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Children as Hematopoietic Stem Cell Donors

COMMITTEE ON BIOETHICS

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American Academy of Pediatrics
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Organizational Principles to Guide and Define the Child Health Care System and/or Improve the Health of all Children

Policy Statement—Children as Hematopoietic Stem Cell Donors

abstract

In the past half-century, hematopoietic stem cell transplantation has become standard treatment for a variety of diseases in children and adults, including selected hematologic malignancies, immunodeficiencies, hemoglobinopathies, bone marrow failure syndromes, and congenital metabolic disorders. There are 3 sources of allogeneic hematopoietic stem cells: bone marrow, peripheral blood, and umbilical cord blood; each has its own benefits and risks. Children often serve as hematopoietic stem cell donors, most commonly for their siblings. HLA-matched biological siblings are generally preferred as donors because of reduced risks of transplant-related complications as compared with unrelated donors. This statement includes a discussion of the ethical considerations regarding minors serving as stem cell donors, using the traditional benefit/burden calculation from the perspectives of both the donor and the recipient. The statement also includes an examination of the circumstances under which a minor may ethically participate as a hematopoietic stem cell donor, how the risks can be minimized, what the informed-consent process should entail, the role for a donor advocate (or some similar mechanism), and other ethical concerns. The American Academy of Pediatrics holds that minors can ethically serve as stem cell donors when specific criteria are fulfilled. *Pediatrics* 2010;125:392–404

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KEY WORDS

stem cell donors, hematopoietic stem cell transplantation, psychosocial risks, child, adolescent, siblings, cord blood transplants

ABBREVIATIONS

HSCT—hematopoietic stem cell transplantation
GVHD—graft-versus-host disease
AAP—American Academy of Pediatrics
G-CSF—granulocyte colony-stimulating factor
IVF—in vitro fertilization
PGD—preimplantation genetic diagnosis
IRB—institutional review board
FDA—Food and Drug Administration
CIRB—Central Institutional Review Board

INTRODUCTION

In the past half-century, allogeneic hematopoietic stem cell transplantation (HSCT) has become standard treatment for a variety of conditions in children and adults, including selected hematologic malignancies, immunodeficiencies, hemoglobinopathies, bone marrow failure syndromes, and congenital metabolic disorders. There are 3 sources of allogeneic hematopoietic stem cells: bone marrow, peripheral blood, and umbilical cord blood.

The ideal allogeneic hematopoietic donor matches the recipient at the major HLA sites; that is, the donor and recipient are identical at the major histocompatibility complex sites. HLA-matched biological siblings are generally preferred as donors by physicians who perform transplants because of reduced risks of graft-versus-host disease (GVHD) and other transplant-related complications as compared with unrelated donors.[1–3]

When an HLA-matched sibling is not available, those in need of HSCT sometimes cannot find an HLA-matched donor despite the listing of more than 7 million living adult persons on the National Marrow Donor

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Program registry and 6 million additional donors and cord blood units in other registries around the world.[4] This is particularly true for members of ethnic minority groups.[5–7]

When the potential recipient is a child, potential sibling donors may be children themselves. In rare cases, children may also be considered as potential donors for an adult sibling, parent, or other family member.

The American Academy of Pediatrics (AAP) believes that minors can ethically participate as hematopoietic stem cell donors. This statement includes a discussion of the ethical considerations regarding minors serving as stem cell donors using the traditional benefit/burden calculation from the perspectives of both the donor and the recipient. This statement also includes an examination of the circumstances under which a minor can ethically participate as a hematopoietic stem cell donor, how the risks can be minimized, what the informed-consent process should entail, and other ethical concerns.

SOURCES OF HEMATOPOIETIC STEM CELLS

The first successful bone marrow transplant occurred in 1963.[8] The patient was a 26-year-old physician with relapsed acute lymphoblastic leukemia that was refractory to chemotherapy. He received bone marrow from 6 family members, although it was shown that his bone marrow was mainly repopulated by cells from 1 brother, with some female cells present. The first successful pediatric bone marrow transplants occurred 5 years later in 1968 for children with severe combined immunodeficiency (SCID) and Wiskott-Aldrich diseases.[9,10] In 1973, the first successful unrelated bone marrow transplant for a 5-year-old with SCID was performed in the United States with an adult European donor.[11]

Gianni et al[12] described the collection of peripheral blood stem cells using granulocyte colony-stimulating factor (G-CSF), a growth factor that stimulates mobilization of bone marrow stem cells into the peripheral blood, in 1989. G-CSF–mobilized peripheral blood stem cells were first used for autologous transplantation; their use was subsequently expanded to include allogeneic transplantation.[13] More recently, some adult bone marrow donors have received G-CSF because stimulated bone marrow is richer in stem cells and, therefore, induces a quicker engraftment.[14–16] Experience with G-CSF–mobilized bone marrow in pediatrics is limited, although a phase 3 trial is in process.[17]

