rhGM-CSF), given to increase the concentration of HSCs in the donor’s circulation. Pegfilgrastim (PEG–G-CSF) has been used successfully to mobilize cells for autologous transplantation in a limited number of patients with malignancies, but there are no data regarding its safety in healthy donors. Symptoms among 1080 peripheral blood HSC donors surveyed by NMDP are shown in Table 2. Bone pain is the most common cytokine-associated symptom and likely results from altered bone metabolism, reflected by increased bone-derived alkaline phosphatase and decreased serum osteocalcin. It is typically diffuse but most prominent in the spine, hips or pelvis, and ribs and resolves promptly after filgrastim is discontinued. Headache is also common. Pain is usually manageable with non-narcotic analgesics. Other symptoms include nausea and vomiting, myalgia, fatigue, insomnia and injection site reactions.

The apheresis procedure is also a source of adverse events. Securing peripheral venous access at antecubital veins may produce bruising, hematoma or minor bleeding. Anti-coagulation with acid-citrate-dextrose (ACD) solution may elicit symptoms of hypocalcemia—perioral numbness, paresthesias and carpal tunnel spasms—requiring oral or parenteral calcium supplementation.

Important hematologic changes are expected with growth factors and apheresis. White blood cells, in particular neutrophils, increase dramatically. At daily filgrastim doses of 10 mg/kg or greater, the total white count may reach 70–80 x 10⁹/L. Although clinically significant leukostasis is not reported, it is generally recommended that the filgrastim dose be reduced if the count exceeds 70-75 x 10⁹/L. Concomitant with leukocytosis, platelet counts decline, usually modestly. Peripheral leukocyte counts fall after apheresis. Mild neutropenia, lymphopenia and anemia are common for a few weeks. Thrombocytopenia is the most significant finding post-apheresis. The platelet count reproducibly declines between 20% and 30% with each standard volume collection (i.e., 12 to 20 liters of processed blood volume) and does not begin to recover until 3 to 4 days after the last collection. Though serious hemorrhage secondary to thrombocytopenia has not been reported, avoiding aspirin during mobilization and collection, and non-steroidal anti-inflammatory drugs during collection, is prudent.

The most significant immediate problem encountered by peripheral blood HSC donors is inadequate venous access. Central lines are required to perform apheresis in up to 20% of collections. Central line complications are uncommon but include pneumothorax, hemorrhage and infection.

Filgrastim administration may precipitate severe sickle crisis in persons with sickle cell anemia or complex sickle cell hemoglobinopathies. A 47-year-old woman with Hb SC disease, who had never had any symptoms from her condition, suffered a fatal sickle crisis during filgrastim mobilization of HSC intended for her sister. It remains to be clarified whether persons with sickle trait (Hb AS) are at any increased risk from filgrastim. Kang et al safely mobilized and collected cells from 9 donors with sickle trait. These donors had higher symptom scores during mobilization than did 8 simultaneous control donors, but there were no symptoms suggestive of sickle crisis. Spontaneous splenic rupture is reported in 3 normal peripheral blood HSC donors. In 2 cases the spleen was surgically removed and disclosed extensive extramedullary hematopoiesis. Platzbecker et al performed ultrasound evaluations of spleen size before and after G-CSF mobilization in 91 healthy donors. There were no adverse splenic events, but increases in spleen length and width were routinely seen. Growth factor may precipitate flares of autoimmune disorders. Flares of rheumatoid arthritis and ankylosing spondylitis are reported following therapy with filgrastim or sargramostim in the non-donation setting. In patients with normal thyroid function, but pre-existing anti-thyroid antibodies, therapy with sargramostim has caused thyroid dysfunction. A variety of eye inflammatory responses are reported in peripheral blood HSC donors, including marginal keratitis, episcleritis and iritis during therapy with

