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# Higher Risks of Toxicity and Incomplete Recovery in 13- to 17-Year-Old Females after Marrow Donation: RDSafe Peds Results

Michael A. Pulsipher[1,*], Brent R. Logan[2], Deidre M. Kiefer[3], Pintip Chitphakdithai[3], Marcie L. Riches[4], J. Douglas Rizzo[2], Paolo Anderlini[5], Susan F. Leitman[6], James W. Varni[7], Hati Kobusingye[3], RaeAnne M. Besser[3], John P. Miller[8], Rebecca J. Drexler[3], Aly Abdel-Mageed[9], Ibrahim A. Ahmed[10], Edward D. Ball[11], Brian J. Bolwell[12], Nancy J. Bunin[13], Alexandra Cheerva[14], David C. Delgado[15], Christopher C. Dvorak[16], Alfred P. Gillio[17], Theresa E. Hahn[18], Gregory A. Hale[19], Ann E. Haight[20], Brandon M. Hayes-Lattin[21], Kimberly A. Kasow[22], Michael Linenberger[23], Margarida Magalhaes-Silverman[24], Shahram Mori[25], Vinod K. Prasad[26], Troy C. Quigg[27], Indira Sahdev[28], Jeffrey R. Schriber[29], Shalini Shenoy[30], William T. Tse[31], Gregory A. Yanik[32], Willis H. Navarro[3], Mary M. Horowitz[2], Dennis L. Confer[3,8], Bronwen E. Shaw[2], Galen E. Switzer[33]

[1] *Children's Hospital Los Angeles, Center for Children's Cancer and Blood Diseases, USC Keck School of Medicine, Los Angeles, California*
[2] *Center for International Blood and Marrow Transplant Research, Division of Biostatistics, Medical College of Wisconsin, Milwaukee, Wisconsin*
[3] *Center for International Blood and Marrow Transplant Research, Minneapolis, Minnesota*
[4] *University of North Carolina Hospitals, Chapel Hill, North Carolina, Division of Hematology and Oncology*
[5] *Department of Stem Cell Transplantation and Cell Transplantation and Cellular Therapy, Division of Cancer Medicine. M.D. Anderson Cancer Center, Houston, Texas*
[6] *Department of Transfusion Medicine, National Institutes of Health Clinical Center, Bethesda, Maryland*
[7] *Department of Landscape Architecture & Urban Planning, Center for Health Systems & Design, Texas A&M University, College Station, Texas*
[8] *National Marrow Donor Program/Be The Match, Minneapolis, Minnesota*
[9] *Department of Pediatrics and Human Development, Helen DeVos Children's Hospital, Grand Rapids, Michigan*
[10] *Department of Hematology and Oncology, Children's Mercy Hospitals and Clinics, Kansas City, Missouri*
[11] *University of California, San Diego Medical Center, La Jolla, California*
[12] *Taussig Cancer Institute, Cleveland Clinic Foundation, Cleveland, Ohio*
[13] *Blood and Marrow Transplant Program, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania*
[14] *Blood and Marrow Transplant Program, Kosair Children's Hospital, Louisville, Kentucky*
[15] *Indiana University Hospital/Riley Hospital for Children, Indianapolis, Indiana*
[16] *Division of Pediatric Blood and Marrow Transplantation, University of California San Francisco Benioff Children's Hospital, San Francisco, California*
[17] *Pediatric Hematology-Oncology, Hackensack Meridian University Medical Center, Hackensack, New Jersey*
[18] *Department of Medicine. Cancer Prevention and Population Sciences CCSG Program. Roswell Park Cancer Institute, Buffalo, New York*
[19] *Johns Hopkins All Children's Hospital, St. Petersburg, Florida*
[20] *Aflac Cancer and Blood Disorders Center, Division of Hematology/Oncology-Bone Marrow Pediatric Hematology & Medical Oncology, Children's Healthcare of Atlanta and Emory University School of Medicine, Atlanta, Georgia*
[21] *Doernbecher Children's Hospital, Oregon Health & Science University, Portland, Oregon*
[22] *Pediatric Hematology Oncology Program, Bone Marrow and Stem Cell Transplantation Program, University of North Carolina Healthcare, Chapel Hill, North Carolina*
[23] *Division of Hematology, Fred Hutchinson Cancer Research Center, Seattle, Washington*
[24] *Blood and Marrow Transplant Program, University of Iowa Hospitals & Clinics, Iowa City, Iowa*
[25] *Florida Hospital Cancer Institute, Florida Center for Cellular Therapy, Orlando, Florida*
[26] *Duke Cancer Institute, Duke University Medical Center, Durham, North Carolina*
[27] *Texas Transplant Institute, San Antonio, Texas*
[28] *Cohen Children's Medical Center of New York, New Hyde Park, New York*
[29] *Cancer Transplant Institute Honor Health, Scottsdale, Arizona*
[30] *Hematology and Oncology, St. Louis Children's Hospital, St. Louis, Missouri*
[31] *Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois*
[32] *The University of Michigan, Ann Arbor, Michigan*
[33] *Division of General Internal Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania*

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* Correspondence and reprint requests: Michael A. Pulsipher, MD, Children's Hospital Los Angeles, 4650 Sunset Blvd, Mailstop #62, Los Angeles, CA 90027.
*E-mail address:* mpulsipher@chla.usc.edu (M.A. Pulsipher).