The use of cord blood for allogeneic stem cell transplantation began in 1988 with the successful umbilical cord blood transplantation from an HLA-matched sibling to a patient with Fanconi anemia.[18] In 1998, the Children's Hospital of Oakland, with the support of the National Heart, Lung, and Blood Institute, created a sibling-donor cord blood program that collects, characterizes, stores, and releases cord blood units from families with children who are affected by conditions that may require HSCT.[19] Today, that program continues in collaboration with Viacord.[20]

Even before the establishment of the sibling-donor cord blood program, families have gone to great measures to conceive an HLA-matched child when an HLA-matched sibling did not exist to obtain umbilical cord blood for transplantation. In 1990, Abe and Mary Ayala became the first successful publicized case in which a family sought to conceive a child (Marissa) to save another child (Anissa).[21] Marissa's cord blood was stored for more than 1 year when additional stem cells were procured from her bone marrow to ensure an adequate number of cells.[22]

The movement to create siblings who can serve as HLA-matched donors has been aided by the development of in vitro fertilization (IVF) and preimplantation genetic diagnosis (PGD). In the first such reported case, cord blood was collected at the birth of Adam Nash, who was conceived using IVF and PGD for his sister Molly Nash, a 5-year-old with Fanconi anemia.[23]

The more common umbilical cord blood transplant, however, occurs not within families but between strangers through public cord blood banks. Public cord blood banks collect blood from the umbilical cords of newborn infants to be used as a source of hematopoietic stem cells for unknown pediatric and adult patients.[24] The National Marrow Donor Program lists 90 000 cord blood units donated by parents after their infant's birth,[4] and there are more than 359 000 cord blood units stored internationally,[25] with ongoing attempts to expand collection and storage and enhance ethnic diversity.[26] These public cord blood banks contrast with private cord blood registries that advertise to pregnant women and couples to encourage prospective parents to store their newborn infant's cord blood as a form of insurance in case their own child (or his or her siblings) will need a transplant.[27] To date, at least 1 child has benefited from her parents' decision,[28] but the likelihood of this occurring is quite low, and the collection and storage in private stem cell banks for families at low risk is discouraged by the AAP, the American Medical Association, the American College of Obstetrics and Gynecology, and the American Society for Blood and Marrow Transplantation.[29–32]

ETHICAL CONSIDERATIONS

Most pediatric physicians who perform transplants believe it is acceptable to expose minors to the risks of a

stem cell donation when that donation offers a substantial prospect of benefit to a close family member and when proper consent is obtained.[33] As detailed later in this statement, the risks to the minors who serve as stem cell donors can be characterized as more than minimal, but they are nonetheless generally modest, with few serious complications.[17,34–40] Although healthy children are restricted to a minimal risk threshold in research,[41] parents expose their children to greater risks in selected activities, such as when they permit their children to participate in certain athletic activities or in the workforce.[42–44] Furthermore, family members are often asked to assist each other, at times at personal cost to themselves.[45–47] Ethically, then, to determine if a stem cell donation by a minor is permissible, one must examine the risks and benefits from the perspective of the donor as well as the risks and benefits to the recipient and to his or her family.[45,48]

Risks and Benefits of Serving as a Hematopoietic Stem Cell Donor

Medical Risks and Benefits

There is no direct medical benefit from serving as a stem cell donor. The benefit is always stated as the psychosocial benefit of helping a sibling or other close family member[36] (discussed in the next section).

The medical risks of stem cell collection depend, in part, on its source and how it is collected. The medical risks of bone marrow collection from children and adults are similar, with the major risk being that of anesthesia, but other serious complications include nerve, bone, or tissue injury.[36] Between 9 and 11 deaths have been reported worldwide, for an estimated incidence of 1 death per 10 000 donations.[37] Two of these deaths were cardiac arrests before donation. Postdonation deaths were caused by cardiac events, respiratory arrest, pulmonary emboli, sickle cell crisis, and stroke.[37] Morbidity risks include blood loss and the potential need for transfusions, wound infection, and pain at the site of marrow aspiration.[35] Common short-term adverse effects associated with bone marrow donation include fatigue, pain at donation site, low back pain, headaches, nausea, difficulty walking, problems sleeping, and, less commonly, bleeding problems.[34,36] Long-term adverse effects are rare, but some donors experience chronic pain at the donation site.[34] Many donors are placed on iron supplementation after marrow collection, although smaller children who donate for larger recipients may require a blood transfusion after the donation procedure.[38]

To collect peripheral blood stem cells for hematopoietic donation, the donors receive G-CSF to increase the number of circulating stem cells. Preparation begins with 4 to 5 daily injections of G-CSF and is usually associated with bone pain. Although the bone pain is often described as the most uncomfortable part of the procedure in adults, the pain appears to be less in children. Stem cells are then collected through a process known as apheresis, which requires 2 large venous catheters. Most children younger than 12 years require central vascular access for apheresis; line placement may require either general anesthesia or conscious sedation.[39] Although complications are uncommon (1.1% overall for adults and children), many of the complications arise from the central venous catheter.[17]

