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Hematopoietic Stem Cell Donation in Children: A Review of the Sibling Donor Experience

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Abstract

Hematopoietic Stem Cell Transplant (HSCT) represents the second most frequent major organ transplant in the United States. Compared to other family members, siblings are more likely to be immunologically matched with the recipient and therefore are often the most suitable donors. Due to a dearth of information on the positive and adverse effects of HSCT on pediatric sibling donors, we sought to examine available data. Eight published reports assessing the pediatric sibling donor experience were identified in the literature. Studies were predominately small ($n < 44$) and cross-sectional. Results suggest a range of psychological distress responses with higher distress in pediatric donor than non-donor siblings. Recommendations include future longitudinal research on sibling donor psychosocial adjustment, identification of sibling donors at high risk for maladaptive responses, and development of educational and psychosocial interventions for this overlooked pediatric population.

Keywords

hematopoietic stem cell transplantation; bone marrow and peripheral blood stem cell transplantation; pediatric sibling donors; psychosocial adjustment

With more than 50 years of research and clinical experience, scientists have developed a sufficient understanding of hematopoietic stem cells to successfully use them as a therapy. Hematopoietic stem cell transplantation (HSCT) is now considered a first-line therapy for many life-threatening hematologic and oncologic diseases (Lipton, 2003). Among pediatric patients undergoing HSCT, 75 percent receive healthy stem cells from a brother or sister (Packman, Gong, VanZutphen, Shaffer, & Crittenden, 2004). Literature on the effects of HSCT for both the recipient and donor is expanding rapidly, yet few studies have addressed the psychological impact of HSCT on healthy sibling donors. Despite the growing numbers of pediatric sibling stem cell donors, even less information is available on the psychosocial adjustment of the pediatric donor population. With approximately 2,000 HSCT transplants performed annually in patients less than 20 years old in the United States (Center for International Blood & Marrow Transplant Research, 2005) an examination of published reports of the sibling experience is

warranted in order to guide clinical care and provide future research directions. This article will begin by describing types of hematopoietic transplantation and techniques for blood stem cell donation. A detailed review of published reports about the sibling donor experience will follow. Lastly, recommendations for future research on sibling donor psychosocial adjustment will be made.

Allogeneic Hematopoietic Stem Cell Transplantation

There are two primary types of HSCT. When a patient's own stem cells are used as the graft source, the transplant is *autologous*. In an *allogeneic* stem cell transplant (allo-SCT) donors are selected based on their histocompatibility with the recipient. In order to determine compatibility with the recipient, blood drawn from a potential donor undergoes a laboratory analysis through a technique known as human leukocyte antigen typing (HLA-typing). HLA-typing is critical in allo-SCT because stem cells from closely matched donors reduce the risk of post-transplant complications. Siblings are often the most suitable match, as they have a 25% chance of being immunologically compatible (i.e., HLA-matched) with the recipient and therefore may provide the recipient with a greater chance of survival and a lower risk of complications (Grupp, Frangoul, Wall, et al., 2006). Once the potential sibling donor is identified, additional medical examinations are required to confirm the suitability of donation. This includes a detailed history and physical examination and extensive laboratory evaluation including transfusion-transmitted viral screening.

Impact of Medical Procedures on Healthy Sibling Donors

Previous research has found that the HLA-typing process among siblings of HSCT patients can cause feelings of ambivalence and distress. Sibling donors may feel proud if they are immunologically compatible and therefore able to be a donor but anxious about the hospital procedures. Non-matched siblings may feel relief but also rejection because they are not a match (Pot-Mees & Zeitlin, 1987). Younger siblings can find the HLA blood-typing frightening and painful and therefore wish not to donate (Kinrade, 1987). Individuals of all ages may find the pre-donation evaluation anxiety producing. Previously unknown medical conditions might be discovered. Further, the screening process includes sensitive and confidential questions (e.g., sexual practices, drug use), the answers to which might preclude donation. Deferral from donation would be expected to result in family member inquiry as to the reason for such. Finally, results of family HLA typing might indicate false paternity. All of these issues can have significant impact on a potential sibling donor.

Following HLA-typing and donor selection, preparation begins for stem cell donation. The procedure used for obtaining cells depends on the source of the stem cells. There are four main methods of hematopoietic stem cell collection from pediatric donors used in transplantation. These are conventional bone marrow collected by needle aspiration, peripheral blood stem cells collected by apheresis after injection of a granulocyte colony-stimulating factor (G-CSF), bone marrow collected by needle aspiration after G-CSF stimulation, and umbilical cord/placental blood obtained after delivery of a newborn (Grupp et al., 2006). Until recently, conventional bone marrow was the most common graft source for allogeneic transplants. For more than 40 years, doctors have performed bone marrow transplants by anesthetizing the stem cell donor, puncturing a bone (most often the iliac crests of the hipbones), and withdrawing bone marrow with a syringe (a process called needle aspiration). Sibling donors have experienced serious psychological reactions from the removal of bone marrow, describing the harvesting procedure as "an act of robbery" or a "threat to body integrity" (Packman, Crittenden, Schaeffer et al., 1997). Increasingly, hematopoietic stem cells are being collected from peripheral blood by using a less invasive procedure called apheresis. The stem cells are transferred to the recipient via a peripheral blood stem cell transplant (PBSCT). PBSCT currently represents nearly 75% of related-donor stem cell transplants in adults, although this

approach is less commonly employed for pediatric donors or transplant recipients (Center for International Blood & Marrow Transplant Research, 2005).