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A B S T R A C T

Although donation of bone marrow (BM) or peripheral blood stem cells (PBSCs) from children to family members undergoing allogeneic transplantation are well-established procedures, studies detailing levels of pain, symptoms, and long-term recovery are lacking. To address this lack, we prospectively enrolled 294 donors age <18 years at 25 pediatric transplantation centers in North America, assessing them predonation, peridonation, and at 1 month, 6 months, and 1 year postdonation. We noted that 71% of children reported pain and 59% reported other symptoms peridonation, with resolution to 14% and 12% at 1 month postdonation. Both older age (age 13 to 17 years versus younger) and female sex were associated with higher levels of pain peridonation, with the highest rates in older females (57% with grade 2-4 pain and 17% with grade 3-4 pain). Multivariate analyses showed a 4-fold increase in risk for older females compared with males age <13 years ($P$ <.001). At 1 year, 11% of 13- to 17-year-old females reported grade 2-4 pain, compared with 3% of males age 13 to 17 years, 0% of females age <13 years, and 1% of males age <13 years (P = .01). Males and females age 13 to 17 years failed to return to predonation pain levels at 1 year 22% and 23% of the time, respectively, compared with 3% and 10% in males and females age <13 years ($P$ = .002). Our data show that females age 13 to 17 years are at increased risk of grade 2-4 pain at 1 year and >20% of females and males age 13 to 17 years do not return to baseline pain levels by 1 year after BM donation. Studies aimed at decreasing symptoms and improving recovery in older children are warranted.



## INTRODUCTION

Donation of bone marrow (BM) by children to siblings or other family members has been an accepted procedure for nearly 4 decades [1]. Over the past 2 decades, the practice of granulocyte colony-stimulating factor (G-CSF)-stimulated collection of peripheral blood stem cells (PBSCs) has become the most common method of donation for adult donors. PBSC products from related pediatric donors have been used to some extent in pediatrics (eg, very-high-risk recipients, reduced-intensity regimens, manipulated products), but the approach is performed in only a minority of donors [2,3]. A combination approach, using G-CSF followed by BM donation ("G-primed" BM) has been investigated by some groups as a technique for improving engraftment without increasing graft-versus-host disease (GVHD) [4] and represents a similarly small portion of pediatric donation procedures.

In 2010, the American Academy of Pediatrics issued a policy statement on children as hematopoietic stem cell (HSC) donors [5]. This statement outlined a series of recommendations, including conditions under which donation is considered reasonable, a call to use the safest and most appropriate donation approach, and a strong statement encouraging research regarding the physical and psychological outcomes associated with donation. A Worldwide Network for Blood and Marrow Transplantation Association working group similarly outlined the need for more detailed data regarding the donation process in children to inform and protect them [6].

Unfortunately, well-characterized assessments of the child donor experience are lacking. For BM donation, a single-center report published in the 1980s described outcomes of 128 child donors age <10 years and 343 donors between 10 and 19 years as part of a description of outcomes of donors of all ages [7]. However, the outcomes described were limited to severe adverse events, "greater than expected" pain, postspinal headaches, and transfusions ("life-threatening complications" were noted in .4%). Between that study and 2012, a report of 23 children age <2 years [8] and several small studies [9-11] and 1 larger study [2] of side effects of PBSC collection in children were published. Finally, in 2012 a larger prospective study of pediatric donors was published by the Pediatric Diseases Working Party of the European Society for Blood and Marrow Transplantation (EBMT) [3]. Although these studies documented low rates of serious adverse events (SAEs) and attempted to describe pain, the tools used were basic (eg, pain yes/no with no description of location and minimal description of intensity) and no longer-term follow up after the procedure was performed.

Data tools that document the donor experience in much greater detail were developed and validated by National Marrow Donor Program (NMDP) over this past decade [12-15]. These approaches describe and quantitate pain by specific location as well as describe and grade specific toxicities common to BM and PBSC donors. The tools have been used to assess donors at predonation baseline and document recovery, both short-term and long-term. Using these more precise data approaches in unrelated donors, it has been noted that women experience greater degrees of pain and side effects [13-15], obese donors of PBSCs experience more pain [13], and BM donation in adults leads to more SAEs and lingering pain compared with PBSC donation [15].

With a lack of detailed data regarding the related HSC donor experience in mind and better donor evaluation tools in hand, a multi-institutional team joined with the NMDP/Center for International Blood and Marrow Transplant Research (CIBMTR) to implement the Related Donor Safety Study (RDSafe) funded by a grant from the US National Heart, Lung, and Blood Institute (NHLBI). This prospective observational trial enrolled related donors of all ages at 53 centers in the United States and prospectively collected detailed predonation and postdonation assessment data through 1 year postprocedure. This report details pain, toxicities, and SAEs occurring in 294 pediatric donors age <18 years who underwent collection at 25 centers between 2010 and 2014. Previously published quality of life studies in a large subset of this cohort reported the important findings that a portion of pediatric donors have significant decreases in health-related quality of life (HR-QoL) associated with the procedure [16], and there is a disconnect between parents' and children's perceptions of the donation process [17]. Those previous studies together with the present report provide the most comprehensive assessment of pediatric HSC donation to date.