Priming of the apheresis circuit with heterologous packed red blood cells is virtually universal for donors who weigh less than 20 kg.[39] This exposes the healthy donors to the risks of heterologous blood products. The donors may also develop thrombocytopenia, although the platelet count is rarely so low that it puts them at risk of bleeding. More than 5% of child donors receive platelet concentrates, particularly when the donor's platelet count decreases and subsequent days of collection are planned.[39]

To ensure that there is an adequate number of stem cells in the peripheral blood, donors require G-CSF mobilization. Some evidence suggests that the effects of G-CSF in healthy subjects may be more complex than originally thought. Although most G-CSF effects are thought to be transient and self-limited, preliminary data suggest that G-CSF affects not only myeloid cells but also chromosomal integrity and gene expression.[49] There is also the theoretic risk of potentially increasing the long-term risk of leukemia,[36,49] but to date, no clinical data support this concern.[50] Peripheral blood stem cell donors complain in the short-term of fatigue, low back pain, sleeping problems, lightheadedness, and difficulty walking.[34] Recovery time, however, is shorter than that for bone marrow donors.[36] Serious adverse events, including splenic rupture after G-CSF administration, have been reported[17,50]; however, to date, splenic rupture has not been described in children.[17]

A review by Pulsipher et al[51] of 2408 adult patients who donated peripheral blood stem cells through the National Marrow Donor Program revealed that severe events occurred in 15 donors (0.6%), the majority of whom required hospitalization for such medical issues as severe symptoms (nausea, chills, bone pain), severe chest pain, bleeding, and thrombocytopenia. In addition, 25 nonhematologic cancers and 1 case of chronic lymphocytic leukemia were reported. When compared with the expected cancer rates according to the National Cancer Institute's Surveillance Epidemiology and End Results database, there was no evidence of increased risk in the donor cohort.[51]

Although G-CSF is not approved for use in healthy children, data from the Pediatric Blood and Marrow Consortium have shown that approximately 23% of all matched sibling transplants use peripheral blood stem cells primed with G-CSF.[36] The most common adverse effects reported in children include pain and arthralgia, which increase with donor age.[36]

An analysis that compared the amount of pain from bone marrow aspiration with that from peripheral blood stem cell collection revealed that the severity of the pain was similar in adult siblings, although the type of pain differed. For bone marrow donors, the pain was at the site of aspiration, whereas for peripheral blood, the pain was bone pain attributable to marrow expansion related to G-CSF.

Finally, stem cells may be collected from cord blood. The collection of umbilical cord blood for hematopoietic stem cell donation occurs in the delivery room. Although one can modify the delivery to maximize the number of cells collected,[52] the Institute of Medicine and the American College of Obstetrics and Gynecology strongly discourage this practice.[52,53] If the mode of delivery is not modified, the collection poses no risks to the infant.[53] The number of umbilical cord stem cells that can be obtained may not be adequate if the recipient is large, and decisions may need to be made about collecting additional hematopoietic stem cells from the cord blood–donating child at a later date.

A major advantage of umbilical cord blood is that HLA-matching is less critical, because lymphocytes in cord blood are less immunologically reactive than are lymphocytes from older donors. This increases the utility of cord blood for unrelated donations, particularly for minority recipients, for whom identifying a fully matched unrelated donor may be difficult.[54] Even within related donor-recipient pairs, however, there is the advantage of a reduced likelihood of acute and chronic GVHD with umbilical cord blood transplants, compared with recipients of bone marrow transplants, even when in both cases the donors are HLA-identical siblings.[55] However, slower immunologic recovery and delayed engraftment may counterbalance some of the benefits of decreased GVHD.

Psychosocial Risks and Benefits

The primary benefit to the donor is the psychosocial benefit of helping a sibling or other close family member. This benefit may accrue even if the transplant is unsuccessful, because the donor and family can at least be reassured that the stem cell transplant was tried.

There is a small but growing literature on the psychosocial risks and harms caused by hematopoietic stem cell donation by children. Data show that many children experience distress related to their role as a donor. Many pediatric donors believe that they did not have a choice about whether to serve as a marrow donor, report being poorly prepared for the procedures, and describe feeling responsible for the recipient's course after transplantation.[56,57]

An important period of psychosocial risk follows the donation and the infusion of the stem cells into the recipient, because the recipient must then go into isolation for weeks to months, and 1 or both parents may be at the hospital for extended periods of time. Data show that many donors feel that they were inadequately prepared for what to expect after the infusion.[58–60] In addition, until engraftment occurs, donors often feel neglected, but this is also true of nondonor siblings. Careful psychological research, then, is necessary to separate the confounding effect of being a donor from that of having a sibling with a life-threatening illness.[36,61–63] That is, part of the distress may be attributable to having a very sick sibling who is the focus of the parents' attention,[62,63] regardless of whether one serves as a donor. Research is needed to compare the harms and benefits of being a sibling donor versus a sibling nondonor. The data that exist were based on small samples. A small study of donor and nondonor siblings revealed a trend toward increased behavioral problems exhibited by donor children when compared with nondonor siblings, which the authors speculated could have been the result of unmet emotional needs in donor siblings.[64] Nondonors, however, felt some envy toward donors who could contribute to the care of the ill sibling.[57] In 2 studies that compared experiences of nondonor siblings and successful donor siblings, one third of the siblings in each group reported a moderate level of posttraumatic stress.[65,66] In addition, donor siblings experienced higher levels of anxiety and lower self-esteem than did nondonor siblings, but donor siblings had more adaptive skills in school, whereas nondonor siblings had more school problems.[65,66] Both donors and nondonors reported loneliness and a lack of attention from parents.[65,66] It is not surprising that siblings of recipients who underwent unsuccessful transplants reported greater negative effects and feelings of guilt than those of recipients whose transplants were successful.[56,58,62] However, all siblings agreed that the psychological benefits and harms of serving as a donor outweighed the physical harms.[62,65,66]