Due to the life threatening nature of the recipient's cancer and intensity of the transplantation procedure, as the preparation for transplantation begins, families and medical staff tend to focus most of their energy on the ill child. Though bone marrow and peripheral blood stem cell donation are considered safe procedures, the medical procedures necessary to obtain stem cells from donors are not without risk (Anderlini, Korbling, Dale, et al., 1997; Bredeson, Leger, Couban et al., 2004; Favre, Beksac, Bacigalupo et al., 2003; Gandini, Roata, Franchini et al., 2001; Sanders, Buckner, Bensinger et al., 1987). The preparation for stem cell harvest for either a PBSC or G-CSF mobilized bone marrow transplant requires a 4–5 day administration by intravenous (IV) or subcutaneous (under the skin) injection of G-CSF to mobilize stem cells (Grupp et al., 2006; Majolino, Cavallaro, Bacigalupo et al., 1997). Research on the subjective experience of adult sibling donors undergoing peripheral blood stem cell donation has found that the G-CSF stimulation period is the most painful part of the harvesting procedure and that blood stem cell donors experience higher levels of anxiety prior to collection than bone marrow donors (Munzenberger, Fortanier, Macquart-Moulin et al., 1999; Fortanier, Kuentz, Sutton et al., 2002; Williams, Green, Morrison et al., 2003). Two reports were located that discussed pain in pediatric donors (Pulsipher, Levine, Hayashi et al., 2005; Sevilla, Díaz, Fernández-Plaza et al., 2004). No studies assessing anxiety, the psychosocial effects of G-CSF administration in pediatric PBSC and G-CSF mobilized bone marrow donors, or comparing the psychosocial impact of apheresis to G-CSF mobilized bone marrow harvest were found.

Apheresis, the procedure used to collect stem cells, is performed following G-CSF administration, and usually takes about 4–6 hours per day. The number of collections depends on the number of stem cells collected with each procedure. Typically, blood is drawn from a vein in the arm to the apheresis machine that separates out the needed components. The rest of the blood is then returned to the donor, usually through a vein in the other arm. Though the PBSC donation procedures in adult and pediatric donors are technically similar, there are potential medical risks and complications of peripheral stem cell collection for pediatric donors. These include difficulty with vascular access with possible need for central venous catheter placement, need for anesthesia or sedation, low platelet count, anemia, need for red blood cell or volume priming prior to apheresis, vasovagal complications, shifts in blood volume with resultant cardiovascular changes, hypocalcemia due to citrate anticoagulant (or iatrogenic hypercalcemia due to supplementation), hypotension, nausea, and vomiting (Grupp et al., 2006; Lipton, 2003; Sevilla et al., 2004; Pulsipher et al., 2005). In the event that enough stem cells cannot be collected by apheresis, a bone marrow harvest may be performed. The incidence and severity of the medical risks of PBSC harvesting are still being studied in pediatric donors and a variety of techniques have been developed to minimize such (Bolan, Yau, Cullis et al., 2003); however, the psychosocial risks of both apheresis and the pre-donation G-CSF administration in PBSCT and remain largely unevaluated.

In assessing the psychological adaptation of a sibling donor, it is helpful to reflect on what is known about the non-donor siblings, who are also dealing with a brother or sister living with cancer. A review of the literature on the immediate and long-term emotional, behavioral, physical, and psychosocial effects on non-donor siblings of pediatric cancer patients (Houtzager, Grootenhuis & Last, 1999) reported that healthy siblings may experience feelings of isolation, anxiety, ambivalence, unimportance, anger, loneliness, jealousy, and/or guilt (Bendor, 1990; Carr-Gregg & White, 1987; Chesler, Allswede, & Barbarin, 1992; Koch-Hattem, 1986; Stuber, 1996; Walker, 1990), low self-esteem (Bendor, 1990; Houtzager, Grootenhuis, Hoekstra-Weebers, & Last, 2005), behavior and conduct problems (Breyer, Kunin, Kalish, & Patenaude, 1993; Fife, Norton, & Groom, 1987; Heffernan & Zanelli, 1997; Sloper & While, 1996), depression (Barrera, Fleming, & Khan, 2004; Carr-Gregg &

