Reviews

Ethical Challenges in Hematopoietic Cell Transplantation for Sickle Cell Disease

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ABSTRACT
Hematopoietic cell transplantation (HCT) using an HLA-identical sibling donor offers a very high likelihood of cure with good outcomes for patients with sickle cell disease (SCD), and alternative donor HCT for SCD is an area of active clinical research. Thus, HCT is a potential option for a growing number of patients with SCD. This expanded use of HCT has raised several ethical questions. Who is eligible for HCT, in terms of both disease severity and psychosocial factors? Should affected children with matched sibling donors undergo HCT only when they have declared themselves as having significant symptomatology? Regarding donors, special ethical challenges include the use of preimplantation genetic diagnosis to conceive an HLA-identical sibling. In this review, we critically analyze various ethical challenges related to HCT for SCD, and offer recommendations to guide clinical care.

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INTRODUCTION
Sickle cell disease (SCD) is an inherited hemoglobinopathy that affects more than 100,000 Americans and millions of individuals worldwide. SCD is characterized by recurrent vaso-occlusive “crises,” bouts of severe pain occurring throughout the body. Along with pain, SCD causes unique complications involving virtually every organ. Outcomes of children born with SCD have improved significantly over the last several decades with better supportive care (e.g., immunizations, penicillin prophylaxis, transcranial Doppler screening) and hydroxyurea treatment [1]. Yet even with these advances, children with SCD still face a future that will likely involve many acute and chronic health problems, as well as a shortened life expectancy [2,3]. Curing SCD is a worthwhile and important medical aim.

Allogeneic hematopoietic cell transplantation (HCT) is a proven cure for SCD. The literature documenting the curative potential of HCT for SCD has grown substantially since the first published report in 1984, culminating in a recent publication describing outcomes in 1000 patients who underwent HCT for SCD using an HLA-identical sibling donor [4,5]. Given this experience in curing SCD for more than 30 years, we should view HLA-identical sibling donor HCT as no longer experimental but instead, at least in certain circumstances, as an established treatment option for SCD. Nonetheless, its use poses a number of ethical challenges. Many of these challenges may also pertain to other nonmalignant immunologic and hematologic disorders for which HCT has curative potential. Offering a therapeutic option like HCT that has a low yet finite risk of mortality in a condition that is generally not fatal in the short term presents a “dilemma of choice.” [6] The unpredictability of future outcomes and lack of validated prognostic criteria in SCD compounds the problem. The fact that SCD disproportionately afflicts minority and disadvantaged populations adds to these ethical challenges. This review explores a number of pertinent ethical questions involving HCT for SCD, offering practical guidance to hematologists, transplantation physicians, and other health care providers confronting these issues.

ELIGIBILITY FOR HCT
To transplant or not to transplant? That is the question that troubles many hematology and transplantation providers as well as parents of children with SCD and adults actually living with SCD. We will not attempt to offer guidance on this difficult and personal question, but rather discuss when it is ethical to offer (and refuse to offer) HCT to a patient with SCD.
HLA-Identical Sibling Donor HCT in Patients With SCD Who Have Not Experienced Serious Complications of the Disease

When the first international clinical trial of HCT for SCD was launched in 1991, only patients who experienced certain major complications were considered eligible for HCT [7]. Strict disease severity eligibility criteria were appropriate at that time, when outcomes of HCT were unknown. Today, in contrast, more liberal criteria seem to be appropriate for patients with an HLA-identical sibling donor given the known excellent outcomes of HLA-identical sibling HCT for SCD reported in multiple recent studies [5,8-12]. Nonetheless, even though HLA-identical sibling donor HCT now offers an approximate 95% chance of cure for SCD, it remains associated with a low risk of major complications that can lead to death. This risk has led some to evoke the ethical principle of nonmaleficence (“first, do no harm”) and conclude that HCT should not be offered to patients who have not experienced serious complications of SCD and thus are highly unlikely to die secondary to SCD in the short term.