## METHODS

Parents of pediatric donors were approached for enrollment if their child had been selected to provide either a first or second BM or PBSC donation for a family member. Parental or legal guardian consent was obtained for all donors, and assent was obtained for donors age >7 years during standard donor counseling sessions at the transplantation center. All centers were required to obtain and maintain Institutional Review Board approval for the study. Donors and/or their parents had to be willing to receive phone calls at 1, 6, and 12 months for follow-up interviews by the CIBMTR Survey Research Group. Potential donors who were unable to speak English, were unable to

complete a phone interview, or had no access to a telephone were excluded from the study. Donors providing unstimulated PBSCs or lymphocytes were not eligible to participate in the study.

All donors underwent a comprehensive medical evaluation, including a physical examination, blood tests, and further workup as deemed necessary. Donors were approved for donation in accordance with transplantation center criteria.

### Data Collection

Eligibility information and donor demographic data were reported after donor consent was obtained. A predonation form was completed at the time of donor clearance for HSC donation. For PBSC or G-primed BM donors, this was performed before any mobilizing agent was administered; for BM donors, it was performed before the day of collection. This form included questions on donor health history to assess any preexisting medical conditions (ie, comorbidities) present before donation. Details on toxicity and pain were collected at 5 time points, including predonation, peridonation, and at 1 month, 6 months, and 12 months postdonation. Toxicity was defined by Common Toxicity Criteria measures for specific symptoms known to be common with PBSC and BM collection. This approach to assessing toxicities has been validated by the NMDP and published previously [12-15]. The specific scale is called the Modified Toxicity Criteria (MTC), and the symptoms assessed included fever, fatigue, skin rash, local reactions to injection, nausea, vomiting, anorexia, insomnia, dizziness, and syncope, scored based on the Common Toxicity Criteria scale, allowing classification as grade 0 to 4. Pain was reported at 10 body sites (back, bones, head, hip, i.v. site, joints, limbs, muscles, neck, and throat) and/or other and was scored as 0 (absent), 1 (mild), 2 (moderate), 3 (severe), or 4 (disabling). Pain and MTC toxicity data were collected by the transplantation centers through direct questions to the donors when possible or to parents for children unable to communicate an assessment at predonation and peridonation time points. The CIBMTR Survey Research group was responsible for follow-up assessments at 1 month, 6 months, and 1 year and followed the same procedure of posing direct questions to the donor whenever possible.

Pain and MTC symptoms for PBSC donors were reported just before apheresis on day +5 of G-CSF (known time of peak effects) and if collection occurred on multiple days, pain and symptoms were assessed each day. For marrow donation, pain and MTC symptoms were reported by the donor through a follow-up call at 24 to 48 hours postdonation. For G-prime BM donation, pain and MTC symptoms were reported just before donation and within 48 hours postdonation.

A product-specific donation form was completed on the day of donation, providing detailed information on the donation procedure, including type of anesthesia used, volume of product collected, whether autologous or allogeneic blood transfusions were given for marrow donation, use of a central line, days of apheresis, and hypocalcemia symptoms for PBSC collections.

Predonation and postdonation complete blood counts were reported for all donors. Adverse events were reported as applicable following standard CIBMTR data reporting procedures.

### Endpoints

Endpoints for this study included the following:

- Incidence of grade 2-4 and grade 3-4 skeletal pain at peridonation and postdonation. Skeletal pain represented pain in at least 1 of the following sites: back, bone, head, hip, joints, limbs, and neck. Severity of skeletal pain was defined as the maximum grade among these pain sites.
- Incidence of grade 2-4 and grade 3-4 body symptoms at peridonation and postdonation. Body symptoms were assessed using the MTC outlined above, and the peak toxicity level across all symptoms was analyzed.
- Recovery to predonation levels by 1 year, defined as a pain or symptom score less than or equal to the score at predonation
- Incidence of blood transfusion after BM donation
- SAEs related to donation.

### Data Analysis

Analyses were conducted separately by donation type; analyses of PB and G-primed BM were descriptive only, owing to small numbers. The chi-square test or Fisher's exact test, as appropriate, was used to compare the incidences of skeletal pain and MTC symptoms as well as recovery to predonation levels for age and sex subgroups in univariate analyses. Multivariate analyses using logistic regression models were conducted to examine prognostic factors for pain and MTC symptoms. The effects were estimated using odds ratios. Stepwise model selection was used to determine donor characteristics to be included. The following donor and collection characteristics were considered for inclusion in the multivariate model: race, sex, age, body mass index, donation year, comorbidity group, predonation counts (WBC, platelets, neutrophils, mononuclear cells, and hemoglobin), predonation symptoms (skeletal pain or max MTC grade), and volume of BM collected per kilogram of donor weight.

## RESULTS

### Demographics

Table 1 presents demographic data for the 294 donors in the study cohort. As expected, most first donation procedures were unprimed BM donation (92%), with small percentages of PBSC (5%) and G-primed BM (3%) donations. Second procedures were rare (only 3.4% of all donations) and were most often PBSC collections. All ages were well represented, with slightly fewer donors in the youngest age group (27%, 38%, and 35% in the 0 to 6 year, 7 to 12 year, and 13 to 17 year groups, respectively). Donor sexes were balanced (48% females). The sample was ethnically diverse; 55% of the donors were Caucasian, 26% were African American, and 13% were Hispanic.