Risks and Benefits to the Hematopoietic Stem Cell Recipient

The main risks and benefits to the recipient are clinical, and they vary depending on the source of stem cells. In general, there is quicker engraftment

after transplantation with primed peripheral blood stem cells. However, there is also greater T-lymphocyte infusion with peripheral blood stem cell transplantation and, therefore, greater risk of chronic GVHD without improvement in survival.[16,67] Transplantation using umbilical cord stem cells is associated with a decreased risk of GVHD, perhaps because fewer lymphocytes accompany the stem cell graft or because those lymphocytes are less immunocompetent.

Recent data suggest that pediatric patients with leukemia have better outcomes when they receive bone marrow rather than peripheral blood stem cell transplants, although bone marrow transplants are associated with slower engraftment.[36,68] This has led to a reemphasis on bone marrow collection. There has also been some research on the use of G-CSF with bone marrow collection to promote more rapid engraftment and reduce risks to the recipient, thus prompting consideration of the use of primed bone marrow. The latter may increase the risks to the donor both short-term (ie, pain from G-CSF for 4–5 days before collection) and long-term (ie, uncertain long-term risks of exposure to G-CSF).

CONDITIONS UNDER WHICH A MINOR MAY PARTICIPATE AS A HEMATOPOIETIC STEM CELL DONOR

Currently, there are no guidelines regarding participation of minors as hematopoietic stem cell donors. The AAP believes it is ethically permissible for minors to participate as donors if 5 criteria are fulfilled. The criteria are: (1) there is no medically equivalent histocompatible adult relative who is willing and able to donate; (2) there is a strong personal and emotionally positive relationship between the donor and recipient; (3) there is some likelihood that the recipient will benefit from transplantation; (4) the clinical, emotional, and psychosocial risks to the donor are minimized and are reasonable in relation to the benefits expected to accrue to the donor and to the recipient; and (5) parental permission and, where appropriate, child assent have been obtained.

Condition 1

The first criterion requires that there be no medically equivalent histocompatible adult relative who is willing and able to donate. Given the relatively modest medical risks of hematopoietic stem cell donation and the great need for histocompatibility, the AAP supports family decisions to screen both adult and child family members in the initial donor search. However, when multiple siblings are histocompatible with a recipient, and donor characteristics that lead to the choice of the best donor are equivalent, a donor above or closest to the age of consent should be approached first about donation, because he or she can better understand the risks, benefits, purpose, and procedures of donation. Likewise, siblings with normal cognitive function should be preferred to siblings with significant cognitive disabilities because of their greater ability to understand the risks and benefits of donation. In the earliest reports of bone marrow donation by children, 1 family explicitly requested the donor to be a sibling with mental retardation, although other siblings may have been available.[69] Although all children are vulnerable, younger children who cannot understand what is happening and children with cognitive disabilities cannot actively assent, and they are considered more vulnerable than cognitively intact or older children.

Although some might argue that a search of adult family members and even the international bone marrow donor registry should be undertaken before children are screened, there are reasons to permit sibling pediatric donors to undergo screening earlier in the process. A sequential search of adults or a requirement to search the international registries takes additional time and is frequently unsuccessful. To require a family to undertake a search for an unrelated donor ignores the fact that authorization of a stem cell donation by a minor is within the proper realm of parental decision-making.[45,48] It also ignores the fact that transplants from HLA-matched siblings are associated with similar or better outcomes and fewer complications for the recipients than transplants from HLA-matched unrelated donors. In particular, although some studies have suggested no difference,[1,70] relative risks of acute and chronic GVHD are generally 1.5 to 3.5 times more frequent after unrelated-donor transplants compared with sibling-donor transplants.[2,3,67,70–72] Finally, a search of the unrelated donor registries will incur costs that may become the responsibility of the family. Therefore, although parents may choose to defer testing their minor children, it is morally permissible to seek stem cells from all sources simultaneously and not to require a sequential search.