Proponents of the nonmaleficence principle may argue that HCT should not be offered to children who are doing “well”, because hydroxyurea treatment offers better survival with less toxicity than HCT. A recent registry study from Belgium found that patients treated with hydroxyurea had a survival advantage compared with patients who underwent HCT [13]. Nonetheless, after additional years of follow-up, these cohorts’ Kaplan–Meier survival curves may cross, with superior long-term survival in HCT recipients. In addition, survival should not be the sole endpoint evaluated for SCD. Proponents of the nonmaleficence argument also argue that even if patients are cured through HCT, they still may be harmed by late transplantation-related toxicities, such as endocrine dysfunction and infertility [14]. These late toxicities hopefully will be minimized by the increased use of reduced-intensity and nonmyeloablative conditioning regimens, but even with these approaches, related toxicities may cause harm years after HCT. This harm should not automatically preclude consideration of HCT, but needs to be balanced with the long-term morbidity and mortality of SCD.

The idea that HCT should not be offered to patients deemed “low risk” in terms of SCD severity is flawed, because it wrongly assumes the existence of a current, validated disease severity prediction algorithm for SCD. Research has been conducted in this area, and certain markers (e.g., elevated reticulocyte count in early infancy, elevated transcranial Doppler velocity) have been found to be associated with later disease severity, but more reliable predictors are needed [15]. Young children with SCD who are doing well may later suffer significant health problems as adults due to their SCD. A multicenter, randomized, placebo-controlled trial clearly demonstrated that the initiation of hydroxyurea therapy in early childhood resulted in significantly fewer pain and acute chest syndrome episodes [16]. Unfortunately, however, even with the early use of hydroxyurea, children still experience organ dysfunction secondary to SCD and likely will face more overt clinical complications as fetal hemoglobin levels decline with age [17].

Although SCD severity is difficult to predict, patients with the hemoglobin (Hb) SC and HbSβ+ thalassemia genotypes as a group have a less severe clinical course compared with patients with the HbSS and HbSβ0 thalassemia genotypes [18,19]. We thus propose that it is inappropriate to offer HCT to “asymptomatic” patients with HbSC and HbSβ+ thalassemia. However, HCT can be considered for patients with these genotypes with overt SCD complications, given that some patients with HbSC and HbSβ+ thalassemia develop significant SCD-related problems [20-22]. When considering HCT for children with HbSS and HbSβ0 thalassemia before the manifestation of overt disease complications, ensuring the correct diagnosis is essential, because in infancy, HbSS and HbSβ0 thalassemia may appear similar to compound heterozygosity for Hbs and deletional hereditary persistence of fetal hemoglobin (HPFH). Individuals with Hbs-HPFH should not be offered HCT, because this condition generally does not cause serious health problems [23].

A second problem with the nonmaleficence argument is that it does not acknowledge that harm may occur by not electively performing early HCT. Unfortunately, the insidious organ damage from SCD begins in infancy. This damage includes harm to the brain; by age 5 years, approximately 1 in 4 children with HbSS have evidence of “silent” cerebral infarction, which has been associated with poor neurocognitive outcomes, and this percentage increases with age [24-26]. Refusal to perform HCT may cause harm by allowing this progressive damage to continue. HCT at a young age may prevent permanent organ dysfunction from SCD [27]. The nonmaleficence argument also ignores the fact that early HCT is associated with better HCT outcomes. In particular, younger patients experience less graft-versus-host disease (GVHD) [28-31]. In patients with SCD, each year of delay for HCT is associated with higher mortality (hazard ratio [HR], 1.1; 95% confidence interval [CI], 1.06 to 1.14; P < .0001) [5]. Thus, not performing HCT early may harm patients by subjecting them to increased risk if they undergo HCT in the future. We have previously evaluated the risks versus benefits of HCT for children with “less severe” SCD, noting that the potential harms of future SCD complications may be similar to the potential harms of HCT [32].

A final problem with the nonmaleficence argument is that it suggests that this principle should inherently trump another important ethical principle: respect for autonomy. Respect for autonomy means that a physician should honor a patient’s right to make his or her own choices even if these choices differ from the physician’s personal recommendations. A physician can and should offer his or her own thoughts on the decision to pursue HCT for an individual patient. For example, given the improved clinical course of patients with HbSS and HbSβ+ treated continuously with hydroxyurea beginning in infancy, a physician may strongly recommend hydroxyurea over HLA-identical donor HCT for a young child who has not suffered a major complication [33]. Although such a recommendation can be justified, refusal to even offer HCT to this child’s family may be considered paternalistic. Medical paternalism is justified when the risk of an intervention clearly outweighs the potential benefit. For example, HCT should not be offered to children with standard-risk acute lymphoblastic leukemia at diagnosis, because the survival of these patients treated with HCT is expected to be inferior to those treated with conventional chemotherapy, with both treatments offering cure. In the case of HCT for SCD, HCT may be associated with an increased short-term risk of death, but it is likely also associated with many long-term benefits through cure. This risk-versus-benefit calculus is very complicated and involves values that are ranked differently by individual patients (Figure 1). In this context, shared decision making, with the physician educating and advising and the patient making the final decision, is ethically appropriate. With pediatric patients, respect for autonomy is complicated by the fact that the patient cannot consent, but, as discussed further below,
parents should be honored as surrogate decision makers for their children. We thus conclude that it is ethical to offer HCT using an HLA-identical sibling donor to a patient with SCD who has not experienced serious complications of the disease as long as safeguards are in place to ensure that patients (or parents) understand the potential risks and benefits.