### Pain and Common Toxicities Associated with the Donation Procedure

Figure 1A shows pain experienced by unprimed BM donors by age reported at 24 to 48 hours after BM donation. The most common sites of pain included skeletal, back, hip, and throat. More than 60% of even the youngest children reported pain, with nearly 25% of them experiencing grade $\geq$2 pain. Both the rate and intensity of pain increased with age, with the 13- to 17-year-old cohort reporting pain nearly 80% of the time, with 44% reporting grade 2-4 pain and 13% reporting grade 3-4 pain ($P$ = .011 and .007, respectively; Table 2).

Child donors reported MTC symptoms at 24 to 48 hours after BM donation less often than pain (Figure 1B), with the most commonly reported symptoms including fatigue, site reaction, dizziness, and nausea. Notably, the older cohort showed a trend toward having more grade 2-4 MTC symptoms compared with younger donors ($P$ = .064; Table 2) with 41%, 29%, and 25% of older donors reporting fatigue, dizziness, and nausea, respectively, compared with 27%, 12%, and 14% of younger donors.

Fifteen of the 15 PBSC donors were undergoing the procedure for the first time. One donor reported grade 2-4 pain, and none reported MTC symptoms with collection. There was a trend toward less grade 2-4 pain ($P$ = .069) and less grade 2-4 toxicities ($P$ = .081) with PBSC donation compared with BM donation, but the numbers are small. G-primed BM numbers were also low (n = 8), with 2 donors reporting grade 2-4 pain and 3 donors reporting grade 2-4 toxicities postdonation (data not shown). Of note, among PBSC donors age 18 to 25 years in the RDSafe study, 48% experienced grade 2-4 pain and 18% had MTC toxicity [18], and earlier studies have shown increasing side effects with PBSC donation with age [2,3], so our small PBSC donor population is likely not fully reflective of the experience of older children who donate PBSCs.

### Univariate Analysis of Pain and Toxicity with BM Donation: Effect of Age and Sex at Donation

The 2 younger age groups reported outcomes that were statistically similar for both pain and MTC symptoms and thus were combined for univariate analysis (Table 2). Age had a major effect on both pain and toxicity reported within 24 to 48 hours after donation, with 44% of donors in the 13- to 17-year-old group reporting grade 2-4 pain and 13% reporting grade 3-4 pain, compared with 27% reporting grade 2-4 pain

**Table 1**
Characteristics of Related Pediatric Donors (Age 0 to 17 Years)

| Variable | First BM | First PBSC | First G-Primed BM | Second BM | Second PBSC | Second G-Primed BM |
|---|---|---|---|---|---|---|
| Number of donors | 261 | 15 | 8 | 6 | 3 | 1 |
| Number of centers | 25 | 14 | 7 | 5 | 3 | 1 |
| Age at donation, n (%) | | | | | | |
| 0-6 yr | 72 (28) | 1 (7) | 3 (38) | 1 (17) | 1 (33) | 0 |
| 7-12 yr | 103 (39) | 5 (33) | 3 (38) | 2 (33) | 0 | 0 |
| 13-17 yr | 86 (33) | 9 (60) | 2 (25) | 3 (50) | 2 (67) | 1 (100) |
| Median age, yr, (range) | 10 (0-17) | 14 (6-17) | 10 (4-17) | 13 (2-16) | 16 (7-16) | 15 |
| Sex, n (%) | | | | | | |
| Female | 128 (49) | 5 (33) | 3 (38) | 3 (50) | 2 (67) | 1 (100) |
| Male | 133 (51) | 10 (67) | 5 (63) | 3 (50) | 1 (33) | 0 |
| Body mass index, kg/m$^2$* | | | | | | |
| Underweight, <5th percentile | 6 (2) | 1 (8) | 0 | 0 | 0 | 0 |
| Healthy weight, 5th-85th percentile | 152 (63) | 6 (46) | 6 (75) | 2 (40) | 1 (50) | 1 (100) |
| Overweight, 85th-95th percentile | 44 (18) | 1 (8) | 1 (13) | 1 (20) | 0 | 0 |
| Obese, ≥95th percentile | 41 (17) | 5 (38) | 1 (13) | 2 (40) | 1 (50) | 0 |
| Unknown | 7 (N/A) | 2 (N/A) | 0 (N/A) | 0 (N/A) | 1 (N/A) | 0 (N/A) |
| Not applicable, age <2 yr | 11 (N/A) | 0 (N/A) | 0 (N/A) | 1 (N/A) | 0 (N/A) | 0 (N/A) |
| Race, n (%) | | | | | | |
| Caucasian | 137 (52) | 11 (73) | 7 (88) | 4 (67) | 2 (67) | 1 (100) |
| Hispanic | 34 (13) | 2 (13) | 1 (13) | 0 | 0 | 0 |
| African/African American | 72 (28) | 1 (7) | 0 | 1 (17) | 1 (33) | 0 |
| Asian/Pacific Islander | 5 (2) | 1 (7) | 0 | 1 (17) | 0 | 0 |
| Native American | 2 (1) | 0 | 0 | 0 | 0 | 0 |
| Multiracial | 8 (3) | 0 | 0 | 0 | 0 | 0 |
| Unknown | 3 (1) | 0 | 0 | 0 | 0 | 0 |
| Collection-related | | | | | | |
| Year of donation, n (%) | | | | | | |
| 2010 | 22 (8) | 1 (7) | 0 | 0 | 0 | 1 (100) |
| 2011 | 64 (25) | 2 (13) | 4 (50) | 1 (17) | 0 | 0 |
| 2012 | 66 (25) | 4 (27) | 1 (13) | 4 (67) | 3 (100) | 0 |
| 2013 | 69 (26) | 5 (33) | 2 (25) | 0 | 0 | 0 |
| 2014 | 40 (15) | 3 (20) | 1 (13) | 1 (17) | 0 | 0 |
| BM-specific | | | | | | |
| Type of anesthesia, n (%) | | | | | | |
| General | 261 (100) | | 7 (88) | 6 (100) | | 1 (100) |
| Spinal | 0 | | 1 (13) | 0 | | 0 |
| Volume of BM product per donor weight, mL/kg | | | | | | |
| Number evaluated | 256 | | 7 | 6 | | 1 |
| Median (range) | 16 (4-36) | | 17 (11-24) | 10 (3-31) | | 22 (22-22) |
| PBSC-specific | | | | | | |
| Number of days agent administered, n (%) | | | | | | |
| 3 | | 0 | 1 (13) | | 0 | 1 (100) |
| 4 | | 7 (47) | 0 | | 1 (33) | 0 |
| 5 | | 7 (47) | 7 (88) | | 1 (33) | 0 |
| 6 | | 1 (7) | 0 | | 0 | 0 |
| 7 | | 0 | 0 | | 1 (33) | 0 |
| Mobilizing agents, n (%) | | | | | | |
| G-CSF | | 15 (100) | 8 (100) | | 3 (100) | 1 (100) |
| Number of days of collection, n (%) | | | | | | |
| 1 | | 11 (73) | | | 2 (67) | |
| 2 | | 4 (27) | | | 1 (33) | |