Condition 2

The second condition requires that there be a strong personal and positive relationship between the donor and recipient or, in the case of directed cord blood, that a strong personal and positive emotional relationship be anticipated. This is important, in part, to increase the likelihood that the donor will experience some psychological benefit. Case reports in the literature help clarify this point. Marissa Ayala, for example, served as a donor for her older sister by combining her cord blood with additional hematopoietic stem cells procured under anesthesia when she was 14

months of age. She then served as a flower girl at her sister's wedding at 2.5 years of age[73] and, at 18 years of age, positively described her participation in an interview while vacationing with her sister in Hawaii.[74] Although one cannot expect nor require most donor-recipient sibling relationships to be this emotionally strong, it would be morally problematic to ask a minor to serve as a donor to an unknown, emotionally distant, or emotionally abusive relative. In *Cruzan v Bosze*, a father sought to have his twin children tested as potential bone marrow donors for their half-brother.[75] The twins' mother objected, in part because the children did not know their stepbrother. In its decision, the court agreed with the mother. In the case of A. R., a younger sister was asked to serve as the bone marrow donor for her teenaged brother, who had sexually assaulted her.[76] Despite an inadequate psychosocial evaluation, A. R. was declared fit to serve as a stem cell donor. Authors of a commentary argued that the sister should never have been evaluated for donor compatibility and that the donation should have been prohibited.[77] Most recently, an adopted child developed acute lymphoblastic leukemia, and his 3 biological siblings with whom he had no relationship were tested for HLA compatibility.[78] None were HLA compatible, but the case raised the question of why the children were HLA-tested in the first place, given the lack of an intimate relationship with the ill child.[79] These cases reveal how parents may be so focused on the ill child that they do not adequately consider the needs and interests of the potential minor donor siblings. Rather, minors should only serve as hematopoietic stem cell donors for family members when there is a strong personal and emotionally positive relationship between the donor and recipient. Exceptions should only be considered with judicial review. Minors should never be considered as potential donors for strangers or listed on an international bone marrow registry except as cord blood donors.

Condition 3

The third condition requires that there be some likelihood that the recipient will benefit from transplantation. It is hard to define what the threshold of likelihood of success for the recipient should be to justify the procurement of donor stem cells, and this is further complicated by the inexactness of the recipient's prognosis. However, the fact that a histocompatible sibling is available does not mean that a transplant should be attempted without regard to the likelihood of success. Although the medical risks of serving as a hematopoietic stem cell donor do not change regardless of the transplant outcome, the psychosocial risks should not be underestimated. This is particularly true for the donor whose sibling dies.[80] Therefore, although the transplant team may be willing to attempt a transplant regardless of likelihood of success, there should be some minimum threshold of anticipated success below which the potential minor donor should not be exposed to the risks of stem cell collection.[33,81] The threshold likelihood of success may be less stringent for donors who are competent older teenagers or adults and who can, therefore, consent for themselves. The donor advocate (or some similar mechanism as befits an individual program as discussed for condition 5) should ensure that the likelihood of success is above some threshold to justify imposing the risks of donation on the minor sibling.

Condition 4

The fourth condition requires that the clinical, emotional, and psychosocial risks to the donor be minimized and be reasonable in relation to the benefits expected to accrue to the donor and the recipient. The transplant team should help ensure that the parents consider the risks and benefits of a sibling donation from the independent perspectives of the recipient and of the donor.

One way to minimize risks is to carefully select the method of stem cell collection. Each method of obtaining stem cells has distinct risks and benefits. Numerous factors should be considered in this decision, including the preferences of the minor and parents and the potential benefit to the recipient. For example, one may want to avoid peripheral blood stem cell donation by young children to minimize the need for central venous catheters and to avoid exposing the donor to third-party blood products. Central venous lines in children have a low risk of harm, but the harms can be serious and include the risks of anesthesia as well as the risks from the catheter placement (eg, pneumothorax, hemothorax).[39,40] Some of the psychological and emotional risks to child donors can be minimized by preparing them through medical play-acting, by allowing them to ask questions, and by including them in the decision-making process, to the extent of their ability.[56–60]

Finally, in some situations, it may be appropriate for the transplant team to educate the family about alternative therapies that may be tried that offer a reasonable likelihood of success. For example, for children with malignancies, chemotherapeutic trials may offer an alternative to HSCT. For children with enzyme deficiencies secondary to genetic conditions, some enzyme-replacement therapies exist, and others are in development. For children with bone marrow failure or hemoglobinopathies, nontransplant alternatives may include chronic transfusion or growth-factor support, and gene transfer is on the horizon.

Condition 5

The fifth condition requires that parental permission and donor assent be obtained. Legally, in pediatrics, parental permission is sufficient for proceeding with clinical treatment (with a few exceptions), whereas parental permission and the child's assent (when possible) is necessary for research purposes.[82] However, stem cell donation by minor siblings is unusual in that it is often performed as a clinical procedure, yet the direct benefits of the clinical procedure accrue to a third party (the recipient) rather than to the donor child. Even in the research setting, the risks and benefits may or may not accrue to the donor (discussed further in the next section). In seeking parental permission, it is important to acknowledge the tension that parents experience when 1 of their children is ill and to appreciate the conflict of interest created if they consider authorizing 1 of their healthy children to serve as a hematopoietic stem cell donor.