**HCT Using Alternative Donors in Patients with SCD Who Have Not Experienced Serious Complications of the Disease**

Most patients with SCD do not have a healthy, HLA-identical sibling to serve as a donor [34,35]. Given this fact, HCT approaches using alternative donors (ie, unrelated bone marrow donors, unrelated cord blood, and haploidentical related donors) are needed. In contrast to HCT using HLA-identical sibling donors, HCT using alternative donors should continue to be viewed as investigational for SCD and not the standard of care. Only a small number of patients with SCD have undergone HCT using an alternative donor, and unfortunately, these transplantations have had relatively poor outcomes [36-39]. Given this background, it is ethically appropriate to restrict alternative donor HCT to patients enrolled on clinical research trials where they meet disease severity eligibility criteria. One could attempt to argue that such a restriction is paternalistic, but as noted above, medical paternalism is justified in circumstances in which the risk of an intervention is felt to clearly outweigh the potential benefit. Rather than undergo an experimental HCT, patients who have not suffered serious complications from SCD would instead benefit from receiving current standard of care supportive therapy, with alternative donor HCT delayed until such a time that research has helped improve the outcomes of these transplantation approaches. We are encouraged by the improved results reported in recent studies of patients with SCD undergoing HCT using alternative donors, but these studies were small and appropriately restricted enrollment to patients who had suffered severe SCD complications [40,41]. These alternative donor HCT approaches should continue to be investigated in larger clinical trials.

One problem that should be acknowledged is the difficulty in objectively defining disease severity eligibility criteria for SCD. It is well accepted that a patient with SCD who has suffered an overt stroke has “severe” disease, but other disease severity criteria are somewhat arbitrary and could be considered problematic by many. For example, in the active BMT CTN 1503 multicenter study of adolescents and young adults with severe SCD, a patient who had 5 prolonged hospitalizations for pain in the last 2 years would not be eligible, but a patient with a history of 3 emergency department visits per year for 2 years for pain (with or without being admitted) would be eligible (Table 1).

**Timing of HCT and Patient Consent**

In the past, older teenagers and adults with SCD were excluded from HCT clinical trials because of concerns about their ability to tolerate myeloablative conditioning secondary to SCD-induced organ dysfunction. However, recent clinical trials have reported excellent outcomes in older patients with SCD following HLA-identical sibling HCT with reduced-intensity

Table 1

Severe SCD Eligibility Criteria for the BMT CTN 1503 Study (NCT02766465)

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<th>Individual is considered to have severe SCD if he or she has had at least 1 of the following:</th>
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<td>■ Clinically significant neurologic event (stroke) or any neurologic deficit lasting ≥24 h</td>
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<td>■ Two or more episodes of acute chest syndrome in the previous 2 yr</td>
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<tr>
<td>■ Three or more pain crises (need for i.v. pain management in the outpatient or inpatient setting) per year in the previous 2 yr</td>
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<td>■ Administration of regular red blood cell transfusion therapy, defined as receiving ≥8 or more transfusions per year for ≥1 yr, to prevent vaso-occlusive clinical complications (ie, pain, stroke, and acute chest syndrome)</td>
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<tr>
<td>■ Echocardiographic finding of a tricuspid valve regurgitant jet velocity ≥2.7 m/s</td>
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or nonmyeloablative conditioning [9,11,42]. This significant advance in HCT for SCD creates the new ethical question of whether to truly respect personal autonomy, it would be better to wait to offer this elective transplantation to adolescent or adult patients who can respectively assent or consent to HCT. As discussed above, a potential problem with this approach is the fact that organ damage from SCD and overall HCT outcomes worsen with age. Although approaches to HCT in adults with compromised organ function secondary to SCD are available, performing transplantation in these patients before irreversible damage has occurred is still preferable. It is also possible that adults with SCD may suffer more chronic pain post-HCT than children because of the changes in brain connectivity and central sensitization that may occur over time [43].