White, 1987), decreased social competence (Cohen, Friedrich, Jaworski, Copeland & Pendergrass, 1994; Houtzager, Grootenhuis, Caron, & Last, 2004; Labay & Walco, 2004), fear of the patient's death, fear of their own death, psychologic and physical isolation from parents (Walker, 1990), impaired quality of life (Houtzager et al., 2005), and other physiological, social, or behavioral stress responses, both positive and negative. Several studies suggest that maladjustment and poor coping in healthy siblings may be attributed in part to a lack of information about the patient's illness, minimal involvement in the treatment process (Fife et al., 1987; Havermans & Eiser, 1994), and feeling invisible (Fanos & Wiener, 1994). A close relationship between healthy sibling and patient (Labay & Walco, 2004), age at patient's diagnosis (Houtzager et al., 2004), gender, severity of the patient's illness, and perceived lack of social support (Barrera et al., 2004) have been reported as factors increasing the risk of problematic adjustment. As healthy sibling donors are actively involved in the treatment process and related discussions, their experience of the patient's illness varies from that of healthy non-donor siblings, though the aforementioned factors and behavioral issues may still be present (Stuber, 1996).

Previous research has found that anxiety, guilt, helplessness, or emotional over-involvement with the patient during the acute phase of a chronic illness can have long-term effects on sibling development, with active involvement in patient treatments, including tissue donation, profoundly increasing these long-term effects (Stuber, 1996). Anecdotal and descriptive reports address the intense stress that siblings experience as a result of the recipient's illness, including separation from family during the period of post-transplant hematopoietic recovery, and possible post-transplant complications, including the subsequent death of the patient (Gardner, August, & Githens, 1977; MacLeod, Whitsett, Mash, & Pelletier, 2003).

There is a critical need to understand the psychological needs of donors, particularly sibling donors, who represent the largest percentage of matched donors for allogeneic transplant procedures (Horowitz & Confer, 2005). The following review will examine the available literature addressing psychosocial adjustment in pediatric hematopoietic stem cell donors including current models of interventions and present considerations for future research.

Methods

Search Strategy

Studies reported in this review were identified through a search of the following online databases: PubMed, PsychINFO, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Social Sciences Citation Index (SSCI), using the key words "pediatric," "sibling," "stem cell," "donor," "social," "psychological adjustment," "psychosocial adjustment," and "cancer."

Inclusion Criteria

Articles were selected using the following inclusion criteria: written in English, social adjustment or psychological adjustment discussed as a variable, and child, adolescent, or young adult sibling hematopoietic stem cell transplantation donors as a sample or sub-sample. Excluded from the review were case studies and unpublished reports. Also excluded were studies where pediatric donors were included in the sample, but the median age of sample was beyond pediatric age and findings for pediatric donors were not distinguished from adult donor findings.

Data Collection

Upon evaluating the selected published articles, information was collected in a standardized format including authors' names, journal, year of publication, and title. Information was also

recorded about the study design, sample and setting, informants, variables, assessment scales, and conceptual models. Sample characteristics included size, participants' mean age, gender ratios, and ethnic group ratios. Information regarding significant findings relative to variables was also recorded.

Results

Using the inclusion criteria, 8 studies were found eligible for review. Results from the data collection for each study are summarized in Table 1. In seven of the eight studies that examined psychosocial adjustment in sibling donors, the recipient underwent conventional bone marrow transplantation (BMT) (Gardner et al., 1977; Heiney, Bryant, Godder, & Michaels, 2002; Packman et al., 1997; Packman et al., 2004; Pot-Mees & Zeitlin, 1987; Shama, 1998; Wiley, Lindamood, & Pfefferbaum-Levine, 1984). One study specifically addressed the experience of both PBSCT and conventional BMT donors utilizing qualitative methods and incorporating interviews with sibling donors and their families (MacLeod et al., 2003). Two cohorts of BMT donors were assessed using psychometric instruments (Packman et al., 1997; Packman et al., 2004; Pot-Mees & Zeitlin, 1987). Three reports discussed qualitative information from informal interviews and clinical observations (Gardner et al., 1977; Pot-Mees & Zeitlin, 1987; Wiley et al., 1984). Two reports used structured interviews and written evaluations (Heiney et al., 2002; Shama, 1998). No studies were found that assessed adjustment in G-CSF mobilized bone marrow donors. Themes that were identified in the studies are reviewed below. These include psychological adaptation of the donor sibling, adaptive and maladaptive responses, age considerations, transplant outcomes, and ethical considerations for donors.