Transplant teams also face a conflict of interest in that their primary responsibility is to the potential recipient; yet, the same physicians may advise, consent, and possibly take the potential donor to the operating room for stem cell procurement. The Advisory Committee on Organ Transplantation of the US Department of Health and Human Services recommends that all living solid-organ donors have a donor advocate,[83] and this recommendation was incorporated into the AAP statement "Minors as Living Solid-Organ Donors."[84] The AAP proposes a similar requirement for all minors who are potential hematopoietic stem cell donors, a mechanism first implemented at the M. D. Anderson Cancer Center in 1994.[36] The primary obligation of the donor advocate (or some similar mechanism as befits an individual program) is to help the donor (and parents) understand the process and procedures and to protect and promote the interests and well-being of the donor. As such, the donor advocate (for the rest of this statement, "donor advocate" will be used to indicate either a specific donor advocate or some similar mechanism) should not be involved in direct patient care of the potential transplant recipient.[85] The donor advocate or, if necessary, a donor advocate team should have (1) training and education in child development and child psychology, (2) skills in communicating with children and understanding children's verbal and nonverbal communication, and (3) working knowledge of hematopoietic stem cell donation and transplantation.[84] The donor advocate should help to ensure that the risks to the child are reasonable and minimized, that the siblings' relationship is a personal and emotionally positive relationship (ie, that there is a healthy emotional relationship between them), that the donation has a reasonable likelihood of success, and that there is no other medically equivalent histocompatible adult relative who is able and willing to serve as a source of stem cells.

The donor advocate should help the parents weigh the risks and benefits for the healthy child to serve as a hematopoietic donor for an ill family member and not just weigh the risks and benefits from the perspective of the potential recipient or from that of the family as a unit. The donor advocate should be involved from the onset, starting with the decision about whether the minor should undergo HLA testing. When older children and adolescents are being considered as hematopoietic stem cell donors, they should be included in all stages of the decision-making process to the extent that they are capable.[82,86] Discussions that involve the potential minor donor must be developmentally appropriate.[86] The psychological as well as medical aspects of the donation should be discussed in language that is understandable to the potential donor. Consistent with his or her capacity, the minor needs to be aware that the donated stem cells may not engraft or may fail after engraftment, the recipient may develop severe or even fatal complications of the transplant (eg, GVHD), or the original disease may recur. The minor needs to be aware that the outcome is beyond his or her control. The literature shows that many donors feel neglected after donation as the focus returns to the ill recipient.[58,62,87] Parents and other family members should be reminded that they need to be attentive to the needs of both the donor and recipient.

Research on minors who served as stem cell donors has revealed that most siblings felt they had no choice about whether to serve as a stem cell donor, but most also agreed that they would do it again.[56] Nevertheless, in some cases, a minor may object to participation. Although the parents' consent alone may be sufficient, unless state law or institutional policy requires the minor's active assent,[88] a donor advocate should explore the reasons for the refusal and determine if further education and discussion can modify the minor's refusal. A child mental health professional and/or an ethics consultant/ethics committee may also need to be involved to help clarify the child's concerns. The donor advocate, child mental health professional, ethics consultant, or ethics committee must have the authority to suspend or prohibit a donation if it is determined that the donation is likely to have a serious and sustained long-term adverse effect on the donor. The recipient should not begin myeloablative preparation for bone marrow infusion (conditioning) unless there is a clear decision to proceed with the do-

nation. Once the recipient has begun conditioning, the child donor should not be offered the opportunity to renege, because this would be lethal to the recipient.

RESEARCH ON HSCT

To advance the effectiveness of HSCT, research will need to be performed on both donors and recipients. When the participants are minors, the research must conform to Subpart D of the federal regulations that govern pediatric research.[41]

Subpart D distinguishes between research that does and does not offer the prospect of direct benefit. Children are permitted to participate in research that offers the prospect of direct benefit, provided the "risk is justified by the anticipated benefit to the subjects" and "the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches."[41] For most research on HSCT, the research offers the prospect of direct benefit to the recipient, but the donor is a healthy child. As such, the research does not offer the prospect of direct benefit to the donor child. Although some have tried to argue that the donor and recipient should be viewed as a dyad, this would permit greater risk taking on the part of a healthy child than most interpretations of the regulations permit.[36]

When research does not provide the prospect of direct benefit, children are permitted to participate in minimal-risk research (eg, surveys of pain experience). What counts as minimal risk, however, is ambiguous.[89–91] Children with a disorder or condition are permitted to participate in research that poses a minor increase over minimal risk. Healthy siblings do not have a disorder or condition. This restriction has raised 3 objections. First, it is not clear what it means to have a "disorder or condition," that is, whether one must have a disease or condition or whether it is adequate to be at risk of having a disease or condition.[92–95] Some have even argued that having an ill sibling constitutes a "condition."[36,92] A second objection is that the regulations are overly restrictive in that the minor increase over the minimal-risk standard is adequate protection for all children.[91] The third objection is that the regulations are unjust in providing greater protection to healthy than to ill children.[96]