The approach of waiting to obtain consent may raise other ethical concerns as well. Failure to offer HCT to a parent of a child with SCD is restricting that child’s theoretical future autonomous choice to have undergone HCT as a child. To honor a child’s future choices, parents are the appropriate surrogates and should decide what is best for their child. In support of this view that parents make appropriate decisions on behalf of their children, parents’ views regarding HCT risk and the decision to undergo HCT appear to be similar to those of adolescent and adult patients with SCD [44-46]. We posit that it is not inherently ethically preferable to wait to offer HCT to children until they are adolescents or adults.

Adult patients with SCD also may present unique challenges with regard to consent. Adults with SCD frequently have evidence of cerebral infarcts without overt neurologic deficits (“silent strokes”), as well as cognitive impairment [47-49]. Thus, some adults with SCD may have difficulty making complex medical decisions like the decision to undergo HCT. Providers should be aware of this potential issue and provide extra assistance if needed to ensure that true informed consent is obtained.

HCT in Patients with SCD and Psychosocial Concerns

Nonadherence to medical recommendations prescribed during HCT can lead to fatal complications. This idea is supported by a study of HCT recipients that found an independent association between problematic adherence and increased mortality, especially from infection or GVHD (complications that could be caused by nonadherence) [50]. For a patient with significant psychosocial problems that will prevent adherence to the many requirements of HCT, it seems prudent to not offer HCT. It is ethical to refuse to offer HCT in this setting because of the principle of nonmaleficence; the likelihood of harm from HCT is appropriately judged to be too high, given that patient nonadherence increases the risk of serious HCT complications.

The foregoing concept seems straightforward, but in practice, restricting HCT because of psychosocial concerns is problematic. Who decides? How? Is it fair to refuse to offer HCT because of circumstances beyond a patient’s control? To further complicate the situation, psychosocial variables have a pathological relationship with the incidence and severity of disease complications in patients with SCD. As in most diseases, patients with SCD who have less financial and emotional support have worse health outcomes [51]. A vicious cycle often occurs in which complications of SCD contribute to psychosocial problems (eg, missed work, loss of employment, poverty, emotional stress) that lead to poor medical care (eg, missed appointments, poor adherence to medicines) and trigger more acute SCD crises, as well as additional chronic SCD complications.

A decision to not offer HCT because of psychosocial concerns can be arrived at objectively, but is inevitably influenced by bias. This bias is a particular concern for SCD, given that most affected patients are members of a discriminated minority group. Patients with SCD should be evaluated fairly, just like patients with other diseases referred for HCT. If a HCT team mobilizes resources to offer HCT to a patient with relapsed leukemia and a challenging psychosocial situation, it should make a similar effort for a patient with SCD. In some respects, a patient with relapsed leukemia should be evaluated and treated differently, because the disease may be more likely to cause death sooner without HCT. Yet, at least in certain circumstances, a patient with SCD who is denied HCT because of psychosocial concerns and not provided support is likely fated for a future with more disease complications compounded by psychosocial stressors. Even though this patient with SCD might not have as great a risk of dying from their disease in the next year as a patient with relapsed leukemia, a future fraught with more frequent pain crises and progressive organ dysfunction may be just as grim. Thus, although it may be ethically appropriate to not offer HCT to patients with SCD because of psychosocial concerns, HCT teams should assist these patients in overcoming or managing their psychosocial challenges so that HCT can be offered in the future. To address these issues, we propose a protocol outlined in Figure 2, which was modified from a program that successfully offered kidney retransplantation to patients with previous graft loss from nonadherence [52].