Psychological Manifestations in Donor Siblings

Using standardized self-report measures to assess depression, Packman and colleagues (1997) found that parents reported significantly higher levels of depression in donors compared to non-donor siblings. No significant differences were found between donor and non-donor responses on the Child Depression Inventory – Short form (CDI-S). Significantly higher levels of anxiety were found in donor siblings through child (i.e., sibling donor) reporting. Moderate to severe levels of post-traumatic stress reactions were found in one third of both donor and non-donor siblings (Packman et al., 1997). Gardner et al. (1977) reported mild to severe psychopathology post-BMT in sibling donors. Through structured interviews sibling donors revealed that they (a) experienced feelings of loneliness and isolation following donation; (b) felt angry with their parents during the HSCT process; and (c) reacted to the stress of the HSCT and parental inattention by withdrawing and internalizing feelings (Packman et al., 1997, 2004). This finding was supported by parent report, which indicated greater withdrawal in donor siblings compared to non-donor siblings (Packman et al., 1997).

Adaptive and Maladaptive Responses

A variety of psychological difficulties were identified. Packman and colleagues (1997, 2004) found lower self-esteem in sibling donors versus non-donor siblings. Pot-Mees and Zeitlin (1987) reported bed-wetting, eating difficulties, sleep disturbances, and disobedience in donors. Wiley et al. (1984) discussed cases in which donor siblings experienced identity problems, psychopathology, withdrawal, guilt, resentment, and anger following the donation procedure. Despite these maladaptive responses, positive changes in sibling donors were also identified, including increased maturity (Packman et al., 1997), better leadership skills (Packman et al., 1997), and heightened intimacy between recipient and donor (Wiley et al., 1984; MacLeod et al., 2003).

Teacher ratings provided additional insight into donor siblings' strengths. Scores from the Behavior Assessment System for Children – Teacher Rating Scale (BASC-TRS) indicated (a) higher levels of social competence in donor siblings, (b) significantly more adaptive skills in donor siblings than in non-donor siblings, (c) more learning and attention problems in non-donor siblings, and (d) more atypical behaviors in non-donor siblings in the classroom setting (Packman et al, 1997).

The use of structured interventions designed for pediatric donors facilitated positive adaptation in sibling donors. Prior to the intervention, the donor children were reported as anxious and fearful of the harvest procedure (Heiney et al., 2002). Following intervention, parents reported that donors seemed more open to asking questions and expressing their emotions about the harvest procedure, gained confidence, were less frightened, were able to manage the stress of being a donor, and were more compassionate towards the recipient (Heiney et al., 2002; Shama, 1998).

Age Considerations

Several studies discussed psychosocial adjustments of HSCT donors specific to stage of development (MacLeod et al., 2003; Heiney et al., 2002; Packman et al., 1997, 2004; Wiley et al., 1984). For the adolescent sibling donor, the significant stress associated with HSCT occurs at the same time as the normal stress of pubertal and development, which could result in unresolved developmental crises (Packman et al., 2004). Compared to non-donors, a majority of adolescent donors reported developmental stress from inadequate resolution of Eriksonian developmental stages, specifically the trust-mistrust, autonomy-shame and doubt, and the initiative-guilt, industry-inferiority, and identity-role dimensions (Packman et al., 2004). MacLeod and colleagues (2003) found that older siblings (older adolescents and young adults) thought more globally about the transplant procedure and considered the possible consequences for the recipient. Younger donors focused primarily on the physical aspects of the donation, specifically expressing concerns about pain (MacLeod et al., 2003) and possible alterations to physical appearance (Heiney et al., 2002). Younger donors were unable to focus on global issues, and expressed resentment for the interruption in normal activities caused by the donation procedure, and later reported that they did not understand that the recipient would die without the transplant (MacLeod et al., 2003; Wiley et al., 1984).

Transplant Outcome

In a qualitative comparison study of sibling stem cell donors from successful or unsuccessful transplants, MacLeod and colleagues (2003) found that sibling donors from successful transplants ("successful" defined as recipient survival at the time of the interview) felt that the transplant positively affected their life in multiple ways. Donors from successful transplants often reported that the HSCT brought their family closer together and improved their relationship with their ill sibling. These donors also reported predominantly positive changes in their thoughts on mortality and illness, relationships, worldviews, and feelings about self. Donors also reported a decrease in feelings of helplessness post-transplant and improved insight into the recipient's illness experience (MacLeod et al., 2003).

Negative emotions regarding the HSCT were reported by sibling donors of successful transplants when the ill sibling experienced complications following the procedure (Gardner et al., 1977; MacLeod et al., 2003; Wiley et al., 1984). In a descriptive report of sibling donor cases, Wiley and colleagues (1984) discussed significant psychological distress to the sibling donor when the patient developed complications such as graft versus host disease (GVHD). Gardner et al. (1977) reported the tremendous responsibility felt by donors for the transplant outcome, as some perceived that their actions caused the recipient to develop GVHD. For

example, one donor believed that her occasional drinking directly caused the complications her sibling experienced (Gardner et al., 1977).