If the proposed research pertains to adequate pain control and the standard therapies are used, then one might state that survey research to quantify the degree of pain entails minimal risk. However, if the research entails the use of a drug (eg, the original expansion of G-CSF from adult volunteer donors to sibling donors), the research is always classified as posing at least a minor increase over minimal risk. Such research can only be performed if the responsible institutional review board (IRB) determines that the donor's participation involves a prospect of direct benefit to the donor himself or herself (45 CFR 46.405 approval) or if the IRB determines that being a donor constitutes a condition and the incremental risks of the research involve no greater than a minor increase over minimal risk (45 CFR 46.406 approval). Either of these determinations by an IRB is likely to be controversial. Otherwise, the research requires national review under 45 CFR 46.407.[97,98] Although this will increase the regulatory burden for performing research on healthy donors, it may also increase the oversight that research that exposes a healthy child to significant risk without prospect of direct benefit deserves.[36,97] In December 2008, the US Food and Drug Administration (FDA) Pediatric Advisory Committee's Pediatric Ethics Subcommittee convened to review a proposed pediatric study under the provisions of 45 CFR 46.407 and the corresponding regulations that govern clinical investigations regulated by the FDA, 21 CFR 50.54. The protocol involved a phase 3 trial in which donors would be randomly assigned to receive G-CSF to determine its effect on engraftment and GVHD.[99] The National Cancer Institute Central Institutional Review Board (CIRB) acknowledged the pressure that normal siblings would experience with respect to participation and "that it would be difficult or impossible to separate this influence from the pressure to act as a bone marrow donor independent of the research."[100] The CIRB elaborated: "the CIRB suggests but does not require the use of a third party informed assent monitor to minimize potential influence, as well as the use of different doctors for the recipients and the donors. The board notes that the latter suggestion is already standard practice in many allogeneic stem cell transplant programs."[100] The FDA approved the protocol under 45 CFR 46.407 but mandated use of a donor advocate as a stipulation of 407 approval. The donor advocate or assent monitor is analogous to the donor advocate proposed in our condition 5 as a mandatory component for all HSCT when the donor is a minor.

Subpart D also gives significant respect to the child's preferences regarding research participation. The regulations are clear that, when the child is "capable of assenting," the child must provide "affirmative agreement" to participate.[41] The regulations also give IRBs the authority to decide from which children assent should be sought.[41] Although no age is provided in the regulations, many studies seek assent of children as young as 6 or 7 years of age. However, given the complexities involved in stem cell transplant research, it would be reasonable for the IRB to restrict the assent requirement to donors older than 9 years.[101]

When an IRB finds that assent is necessary and the child donor refuses to assent, transplant teams, families, and donor advocates should try to understand the reason for a refusal and try to address the objections. However, under current regulations, if the child is determined to have sufficient capacity to assent, then his or her refusal to participate in research is definitive.

CHILDREN CONCEIVED TO SAVE A SIBLING

In some families, parents intentionally conceive a child to serve as an umbilical cord blood stem cell donor for an older sibling. Often, these children are conceived through IVF and PGD to ensure an HLA match.[102] PGD may be performed either to ensure that the embryo is HLA-identical while simultaneously avoiding the birth of a child with a severe heritable condition (eg, Fanconi anemia) or purely to ensure that the embryo is HLA-identical. As of 2005, 5 PGD centers in 4 countries have performed HLA-genotyping in 180 IVF cycles. In 122 cycles, the goal was to avoid a genetic condition (thalassemia being the most common) and to create an HLA-matched sibling. In 58 cycles, PGD was used solely for HLA-typing.[102]

Some people have moral or religious objections to the use of IVF and PGD because they can result in excess embryos, many of which are discarded. Even those who accept IVF and PGD to avoid the birth of a child with a severe heritable condition and simultaneously to ensure a specific HLA identity may be troubled by the use of PGD when it is used only to ensure an HLA-identical sibling.[103–107] When PGD is used purely for HLA-matching, the objection is that the child is used solely as a means (donor) for the sibling-recipient and that all children should be treated as ends in themselves.[108] This is a misunderstanding of the Kantian ethical principle. There is no absolute moral prohibition against using a person as a means, provided that the person is not used solely as a means. Available evidence is anecdotal but reveals that children conceived to save siblings are loved both for their role in saving their sibling's life (means) and as another member of the family (end-in-itself) which is consistent with the moral permissibility of children as hematopoietic stem cell donors.[103–107]

Pediatricians may be asked about PGD by parents who are willing to attempt to conceive an HLA-matched sibling. Pediatricians should educate these parents about the risks and benefits of attempting to conceive a child who will serve as a hematopoietic stem cell donor and should support them emotionally throughout the process or refer them to a colleague who has the competency and expertise to do so. The willingness of health care professionals to collect cord blood for stem cells in the delivery room must be ensured before delivery, although the pregnant woman and couple must also understand that the health of both the newborn infant and the pregnant woman have priority and that peripartum events may preclude collection.[29] To avoid exposing the newborn infant to any risks from the donation, the delivery should not be modified to maximize the number of cells collected. If delivery is not modified, the procedure poses no risk to the newborn infant, and there is no need for a donor advocate.