(*continued on next page*)

**Table 1** (*Continued*)

| Variable | First BM | First PBSC | First G-Primed BM | Second BM | Second PBSC | Second G-Primed BM |
|---|---|---|---|---|---|---|
| Precollection WBC, $\times 10^9$/L | | | | | | |
| Number evaluated | | 15 | | | 3 | |
| Median (range) | | 29.7 (14.4-75.9) | | | 46.6 (20.9-51.7) | |
| Average daily G-CSF dose per donor weight, μg/kg/d | | | | | | |
| Number evaluated | | 13 | 8 | | 3 | 1 |
| Median (range) | | 10.3 (8.0-11.9) | 5.0 (4.8-11.2) | | 6.3 (5.1-15.6) | 6.0 (6.0-6.0) |
| $CD34^+$ cells before collection, $\times 10^6$/L | | | | | | |
| Number evaluated | | 9 | | | 1 | |
| Median (range) | | 64.1 (22.1-98.7) | | | 72.4 (72.4-72.4) | |
| Volume of whole blood processed, L | | | | | | |
| Number evaluated | | 13 | | | 3 | |
| Median (range) | | 18 (5.0-40.0) | | | 14.8 (10.6-21.0) | |
| Central line placement, n (%) | | | | | | |
| Yes | | 10 (67) | | | 2 (67) | |
| Femoral | | 6 | | | 0 | |
| Subclavian | | 0 | | | 1 | |
| Internal jugular | | 3 | | | 1 | |
| Other site‡ | | 1 | | | 0 | |
| No | | 5 (33) | | | 1 (33) | |

The median time from enrollment to collection was 13 days (range, -12 to 183 days).
* Body mass index was calculated from height and weight reported at time of enrollment.
‡ Other site: right atrium/superior vena cava (PBSC first time).

and 4% reporting grade 3-4 pain in the younger group ($P = .011$ and .007, respectively). In addition, older donors trended toward reporting more grade 2-4 symptoms (26% versus 16%; $P = .064$). A similar effect was noted by sex, with more grade 2-4 pain reported by female donors (all ages, 39% versus 27% in male donors; $P = .046$).

When age and sex were assessed together by univariate analysis, there was a clear effect of being female and older, with 57% of 13- to 17-year-old females experiencing grade 2-4 pain and 17% experiencing grade 3-4 pain, compared with 30% and 9%, respectively, of 13- to 17-year-old males, 30% and 4% of <13-year-old females, and 25% and 3% of <13-year-old males ($P = .004$ for grade 2-4 and .023 for grade 3-4; Table 3). A combined age and sex effect was not observed for nonpain symptoms.

### *Time to Recovery and Persistence of Pain at 1 Year*

Predonation levels of pain and symptoms were low for children at baseline, especially for those in the youngest age group (Figure 2). Of note, a higher percentage of donors in each age group reported grade 1-2 pain at 1 year postdonation compared with predonation (age 0 to 12 years: 2% predonation and 8% at 1 year postdonation, $P = .02$; age 13 to 17 years: 9% predonation and 22% at 1 year postdonation, $P = .05$).