Eligibility Criteria for Patients with SCD from Low-Income Countries

Because the majority of individuals with SCD live in low-income countries, it is important to consider the use of HCT specifically in this population. The prognosis for an individual with SCD living in a low-income nation is generally much worse than that for an individual in a high-income nation. For example, although death in childhood from SCD is rare in the United States and Europe, a large proportion of children with SCD die in Africa before age 5 years [1,53-55]. Given this background, one could argue that patients from low-income countries who plan to move back to these countries should be evaluated differently when considering HCT eligibility. Because SCD has a much higher risk of causing early death in low-income countries, is it appropriate to allow individuals from these countries to take on more risk to achieve cure? It appears that in the 1990s (when HLA-identical HCT was still experimental for SCD), an HCT center in Belgium considered it permissible for individuals from low-income countries to assume this risk. This center performed HCT in 14 African children who were “asymptomatic” or had “minimal symptoms” of SCD, because “their family had to return to Africa where medical care would not be optimal.” [56] Today this approach is acceptable, because HLA-identical HCT is now a proven therapy for SCD with good outcomes, but we have concerns about the ethical rationale that might have been used to justify different eligibility criteria for what was an experimental therapy at that time.

Although ethically challenging, it is understandable that resource constraints and lack of access to high-quality care may result in a different standard of care for patients with the same disease in different geographical regions of the world. Nonetheless, eligibility criteria for enrollment onto an investigational clinical trial should be the same regardless of
the country from which the trial subjects are recruited. In addition, individuals from low-income countries should be considered a “vulnerable” research population. Given concerns that researchers may exploit certain vulnerable research groups, particularly the economically disadvantaged, some have proposed excluding these groups from research. As discussed by Denny et al. [57], such a policy is problematic, and economically disadvantaged individuals should be given the opportunity to participate in clinical research.

**HCT DONOR ISSUES**

**Children as Hematopoietic Stem Cell Donors for Siblings With SCD**

Although bone marrow and peripheral blood stem cell (PBSC) collection are generally safe procedures, they have very rarely been associated with significant adverse events [58]. As long as they are informed of the risk of these events, competent adults can consent to donate hematopoietic cells without significant ethical concerns. Because minor sibling donors are unable to provide consent, the use of siblings as donors for HCT has undergone significant ethical scrutiny. The ethical issues surrounding the use of children as hematopoietic stem cell donors have been discussed extensively elsewhere [59-68]. There is consensus that as long as certain safeguards are honored, children can ethically serve as stem cell donors. The American Academy of Pediatrics (AAP) explicitly proposed 5 criteria that must be satisfied for children to act as donors (Table 2) [63]. Specific aspects of the AAP’s policy statement have been criticized, but nonetheless it serves as a useful document, along with recent recommendations from the Worldwide Network for Blood and Marrow Transplantation, to guide the ethical practice of collecting stem cells from pediatric donors [59,64-68]. In addition to following these recommendations, the use of donor advocates can help ensure that the rights of child donors are respected.

Given the elective nature of HCT for SCD, it does raise unique issues with regard to potential child donors. Because pediatric SCD generally does not carry a high risk of short-term mortality with current supportive care, the timing of HCT can be delayed, unlike for some other conditions (eg, severe aplastic anemia, relapsed leukemia) that require more emergent HCT. Thus, if it would be in the child donor’s best interest to delay HCT, such a delay would seem ethically appropriate. For example, if a large adolescent patient has an HLA-identical infant sibling, it is unlikely that an adequate number of stem cells for transplantation can be safely collected from the smaller sibling using standard collection procedures. If transplantation using bone marrow with previously collected cord blood (which has been shown to have excellent results) [69,70] is not possible, it would be ethically preferable to wait to perform HCT until the younger sibling has grown sufficiently to minimize the risks to this sibling donor. However, if the patient with SCD is experiencing recurrent serious disease complications, has evidence of progressive organ dysfunction, or requires chronic transfusion therapy, 2 stem cell collection procedures in the younger, smaller sibling could be considered to obtain an adequate amount of stem cells for transplantation. The patient would also benefit from HCT sooner as older age has been associated with worse HCT outcomes [5]. In such a situation, the

![Diagram](image-url)

**Figure 2.** Protocol for evaluating psychosocial concerns. *Objective criteria for demonstrating adherence may include: in next 6 months must attend scheduled hematology clinic appointments; take prescribed hydroxyurea, as evidenced by laboratory monitoring; and immediately present to the emergency department for fever.