COURT REVIEW

The earliest cases of bone marrow transplant with a minor donor often involved judicial review.[109] Given that legal precedent for stem cell donation by incompetent adults and children is firmly established, as a general matter, donation by a minor should not require court review or approval. Historically, the primary value of the judicial review process was to ensure an independent advocate for the incompetent potential donor.[69] In solid-organ transplantation, there is now a requirement to provide an independent donor advocate for living donors.[83] The AAP supports the appointment of a donor advocate in any HSCT that involves a donor younger than 18 years (except for cord blood stem cell donation). The donor advocate should assess whether the recipient for whom the minor is being asked to donate is an appropriate candidate (eg, a child sibling who has a reasonable chance of benefit from the transplant procedure), should ensure that the donor and recipient have a strong personal and emotionally positive relationship, and should verify that no adult family members are appropriate and willing donors. The donor advocate should also work with the child to provide developmentally appropriate education and support and to ensure that the family attends to the needs and interests of the donor. In cases for which there is concern regarding parental motives or what is in the donor's best interest, ethics consultation with either an ethics consult service or ethics committee may be an appropriate next step.[32,84] Judicial review should be reserved as a last resort or to permit exceptions to any of the conditions listed above. For example, a court may be asked to adjudicate the permissibility of a stem cell donation by a minor when no strong personal relationship exists between the minor donor and recipient.

LONG-TERM FOLLOW-UP

There is an urgent need for improved understanding of the long-term effects, both medical and psychosocial, of minors who serve as hematopoietic stem cell donors. Ideally, national donor registries would be established that would collect short-term and long-term medical and psychological data that would allow for more accurate assessment of the risks, benefits, and

outcomes of hematopoietic stem cell donation. Currently, there is 1 such project titled RDSafe (related donor safety initiative) that is evaluating approximately 10 000 related and unrelated donors over the next 5 years. The researchers plan to examine both psychological and medical issues for 1 year. This project is laudable, although when the donors are children, follow-up will be needed for a much longer time frame. In this vein, the AAP supports health care professionals who seek authorization from minor donors and their parents for long-term collection and storage of donor health data. Parents should be responsible for authorizing the child's registration, but the child should be asked to give his or her own consent when he or she reaches the age of majority.

RECOMMENDATIONS

1. Children who are medically appropriate potential donors may ethically serve as hematopoietic stem cell donors if 5 criteria are fulfilled: (1) there is no medically equivalent histocompatible adult relative who is willing and able to donate; (2) there is a strong personal and emotionally positive relationship between the donor and recipient; (3) there is a reasonable likelihood that the recipient will benefit; (4) the clinical, emotional, and psychosocial risks to the donor are minimized and are reasonable in relation to the benefits expected to accrue to the donor and to the recipient; and (5) parental permission and, when appropriate, child assent are obtained (see recommendation 3).
2. A donor advocate (or some similar mechanism as befits an individual program) with expertise in pediatric development should be appointed for all individuals who have not reached the age of majority and who are being considered as hematopoietic stem cell donors. The donor advocate must be independent of the team responsible for direct care of the recipient and should be involved from the onset, starting with the decision about whether the minor should undergo HLA-testing. A donor advocate is not necessary in cord blood donation. Donor advocates should ensure that the criteria in recommendation 1 are met.
3. When children and adolescents are being considered as hematopoietic stem cell donors, they should be included in all stages of the decision-making process to the extent that they are capable. The donor advocate should facilitate their inclusion. Parents may authorize their child's participation as a hematopoietic stem cell donor. A minor's dissent should lead to further discussion and involvement of the donor advocate, child mental health professional, and ethics consultants and/or ethics committee if necessary. The donor advocate, with the assistance of child mental health professionals and ethics consultants and/or ethics committee as needed, should have the authority to prevent or delay the donation if the donation is likely to have a serious and sustained long-term adverse impact on the donor. The recipient should not begin conditioning unless there is a clear decision to go ahead with the donation. Once the recipient has begun myeloablative preparation for bone marrow infusion (conditioning), the child donor cannot renege, because this would be lethal to the recipient.
4. Pediatricians should be aware that they may be asked about IVF with PGD to ensure the conception of an HLA-matched sibling for cord blood donation. If delivery is not modified, umbilical cord blood procurement poses no risk to the newborn infant. In some cases, it will be necessary to collect additional hematopoietic stem cells from this child at a later date. In those cases, the other criteria enumerated in recommendation 1 regarding pediatric donors must be met.
5. To advance the effectiveness of different hematopoietic stem cell transplants, research will need to be performed on donors and recipients. When the donor is a minor, the research must conform to the federal regulations governing pediatric research. This may require national review when the research imposes more than minimal risk without prospect of direct benefit to donor subjects.
6. Long-term follow-up data should be collected to help determine the actual medical and psychological benefits and risks for child donors. These data should then be used to modify future recommendations regarding the permissibility of minors serving as hematopoietic stem cell donors.

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