Univariate analyses of pain from predonation through 1 year postdonation and lack of recovery (return to predonation pain/symptom level) showed a similar age and sex effect. The rate of grade 2-4 pain at 1 year postdonation was 7% in donors age 13 to 17 years versus 1% in younger donors ($P = .017$). Older donors had a higher risk of failure to return to predonation levels at 1 month and 1 year (21% versus 10% at 1 month and 22% versus 6% at 1 year; $P = .032$ and .002, respectively). Failure to return to predonation pain levels was reported by 20% of females at 1 month and 16% of females at 6 months, compared with 7% and 8% of males at these respective time points ($P = .010$ and .099, respectively; Table 2). Combining age and sex variables, 11% of the 13- to 17-year-old female donors reported grade 2-4 pain at 1 year compared with 3% of 13- to 17- year-old male donors, 0% of <13-year-old female donors, and 1% of <13-year-old male donors ($P = .011$). Failure to return to predonation levels by 1 year postdonation was seen in 22% of male donors and 23% of female donors age 13 to 17 years, compared with 3% of males and 10% of females age <13 years ($P = .002$; Table 3).

### *Comorbidities in Childhood Donors*

A variety of comorbidities were reported in children undergoing BM or PBSC donation. Table 4 describes comorbidities reported in the first-time BM donors by age, most commonly associated with pulmonary, central nervous system, psychiatric, or gastrointestinal conditions. We analyzed the effect of these comorbidities in 2 ways. We first looked at the effect of any given comorbidity on outcomes. Because each comorbidity was rare, it is not surprising that no significant effects were noted. We then classified the comorbidities into 3 categories: comorbidities that would clearly lead to deferral based on NMDP policies, comorbidities that were considered acceptable for donors by NMDP policy, and comorbidities that would have required detailed assessment by the transplantation center and further information to make a judgment regarding donation. Notably, no pediatric donors had comorbidities that would have been a contraindication to donation according to NMDP standards. Although the presence of comorbidities was associated with a small increase in predonation pain (8% versus 0% grade 2-4; $P = .010$), there were no differences in pain, MTC

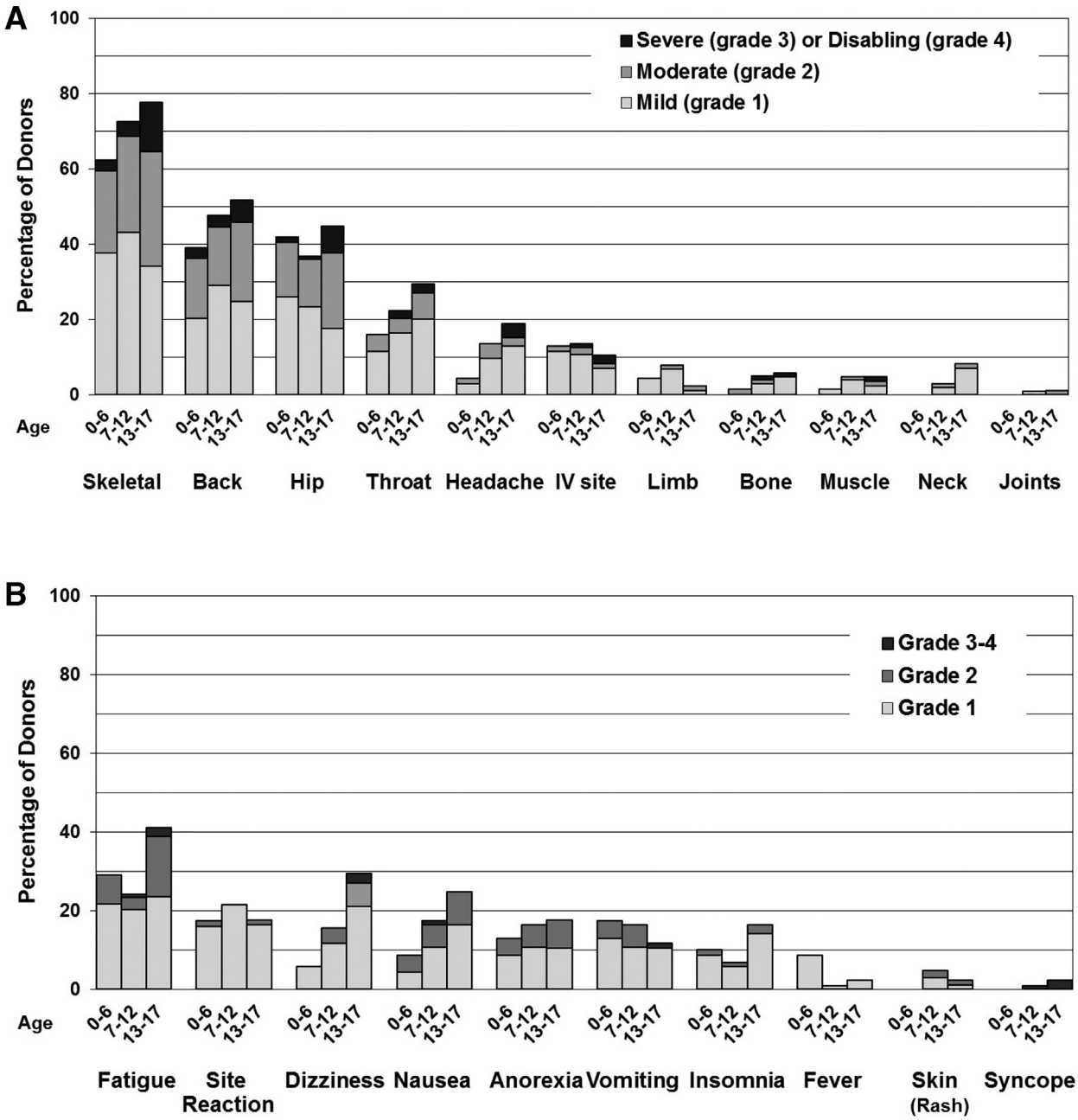


**Figure 1.** Location and grade of pain and type and grade of BM collection-related toxicities reported by children within 48 hours after BM collection by age group. (A) Sites of pain in BM donors. (B) Collection-related toxicities in BM donors.