Unsuccessful Transplants

Sibling donors from unsuccessful transplants (“unsuccessful” defined as recipient death) reported both positive and negative responses to the transplant process, with anger, guilt, and blame being the most commonly expressed emotions (MacLeod et al., 2003). Such negative emotions were typically found in interviews with siblings who (a) reported feeling inadequately informed of possible complications from the procedure and the cause of the recipient’s death, (b) perceived a lack of support from family and doctors after the sibling’s death, and (c) internalized their feelings.

Ethical Considerations

Siblings may feel pressure from family members or medical staff to become a donor (MacLeod et al., 2003; Packman et al., 2004). MacLeod and colleagues (2003) describe an interview with a 9-year-old sibling donor who said her parents told her to “say yes” to the transplant, stating, ‘I was the only one who didn’t want to do it. My mom and dad would have died to do it. It wasn’t ‘cause I didn’t want to help him, but I was scared...and they made me feel privileged to be the one that got to do it, but I did not want to.’ These studies demonstrate that sibling donors often express feelings of “no choice” in becoming a donor (Packman et al., 2004; MacLeod et al., 2003). This feeling has been expressed in two ways—siblings feel that they were coerced into donating by family and friends or felt that they had no choice in the matter due to personal beliefs and a desire to help their ill sibling (MacLeod et al., 2003). Siblings also reported in post-transplant interviews that (a) the psychosocial aspects of the donation procedure were more distressing than the physical aspects (MacLeod et al., 2003), (b) they felt unprepared for the range of emotions they experienced during the HSCT process (MacLeod et al., 2003; Packman et al., 2004), (c) more information on the emotional aspects of being a donor should be provided (MacLeod et al., 2003; Packman et al., 2004), and (d) they wanted to be more involved in the donation decision-making process (Packman et al., 2004).

Discussion

Being a stem cell donor can be a stressful experience for pediatric siblings and can potentially lead to the development of long-term distress responses. Results of the studies reviewed identified these youngsters as being at risk for depression, withdrawal, behavioral problems, and lowered self-esteem. These difficulties are similar to those found in reports of non-donor siblings which include trouble sleeping, behavior problems, low self-confidence, depression, and problems in school performance (Barrera et al., 2004; Carr-Gregg & White, 1987; Houtzager et al., 1999; Packman et al., 1997; Weisz & Robbennolt, 1996) suggesting that siblings of pediatric cancer patients in general experience considerable stress, and that stem cell donors may be at higher risk of distress. The presence of post-trauma symptoms were found in both donor and non-donor siblings (Packman et al., 1997, 2004). Packman and colleagues (1997) found that sibling donors manifested more internalizing behaviors such as depression, withdrawal, and anxiety whereas non-donor siblings responded with more externalizing behaviors such as attention and learning problems suggesting that the psychological reactions of donor siblings may present and need to be conceptualized differently than those of non-donor siblings.

An association between age and psychosocial adjustment has been noted in several studies of non-donor siblings of pediatric cancer patients (Houtzager et al., 2004; Stuber, 1996). Younger siblings tend to experience low self-esteem, anxiety, and depression, and adolescent siblings tend to experience family conflict, less family cohesion, and anger that increases with age

(Weisz & Robbennolt, 1996). A recent study indicated that when the child with cancer was born later in the birth order, the siblings exhibited more behavioral, social, and academic problems, perhaps reflecting an increase in family responsibilities placed on older siblings or an expectation of self-sufficiency (Labay & Walco, 2004). Our review suggests that being a stem cell donor during adolescence may add additional challenges to the adjustment process, as developmental tasks may be interrupted. Specific threats to adolescent development include loss of control and separation from peer groups. Consequently, acting out behaviors, low self-esteem, self-criticism, and increased self-centeredness may be more prevalent in the adolescent's response to HSCT than in the younger child's response (Packman et al., 2004). It has been suggested that the adolescent donors' low self-esteem may be attributed to the lack of choice in the decision to donate. Furthermore, donors' lack of involvement in the decision to serve as a donor may damage the child donor's sense of trust and autonomy, resulting in poor resolution of this developmental stage dimensions (Packman et al., 2004).

Feeling responsible for the transplant outcome is of notable concern for sibling donors. As the outcome of a HSCT relies in part on the histocompatibility of the donor and recipient, when the recipient experiences transplant complications, sibling donors may believe that they caused the complications because their marrow or stem cells were not "good enough" (Rappaport, 1988). This is particularly germane to graft-versus-host disease (GVHD), a common post-transplant complication caused by donor cell immune reaction against recipient tissues (Pulsipher et al., 2006; Fortanier et al., 2002; Majolino et al., 1997; Verdeguer et al., 1999). Descriptions of guilt, illustrated by statements such as, "I looked at him, and he was so crippled. I know I did that to him," were found in several reports (Gardner et al., 1977; Kinrade, 1987; MacLeod et al., 2003; Phipps, 1994). In many cases, GVHD ultimately resolves, but it can lead to death and chronic irreversible physical changes that significantly impact patient quality of life. Such long-term complications in recipients may create significant psychological distress in sibling donors (Wiley et al., 1984).