Table 2. Symptoms reported by National Marrow Donor Program (NMDP) peripheral blood stem cell (PBSC) donors, excluding reports of bone pain.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>All Donors (N = 1080)</th>
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<tbody>
<tr>
<td>Myalgia</td>
<td>54%</td>
</tr>
<tr>
<td>Headache</td>
<td>52%</td>
</tr>
<tr>
<td>Malaise</td>
<td>49%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>28%</td>
</tr>
<tr>
<td>Nausea</td>
<td>15%</td>
</tr>
<tr>
<td>Sweats</td>
<td>14%</td>
</tr>
<tr>
<td>Other flu-like Symptoms</td>
<td>12%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>11%</td>
</tr>
<tr>
<td>Fever</td>
<td>6%</td>
</tr>
<tr>
<td>Chills</td>
<td>6%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2%</td>
</tr>
</tbody>
</table>
filgrastim. Chest pain is occasionally encountered during peripheral blood donation and is generally non-cardiac in origin, though one myocardial infarction has been reported.

Death after HSC donation
Death has occurred among normal marrow and peripheral blood HSC donors. Nine deaths are documented, 6 in marrow donors and 3 in peripheral blood donors. Two of the reported deaths in marrow donors (both from cardiac arrest) actually occurred before the donation procedure could be done. The remaining 4 were from ventricular fibrillation, respiratory arrest, myocardial infarction and pulmonary embolism. The risk of death with marrow donation is estimated to be ~1 in 10,000. The 3 deaths after peripheral blood donation were from sickle crisis (described above), stroke and cardiac arrest. Given the relatively limited experience with allogeneic peripheral blood donations, the risk of death cannot currently be estimated but does not appear to be higher than with marrow donation.

Infants and Children as Donors
Children may safely donate marrow. They are probably more likely than are adults to receive allogeneic blood transfusion, but serious complications among pediatric donors are rare. Sanders et al reported on 23 marrow donors under the age of 2. Harvested volumes were between 11.5 and 19.3 mL/kg donor weight. One 14-month-old donor was discovered during predonation evaluation to have a stage 1 neuroblastoma. The tumor was resected at the time of marrow donation. Aside from this case, no serious complications were encountered, but 22 of the 23 infants required allogeneic blood. For children, recovery of autologous RBC from the collected bone marrow product may be a useful strategy.

Successful marrow collection from a 3.95 kg donor is also reported. The collection volume represented two-thirds of the donor’s total blood volume, essentially necessitating exchange transfusion. Another case reported collecting 335 mL of marrow from a 9.4 kg infant (total blood volume 750 mL). In this instance, recovery of autologous red cells from the collected marrow avoided allogeneic blood transfusion.

In a survey of pediatric marrow transplant physicians, only 7 of 56 responders were unwilling to collect marrow from infant donors 0 to 6 months old. There was little agreement, however, on the management of large volume collections. Of 52 respondents, 6 would limit collections to 25% or less of the donor’s blood volume, whereas 24 placed the limit at 50% or higher. Twenty-two respondents preferred to manage large volume collections in two stages.

Children appear similar to adults with respect to their response to filgrastim and collection by apheresis. However, central venous access may be required more often for successful collection from children.

Assessing Risks to the Donor

Pre-donation history and physical
The medical history, which addresses risk to the donor, as opposed to the screening history described above, should focus on matters relevant for the anticipated donation, including psychological issues. For all donors, this includes a review of known health problems, medications and allergies, and family history. Marrow donors should be questioned about prior surgical procedures and types of anesthesia received. Marrow donors should also have a careful review of systems directed toward neurological, respiratory, cardiovascular and musculoskeletal problems. Peripheral blood donors should be questioned about prior whole blood or apheresis donations. The review of systems for peripheral blood donors should include a careful cardiovascular and neurological review as well as specific questions about a history of venous access problems, autoimmune diseases, splenic disorders and hemoglobinopathies. The donor’s physical examination should focus upon the neurological, respiratory and cardiovascular systems. Additionally, marrow donors need an assessment of the oral airway and an evaluation of access to the iliac crests. Among obese donors, the ease of palpating the posterior, superior iliac spine varies widely. Donors with a history of musculoskeletal symptoms need a careful examination of the spine and lower extremities. Examination of peripheral blood HSC donors should additionally include evaluation of venous access and an abdominal examination for splenomegaly.