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### Table 2

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<th>American Academy of Pediatrics Five Conditions Under Which a Minor May Participate as a Stem Cell Donor [63]</th>
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<td>1. No medically equivalent related adult donor who is willing and able to donate</td>
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<td>2. Strong personal and positive relationship between the donor and recipient</td>
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<tr>
<td>3. Some likelihood that the recipient will benefit from transplantation</td>
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<td>4. Clinical, emotional, and psychosocial risks to the donor minimized and reasonable in relation to the benefits expected to accrue to the donor and recipient</td>
</tr>
<tr>
<td>5. Parental permission and donor assent obtained</td>
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significant benefits of performing HCT may outweigh the slightly increased risks to the donor from undergoing 2 separate procedures [71]. To be considered ethical, clearly the risks to the donor should still be viewed as acceptable: the volume of the product collected would need to be limited and the procedures spaced out to try to avoid any complications, including the need for allogeneic blood product transfusion.

Use of Granulocyte-Colony Stimulating Factor in Donors with Sickle Cell Trait
Administration of granulocyte-colony stimulating factor (G-CSF) is necessary to mobilize PBSCs for donation. G-CSF treatment of a healthy HCT donor may potentially increase the risk of donor adverse events. In particular, based on studies demonstrating a significant association between G-CSF treatment and leukemia in certain patient populations, concerns have been raised that administration of G-CSF could increase donors’ risk of later cancer [72,73]. These concerns have been tempered by recent studies reporting no increased incidence of cancer or other serious adverse events in healthy HCT donors who received G-CSF [74,75]. Thus, the added risk of G-CSF treatment is likely very small compared with the other risks associated with hematopoietic cell donation. Specifically regarding the use of G-CSF in healthy child donors, experts have previously discussed the issue in detail, concluding that the administration of G-CSF in child sibling donors is ethically acceptable [62,76].

In contrast to the safety of G-CSF for healthy donors, G-CSF treatment has been strongly implicated in the development of serious adverse events, including death, in patients with SCD [77]. Owing to concerns that G-CSF could also trigger complications secondary to sickling in individuals with sickle cell trait (SCT), the National Marrow Donor Program currently excludes healthy donors with SCT from donating hematopoietic stem cells with the administration of G-CSF. This concern is supported by a single case report of a cancer patient with SCT who received pegylated G-CSF for chemotherapy-induced neutropenia and subsequently developed “shortness of breath, severe subternal chest pain, and diffuse body aches” that allegedly mimicked a sickle cell crisis [78]. Conversely, a growing literature of small studies involving healthy HCT donors with SCT have not reported G-CSF triggering sickling complications and have found no increased risk of donor adverse events [79–82].

Given that studies of HCT donors with SCT do not support concerns that G-CSF causes more adverse events in this donor group, we suggest that it may be ethically permissible to administer G-CSF to a HCT donor with SCT as long as the donor is informed of the potential risk of adverse events secondary to SCT. For sibling child donors with SCT who cannot consent, the situation is more challenging. Since a significant proportion of HCT donors for patients with SCD will have SCT (more than two-thirds of HLA-identical siblings for patients with HbSS), policies restricting the use of G-CSF in HCT donors with SCT have major implications for patients with SCD. Although registry data demonstrate that bone marrow harvested from donors (G-CSF treatment not required) is the preferred stem cell source for SCT HCT, recent excellent outcomes of a nonmyeloablative HCT regimen using PBSCs from G-CSF-stimulated sibling donors underscore the need for policies regarding the use of G-CSF in minor donors with SCT [5,9,11].

Preimplantation Genetic Diagnosis to Conceive Stem Cell Donors
Preimplantation genetic diagnosis (PGD) helps couples at risk of conceiving a child with an inherited disease like SCD to have a child without the disease through the use of assisted reproductive technology [83]. Embryos created through in vitro fertilization (IVF) are tested for the indicated disease, and an unaffected embryo is then selected for transfer to the uterus. Some object to the discarding of “affected” embryos, but our society has accepted PGD as a medical option, and many consider it preferable to prenatal diagnosis with pregnancy termination of an affected fetus. PGD also can include HLA antigen testing and thus can be used to conceive HLA-identical siblings (“savior siblings”). Savior siblings born after PGD have been used to successfully perform HCT in children with a variety of conditions, but some have expressed ethical concerns about this practice [84,85].