Outcomes following HSCT appear to have a direct affect on the sibling stem cell donors' psychosocial adjustment. Donors whose siblings were reported to have a successful outcome described the transplant experience as positively affecting their life (MacLeod et al., 2003; Wiley et al., 1984). Improved family relationships, cohesion, decreased feelings of helplessness and changes in attitude regarding illness and mortality were reported as positive results. While some encouraging responses were found in donors whose sibling died post transplant, negative emotions were more commonly expressed. Sibling donors of unsuccessful transplants expressed personal responsibility for their sibling's death (Phipps, 1994), anger, guilt and blame (MacLeod et al., 2003; Carr-Gregg & White, 1987). Siblings who felt they were not adequately prepared for possible complications and those who expressed lack of support from family and physicians after their sibling's death often described negative emotions. An association between negative emotions and a tendency towards emotional internalization was also reported (Packman et al., 2004).

Teacher reports identified higher levels of social competence and adaptive skills among sibling donors. This may reflect that siblings' strengths are being overlooked at home as the needs of their ill brother or sister overshadow their own accomplishments. It is possible that the donor exhibits most difficulty within the confines of the home environment and works hard to please and do well in a less stressful environment. It is also feasible that teachers, being aware of a child's donor status, may be more forgiving or less critical donor sibling's misbehavior in class. Packman and colleagues (1997) suggested that school and peer relationships may provide opportunities for mastery, support, and distance from the illness experience, and therefore donors may focus on school to create a sense of competence in a time of stress at home.

Potential ethical concerns were revealed in the literature review. Sibling donor reports of feeling pressured and coerced to become a donor were described (MacLeod et al., 2003; Packman et al., 2004). Some donors felt that there was a lack of attention to both their physical fears associated with donation and their psychological concerns (Kinrade, 1987). Sibling donors do not derive any direct therapeutic benefit from the transplant procedure and appear to be motivated by psychological gain, the hope that the transplant will cure their sibling, or by pressure from family members to donate (Phipps, 1994; Grupp et al., 2006; Weisz & Robbennolt, 1996). If the outcome is suffering and subsequent death, the sibling donors may be left questioning if their brother or sister would have survived if they had not agreed to be the stem cell donor.

Approaches designed to address the psychosocial care of pediatric HSCT donors have been described in several reports (Heiney et al., 2002; Kinrade, 1987; Shama, 1998) and several reports provided insight as to how future interventions should be structured (Gardner et al., 1977; MacLeod et al., 2003; Packman et al., 1997, 2004). Among these reports the following themes emerge: (a) education about the HSCT process alone is inadequate preparation (Gardner et al., 1977; Heiney et al., 2002; Kinrade, 1987; Shama, 1998), (b) children should receive preparatory information and have opportunities to express concerns and questions in order to manage anxiety and guilt (Kinrade, 1987), (c) children should have the opportunity to express emotions throughout the HSCT process (Gardner et al., 1977; Packman et al., 1997), and (d) parents should be involved in the donor's preparation and follow-up to ensure family communication during HSCT (Heiney et al., 2002). While intervention structure varies, most authors describe the necessity for educational information sessions for both pediatric donors and parents with therapeutic follow-up sessions. Some approaches also include a tour of the hospital and an introduction to staff to allow donors to familiarize themselves with the hospital environment before the day of donation (Heiney et al., 2002).

Educational sessions can address the need for information about potential complications. Pre-transplant clinical assessments with therapeutic follow-up can ensure that timely interventions are provided for siblings with pre-existent vulnerabilities and those experiencing subsequent psychological distress. Prior experiences, beliefs, and individual traits may influence how siblings adjust to the donor experience. Kinrade (1987) demonstrates the effects of previous experience in a case study of an 8-year-old donor who was afraid of donating bone marrow because in a previous visit to the hospital to see her brother, she had met two pediatric bone marrow recipients who subsequently died during transplantation. The inception of family-focused interventions in pediatric oncology programs may help siblings return to a normal developmental trajectory that is not organized around their brother/sister's illness (Stuber, 1996).

Limitations

Despite well-designed investigations of the emotional and psychological impact of cancer in children, research on the psychological impact of HSCT on sibling donors in general and specifically of donation is significantly lacking. The conclusions of this review are limited by the following factors (a) small sample sizes, (b) non-representative samples taken from single institutions, and (c) qualitative and cross-sectional designs. Limitations specific to each study are presented in Table 1. Despite these shortcomings, the studies included in this review present critical preliminary information on the needs of pediatric sibling donors.