symptoms, and recovery experienced by pediatric donors reporting comorbidities and those not reporting comorbidities.

### *Blood Transfusions after First-Time BM Donation*

Allogeneic blood transfusion occurred very rarely in this cohort of children and only in the younger groups (4% of children age 0 to 6 years and 2% of those age 7 to 12 years). Only 9% of 13- to 17-year-olds received autologous PBSC transfusions; none of them received allogeneic PBSCs.

### *SAEs*

Two SAEs were reported in this cohort. A 5-year-old donating BM was admitted for observation for a possible aspiration event after emesis postextubation, and a 13-year-old was admitted post-BM donation for observation after exhibiting rhythm abnormalities and hypertension associated with the procedure. The 13-year-old had a preexisting seizure disorder and experienced a seizure during this night of observation, which further prolonged hospitalization. These 2 events were considered expected events, because anesthesia-related events are known to occur in a small percentage of patients after BM donation [15].

### *Multivariate Analysis*

Multivariate analysis confirmed that age and sex significantly influenced grade 2-4 pain within 24 to 48 hours after BM donation, with females age 13 to 17 years having a 4-fold greater risk compared with younger males ($P < .001$; Table 5). Also notable was the decrease in risk during the latter 2 years of the study (odds ratio, .52; $P = .022$).

**Table 2**
Univariate Comparisons of Skeletal Pain and Common Toxicities Experienced by Pediatric RDSafe BM Donors, by Age and Sex at 2 Days, 1 Month, 6 Months, and 1 Year Postdonation

| | Age 0-12 yr | | Age 13-17 yr | | | Male | | Female | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Event and time point | Rate | 95% CI* | Rate | 95% CI* | *P* Value† | Rate | 95% CI* | Rate | 95% CI* | *P* Value† |
| Pain | | | | | | | | | | |
| Baseline, grade 2-4 | 1 | 0-3 | 1 | 0-6 | .551 | 0 | 0-3 | 2 | 0-6 | .240 |
| Baseline, grade 3-4 | 1 | 0-3 | 0 | 0-4 | 1.000 | 0 | 0-3 | 1 | 0-4 | .490 |
| At collection, grade 2-4 | 27 | 21-35 | 44 | 33-55 | .011 | 27 | 20-35 | 39 | 30-48 | .046 |
| At collection, grade 3-4 | 4 | 1-7 | 13 | 7-22 | .007 | 5 | 2-11 | 8 | 4-14 | .460 |
| At 1 mo, grade 2-4 | 2 | 0-6 | 7 | 2-16 | .119 | 3 | 1-8 | 5 | 2-11 | .499 |
| At 1 mo, grade 3-4 | 1 | 0-4 | 0 | 0-5 | 1.000 | 0 | 0-3 | 1 | 0-5 | .498 |
| At 6 mo, grade 2-4 | 1 | 0-5 | 3 | 0-9 | .602 | 2 | 0-6 | 2 | 0-7 | 1.000 |
| At 6 mo, grade 3-4 | 1 | 0-4 | 1 | 0-7 | 1.000 | 1 | 0-5 | 1 | 0-5 | 1.000 |
| At 1 yr, grade 2-4 | 1 | 0-4 | 7 | 2-17 | .017 | 2 | 0-7 | 4 | 1-10 | .434 |
| At 1 yr, grade 3-4 | 0 | 0-3 | 0 | 0-5 | | 0 | 0-4 | 0 | 0-4 | |
| Nonrecovery at 1 mo | 10 | 5-16 | 21 | 12-32 | .032 | 7 | 3-14 | 20 | 13-28 | .010 |
| Nonrecovery at 6 mo | 10 | 6-16 | 16 | 9-27 | .198 | 8 | 4-15 | 16 | 10-25 | .099 |
| Nonrecovery at 1 yr | 6 | 3-12 | 22 | 13-34 | .002 | 9 | 4-16 | 14 | 8-23 | .268 |
| Max MTC | | | | | | | | | | |
| Baseline, grade 2-4 | 0 | 0-2 | 2 | 0-8 | .109 | 1 | 0-4 | 1 | 0-4 | 1.000 |
| Baseline, grade 3-4 | 0 | 0-2 | 1 | 0-6 | .332 | 0 | 0-3 | 1 | 0-4 | .494 |
| At collection, grade 2-4 | 16 | 11-22 | 26 | 17-37 | .064 | 21 | 14-29 | 18 | 11-25 | .634 |
| At collection, grade 3-4 | 2 | 0-5 | 6 | 2-13 | .121 | 2 | 0-7 | 4 | 1-9 | .492 |
| At 1 mo, grade 2-4 | 5 | 2-10 | 4 | 1-12 | 1.000 | 5 | 2-10 | 5 | 2-11 | 1.000 |
| At 1 mo, grade 3-4 | 1 | 0-4 | 0 | 0-5 | 1.000 | 1 | 0-5 | 0 | 0-3 | 1.000 |
| At 6 mo, grade 2-4 | 3 | 1-7 | 4 | 1-11 | .689 | 3 | 1-7 | 4 | 1-10 | .708 |
| At 6 mo, grade 3-4 | 0 | 0-2 | 1 | 0-7 | .335 | 1 | 0-5 | 0 | 0-4 | 1.000 |
| At 1 yr, grade 2-4 | 2 | 0-5 | 4 | 1-12 | .338 | 2 | 0-7 | 3 | 1-9 | .677 |
| At 1 yr, grade 3-4 | 0 | 0-3 | 0 | 0-5 | | 0 | 0-4 | 0 | 0-4 | |
| Nonrecovery at 1 mo | 11 | 6-17 | 11 | 5-21 | 1.000 | 8 | 4-15 | 14 | 8-22 | .201 |
| Nonrecovery at 6 mo | 11 | 6-17 | 12 | 6-22 | .823 | 9 | 5-16 | 14 | 8-22 | .396 |
| Nonrecovery at 1 yr | 10 | 5-16 | 10 | 4-20 | 1.000 | 8 | 3-15 | 12 | 6-20 | .349 |