In some respects, the use of PGD to conceive an HLA-identical sibling in the context of SCD is less ethically controversial than in the context of noninherited bone marrow conditions. Parents of a child with SCD have at least a 25% chance (higher if a parent has SCD) of having another child with SCD, and so the use of PGD for these couples can be justified to simply ensure that a conceived child does not have SCD. Nonetheless, use of PGD to select an embryo that is HLA-identical to an existing sibling (as well as not having SCD) does raise unique ethical concerns. Specifically, ethical arguments have been made against this practice: (1) that savior siblings are being treated as commodities; (2) that permitting the creation of savior siblings will lead to “designer babies”; and (3) that savior siblings will be psychologically harmed. Sheldon et al. [85] refuted these claims in detail. In brief, first, the thinking that savior siblings are being treated as objects because the impetus for their conception was to create a hematopoietic stem cell donor must acknowledge that individuals are often motivated to conceive children for much more selfish reasons [86]. A disconnected couple may decide to have a child because they think a child will improve their marriage, or a single woman may become pregnant because she does not want to be alone. If individuals can decide to have children for these reasons, then it seems inappropriate to consider parents who who wish to conceive a child with PGD to improve the health of another child as being morally wrong. Second, it is wrong to assume a slippery slope in which allowing HLA selection will lead to the selection of cosmetic traits, given that a clear distinction can be made between the these circumstances: HLA selection can help cure a sibling, whereas cosmetic trait selection provides no such benefit. And finally, even though it is possible that savior siblings could suffer psychological harm from having served as a donor, such harm is not proven and should be balanced with the potential psychological benefits [87,88]. Furthermore, the AAP considers the practice of PGD to conceive an HLA-identical sibling and collect umbilical cord blood to be safe as long as the delivery is not modified to maximize the number of cells collected [63].

On a societal level, PGD raises issues regarding justice, the principle that equals are treated equally with the fair distribution of resources. IVF with PGD is expensive and generally not covered by health insurance, so the economically disadvantaged cannot benefit from it. Is it just that a rich family can conceive with PGD an HLA-identical sibling to cure their child, but a poor family cannot? Justice concerns regarding access to PGD are especially relevant to SCD given that the disease predominantly afflicts minorities
that have a higher prevalence of poverty. Unfortunately, most families with SCD are likely not even aware of PGD [89]. We believe that it is ethical to use PGD to conceive a stem cell donor to cure a sibling with SCD, and recommend that families be educated about this option. Health policy officials should also consider that IVF, PGD, and HCT using the conceived sibling to cure a patient with SCD may actually cost society less than the lifelong care of a patient with SCD [90].

HCT RESEARCH
Research on HCT for SCD is needed not only to decrease toxicities and improve outcomes, but also to directly compare HCT with supportive care. Such research would help better inform both providers and patients/families. A randomized controlled trial generally provides the strongest evidence to guide care, but a study design that randomly assigns patients with SCD to undergo or not undergo HCT is problematic. One could argue that this randomization in patients with SCD is ethically acceptable because equipoise exists between the treatment arms (HCT versus supportive care); however, implementing such a study would be very difficult, because most patients with available donors who are interested in HCT may refuse to enroll on a study in which they could be assigned to not receive HCT. This problem would cause poor study accrual and severely delay trial completion. Such a delay would risk rendering the study results not clinically useful, as care practices would likely advance during the many years of the study. In an attempt to overcome this challenge, the open BMT CTN 1503 study involves biological randomization; subjects are enrolled before HLA typing and assigned to undergo HCT if they have a matched donor or to continue supportive care if they have no matched donor.

CONCLUSION
A consideration of the ethical challenges explored in this review should help empower hematologists and transplant physicians to feel more comfortable in offering HCT to patients with SCD. Nonetheless, in certain circumstances (eg, alternative donor HCT outside the context of a clinical trial, legitimate psychosocial concerns), it may be appropriate to refuse to offer HCT. The ethical challenges faced by patients, parents, and health care providers considering HCT for SCD will likely evolve over time with the validation of accurate models to predict disease severity and further improvements to SCD and HCT care. For example, some exciting clinical developments for patients with SCD have been reported in just the last year: positive results from a double-blind, randomized, placebo-controlled trial of a new agent (crizanlizumab) that effectively reduced SCD pain crises [91], and a case report of a child who appears cured of SCD through gene therapy [92]. More research is key, but we should always consider the ethical issues raised by research advances to truly improve the lives of individuals with SCD.

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REFERENCES


Panch SR, Yau YY, Fitzugh CD, Hsieh MM, Tsidsale JF, Leitman SF. Hematopoietic progenitor cell mobilization is more robust in healthy African American compared to Caucasian donors and is not affected by the presence of sickle cell trait. *Transfusion*. 2015;56:1058-1065.
References