Implications for Clinical Practice

As peripheral stem cell transplants and G-CSF mobilized bone marrow transplants are more widely used for pediatric cancer patients, the need for understanding the psychosocial impact of stem cell collection and in pediatric donors becomes more critical. Only one study was

identified that included peripheral stem cell sibling donors (MacLeod et al., 2003), but the results from this sub-sample were not separated from that of the conventional BMT cohort due to small sample size. Unlike conventional BMT, PBSCT does not require general anesthesia and surgery, which may make the procedure seem more benign to parents and hospital staff. Moreover, as attention is focused on the ill child, the relatively quick procedure and short recovery time after peripheral blood stem cell apheresis may make the trauma of stem cell donation less noticeable. Significant psychological distress may result from an unsuccessful outcome, and careful follow-up and support is needed to help sibling donors come to terms with their siblings' morbidity and mortality and resultant feelings of guilt.

Typically clinical and psychological follow-up is limited to the peri-transplant period, as donors are not available beyond that time (Phipps, 1994). Investigations should include multiple measures of psychosocial adjustment before, during, and after stem cell collection and post-transplant as well as qualitative designs that allow investigators to learn from the donors themselves how they perceive the HSCT experience. Current investigations examining the potential benefits of G-CSF mobilized bone marrow donation are underway. While the risks and survival benefits for recipients will be carefully examined, it is important that research on quality of life and the psychosocial impact of the different types of donation techniques on sibling donors does not lag behind.

Future studies should assess the effectiveness of psychoeducational interventions designed to prepare sibling donors for the transplant experience. Investigations are needed to determine whether interventions implemented at one or more points prior to the transplant, during the transplant or following transplant are most effective. Specific interventions to reduce the stress associated with stem cell collection, including G-CSF mobilization, are also needed.

Conclusion

Understanding sibling donor adjustment is a complex task given the multitude of individual, family, transplant, biologic, and system variables that mediate the impact of childhood cancer in general and HSCT in particular (Labay & Walco, 2004). However, with the increasing number of HSCT transplants performed each year in the United States, there is an urgent need to obtain a more comprehensive and longitudinal understanding of the positive and adverse effects on pediatric sibling donors. While the results from the present review should be interpreted with caution until replicated in expanded studies with larger samples, they strongly suggest that for these youngsters, psychological distress exists before, during, and after stem cell donation and transplantation, regardless of outcome.

The development of comprehensive preparation and follow-up procedures post stem cell collection and transplantation would appear to reduce the negative affects for pediatric donors. A model that includes ongoing assessment and support of the psychological well-being of the sibling donor could identify those who are psychologically vulnerable and ensure the receipt of timely and appropriate clinical interventions. It is our hope that this review encourages investigators to design research and interventions that target these siblings. The results of such research might allow pediatric transplant clinicians and health care providers to provide timely and effective psychological interventions for this often overlooked population throughout the donation/transplantation continuum.

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Review of Studies Addressing Psychosocial Adjustment in Pediatric Sibling HSCT Donors