The history and physical examination of donors is not a comprehensive evaluation. Routine health care screening (e.g., fecal blood testing, Pap smears, mammograms) is irrelevant for hematopoietic cell donations. However, the evaluation for donation represents an opportunity to re-examine individuals of the importance of such screening. Donors who are delinquent with their general health care should be advised to visit their personal physician or clinic.

Laboratory and procedural evaluations of donors
The laboratory evaluation of all donors should include the following: complete blood count with white blood cell differential, serum electrolytes, alanine aminotransferase (ALT), bilirubin, creatinine or blood urea nitrogen (BUN), total serum protein and albumin. Peripheral blood HSC donors should also have determinations of alkaline phosphatase (AP) and lactate dehydrogenase (LDH). Additional evaluations, depending on findings of the history and physical, may include urinalysis, chest X-ray, electrocardiogram and serum immunoglobulins.

Apparently normal HSC donors whose intended recipients suffer from inherited conditions, such as hemoglobinopathies or inborn errors of metabolism, may require specific testing to rule out carrier states that could affect transplant outcome as well as donation complications. Donors with sickle cell trait and thalassemia minor can serve as donors in successful bone marrow transplants. As
discussed above, however, donors with S-beta thalassemia, SC or other complex sickle hemoglobinopathies should not receive rhG-CSF. A pregnancy assessment must be performed for female donors with childbearing potential. Pregnancy is considered an absolute contraindication to marrow donation for unrelated recipients but, in some circumstances, harvesting marrow from a pregnant relative may be considered for patients with urgent clinical situations. Safe and successful collection in the second trimester is reported. Pregnant women cannot be peripheral blood donors as hematopoietic growth factor administration is contraindicated.

**Psychological aspects of marrow donation**

The psychological condition of the donor should be assessed. In particular, what are the donor’s motivations for considering the HSC donation? Is the donor acting out of a genuine desire to help, or are there other motives involved; perhaps an unrealistic expectation of reward or personal gain? Related donors may have different motivations from unrelated donors and may be subject to increased emotional and physical stress associated with donation. Occasionally donors may be subjected to coercion. Switzer et al have reported that unrelated donors who feel they were pressured, either encouraged or discouraged about donation, are less likely to have a positive donation experience. In an early report of unrelated donors, 9 of 20 reported being discouraged from donation by a relative or a friend. To ensure unbiased evaluation and counseling of individuals intending to donate, whether it is to a related or an unrelated recipient, donor evaluation should be done by a clinician who is not involved in the care of the prospective recipient. Children who are being evaluated as potential marrow donors deserve special attention. Their fears and concerns may be complex and accompanied by significant ambivalence.

**Donor consent for HSC donation**

HSC donors must provide written consent prior to donation. Like a research subject, the HSC donor is a volunteer who must receive full and complete information about his or her donation. This means receiving a clear description of the procedure, its risks and potential alternatives. Donors must also have the opportunity to have questions satisfactorily addressed. Consent for children presents special concerns. In general, children are only considered for HSC donation to a relative, usually a sibling. In most instances, parents are expected to consent for their children, which may create conflict of interest situations. A survey of pediatric transplant physicians in the US confirmed that most felt the role of consent appropriately rested with the parents. Outside the US, “altruism by proxy” has stirred debate in the medical literature. In some countries, it is standard practice to appoint legal guardians to determine whether HSC donation is in the child donor’s best interest. When governing law allows parents to render consent, it is incumbent on the physician to recognize the potential for conflict of interest, to seek expert ethical guidance when needed, and to ensure to the extent possible that the child donor is a willing and informed participant. Children who are able should provide assent for donation.

**Summary**

Allogeneic HSC donation is a safe procedure with very low rates of serious adverse events. Nevertheless, all donors must be carefully evaluated and fully informed prior to HSC donation by clinicians with good understanding of the potential physical and psychological complications and factors that may increase risk. Donors must be able to provide informed consent without coercion or pressure. Special attention to the clinical and psychological needs of pediatric donors is necessary.

**References**

13. Stroncek D, McCullough J. Policies and procedures for the