Table 1

Study/Focus	Methods	Instruments	Major/Significant Findings	Limitations
Gardner et al. (1977) Psychological issues in BMT	<i>Sample:</i> 7 sibling donors, ages 7 – 19 years (3 males, 4 females)	<i>Instruments:</i> none. Used informal interviews.	Sibling donor psychopathology post-BMT ranged from very mild to severe. Donors reported feeling responsible for transplant outcome and guilt when complications arose. Donors expressed guilt several months post-transplant. Transplant experience was reflective of pre-transplant donor-recipient relationship through a heightened sense of intimacy has been observed post-transplant. Donors expressed guilt when recipient experiences complications.	Descriptive study, small sample size, patients from a single institution.
Wiley et al. (1984) Donor-patient relationship in pediatric BMT	Discussion of selected pediatric BMT cases at single institution		Entire family affected by BMT. Parents reported sibling behavior problems such as bed-wetting, eating difficulties, sleep disturbances, and disobedience during treatment stage. Behavior problems found in 5 of 9 donors, but in only 1 of 10 non-donor siblings.	Descriptive study of selected cases at a single institution, non-representative sample, only acute effects of BMT examined
Pot-Mees & Zeitlin (1987) Psychosocial Consequences of bone marrow transplantation in children	<i>Sample:</i> 15 families, pediatric patients and siblings ages 0 to 16 years.	<i>Instruments:</i> Richman Behavior Checklist (BCL), Rutter A Scale, Ruth Griffiths Developmental Scales, General Health Questionnaire (for parents), questionnaires on prior experience (past 12 mo), and 45-min semi-structured interview.		Small sample size, no child self-reports used, families selected from a single institution, patients with a wide variety of chronic illnesses and malignancies.
Packman et al. (1997) Psychosocial Consequences of BMT in donor and non-donor Siblings	<i>Sample:</i> 44 siblings (21 donors, 23 non-donors) ages 6 - 18 (M = 11 yrs) 71% female. 73 % from two-parent families. Recipient siblings: 29 w/ acquired disorders (most commonly leukemia), 17w/genetic disorder; all patient recipients survived. 12 Adolescents (6 sibling donors, 6 non-donor siblings 3 male and 9 female; M age at HSCT = 12 yrs, M age at study = 15 yrs).	<i>Instruments:</i> Behavior Assessment System for Children (BASC) rating scales for parents and teachers, Child Depression Inventory (CDI-S), Kinetic Family Drawing-Revised (KFD-R), Revised Children's Manifest Anxiety Scale, Child Post-Traumatic Stress Reaction Index, Rosenberg Self-Esteem Scale (RSE), Children's Self-Image Scale (CS) Measure of Psychosocial Development (MPD), semi-structured interviews	<i>Parents:</i> reported higher depression and more withdrawal in donors compared to non-donors <i>Teachers:</i> reported significantly more adaptive behaviors in donors; significantly more maladaptive behaviors in non-donors <i>Sibling Self-Reports:</i> significantly more anxiety in donors; significantly lower self-esteem in donors; moderate-to-severe post-traumatic stress reactions in siblings from both groups	Small sample size, cross-sectional study with single evaluations, patients from a single institution.
Shama (1998) The Experience and Preparation of Pediatric Sibling Bone Marrow Donors	<i>Sample:</i> 16 pediatric donors (age 5 – 18 yrs.) and their parents who participated in a structured intervention for sibling donors	<i>Instruments:</i> post-transplant follow-up evaluation of the intervention for parents	<i>Evaluation results:</i> 97.5 % of parents found intervention program useful. Parents reported child donors had a sense of importance, felt special, proud to help, able to manage stress, comfortable with medical equipment and personnel, and able to deal with fear and anxiety. <i>Themes from parent interviews:</i> Following intervention, donors more open to asking questions and expressing emotions about the procedure; decrease in donor fears; donors were compassionate towards recipients <i>Successful HSCT interviews:</i> predominantly positive impact on life domains such as relationships, view of world, and feelings about self. <i>Unsuccessful HSCT interviews:</i> guilt and blame overshadowed positive effects	Small sample size, single evaluation immediately post-transplant, no child reports, no standardized measures
Heiney et al. (2002) Preparing children to be bone marrow donors	<i>Sample:</i> 12 child donors (age 5 to 18 years) and 12 parents or primary caregivers	<i>Instruments:</i> structured interviews for parents and primary caregivers regarding their child's experience of structured therapeutic interventions for pediatric donors		Small sample size, no formal child self-report, no standardized measures to report efficacy of intervention
MacLeod et al. (2003) Pediatric sibling donors of successful/Unsuccessful HSCT	<i>Sample:</i> 15 sibling donors: 7 from unsuccessful ⁶ HSCTs, 8 from successful HSCTs; age at transplant 7 – 20 yrs (M age = 13.3 yrs), age at interview 12 – 28 yrs (M = 19.6yrs) 11 male and 4 females; 14 of 15 were Caucasian	<i>Instruments:</i> none. Used individually conducted semi-structured open-ended interviews		Small sample size, non-representative of pediatric donor population, time since transplant varied between successful (4.1 years) and unsuccessful transplant donor (7.3 years) groups, one-time evaluations Study included bone marrow and peripheral

Study/Focus	Methods	Instruments	Major/Significant Findings	Limitations
Packman et al. (2004) <i>b</i> Psychosocial adjustment of adolescent siblings of HCST	<i>Sample:</i> 12 Adolescents (6 sibling donors, 6 non-donor siblings 3 male and 9 female; <i>M</i> age at HSCT = 12 yrs, <i>M</i> age at study = 15 yrs.).	<i>Instruments:</i> Rosenberg Self-Esteem Scale (RSE), Measure of Psychosocial Development (MPD), semi-structured interviews	<i>MPD results:</i> assessment for resolution of Eriksonian stages, 5 of 6 Donors reported low to moderate resolution in at least 1 of 5 stages assessed whereas non of 6 Non-donors were below the normal range of resolution. <i>Interview Results:</i> sibling donors expressed they felt “no choice” and a desire for more involvement in the decision-making process, considerable loneliness following transplant process; felt they received minimal explanation of HSCT process, and reported they reacted to the stress of HSCT and parental inattention by drawing inward	blood stem cell donors, but differences between two groups were not discussed. Small sample size, cross-sectional study with single evaluations, patients from a single institution.

a“Unsuccessful” transplants were defined by recipient death.
b This article further assesses the adolescent siblings from the Packman et al. (1997) cohort.