* Exact confidence interval.
† Fisher's exact test *P* value.

## DISCUSSION

Data detailing the experiences of normal pediatric BM and PBSC donors are limited, including older studies focused on SAEs [7,8], retrospective experiences of PBSC or G-primed BM donation [9-11,19-22], and a single prospective study from the EBMT [3]. The prospective study provided valuable insights into complications of anesthesia and apheresis, blood transfusions, pain, and hospital stay. However, the study focused on pericollection toxicities; pain and toxicity assessments were limited, and no long-term follow up was performed. These studies showed that severe complications in pediatric donation are rare, but they left significant gaps in understanding the pediatric donation experience. Compelling questions include the following: Where specifically does pain occur and how severe is it? What other symptoms are experienced? How long do the pain and symptoms last? What are the longer-term outcomes (are there children who do not recover fully)? Are there specific factors that increase risk of early pain/symptoms or failure to fully recover? What is the experience like from a psychosocial HR-QoL perspective?

Earlier publications from the pediatric RDSafe HR-QoL cohort documented important psychosocial findings that are currently being assessed in follow-up studies [16,17]. The RDSafe pediatric medical toxicity study toxicity presented here addresses the other questions enumerated above with compelling findings. We show that the experience of the large majority of children donating HSCs includes at most mild to moderate temporary discomfort followed by full recovery. We

**Table 3**
Univariate Comparisons of Skeletal Pain and Common Toxicities Experienced by Pediatric RDSafe BM Donors, by Age and Sex at Baseline and 2 Days, 1 Month, 6 Months, and 1 Year Postdonation

| | Male, Age 0-12 yr | | Female, Age 0-12 yr | | Male, Age 13-17 yr | | Female, Age 13-17 yr | | |
|---|---|---|---|---|---|---|---|---|---|
| Event and time point | Rate | 95% CI* | Rate | 95% CI* | Rate | 95% CI* | Rate | 95% CI* | *P* Value |
| Pain | | | | | | | | | |
| Baseline, grade 2-4 | 0 | 0-4 | 1 | 0-6 | 0 | 0-8 | 2 | 0-12 | .428 |
| Baseline, grade 3-4 | 0 | 0-4 | 1 | 0-6 | 0 | 0-8 | 0 | 0-8 | .655 |
| At collection, grade 2-4 | 25 | 17-36 | 30 | 20-41 | 30 | 17-46 | 57 | 41-72 | .004 |
| At collection, grade 3-4 | 3 | 1-10 | 4 | 1-10 | 9 | 3-22 | 17 | 7-31 | .023 |
| At 1 yr, grade 2-4 | 1 | 0-8 | 0 | 0-6 | 3 | 0-16 | 11 | 3-27 | .011 |
| Nonrecovery at 1 mo | 7 | 2-15 | 13 | 6-24 | 9 | 2-25 | 31 | 17-48 | .007 |
| Nonrecovery at 1 yr | 3 | 0-10 | 10 | 4-20 | 22 | 9-40 | 23 | 10-40 | .002 |
| Max MTC | | | | | | | | | |
| Baseline, grade 2-4 | 0 | 0-4 | 0 | 0-4 | 2 | 0-12 | 2 | 0-12 | .109 |
| Baseline, grade 3-4 | 0 | 0-4 | 0 | 0-4 | 0 | 0-8 | 2 | 0-12 | .332 |
| At collection, grade 2-4 | 19 | 12-29 | 12 | 6-21 | 23 | 12-39 | 29 | 16-45 | .121 |
| At collection, grade 3-4 | 2 | 0-8 | 1 | 0-7 | 2 | 0-12 | 10 | 3-23 | .113 |

* Exact confidence interval.†Fisher's exact test *P* value.

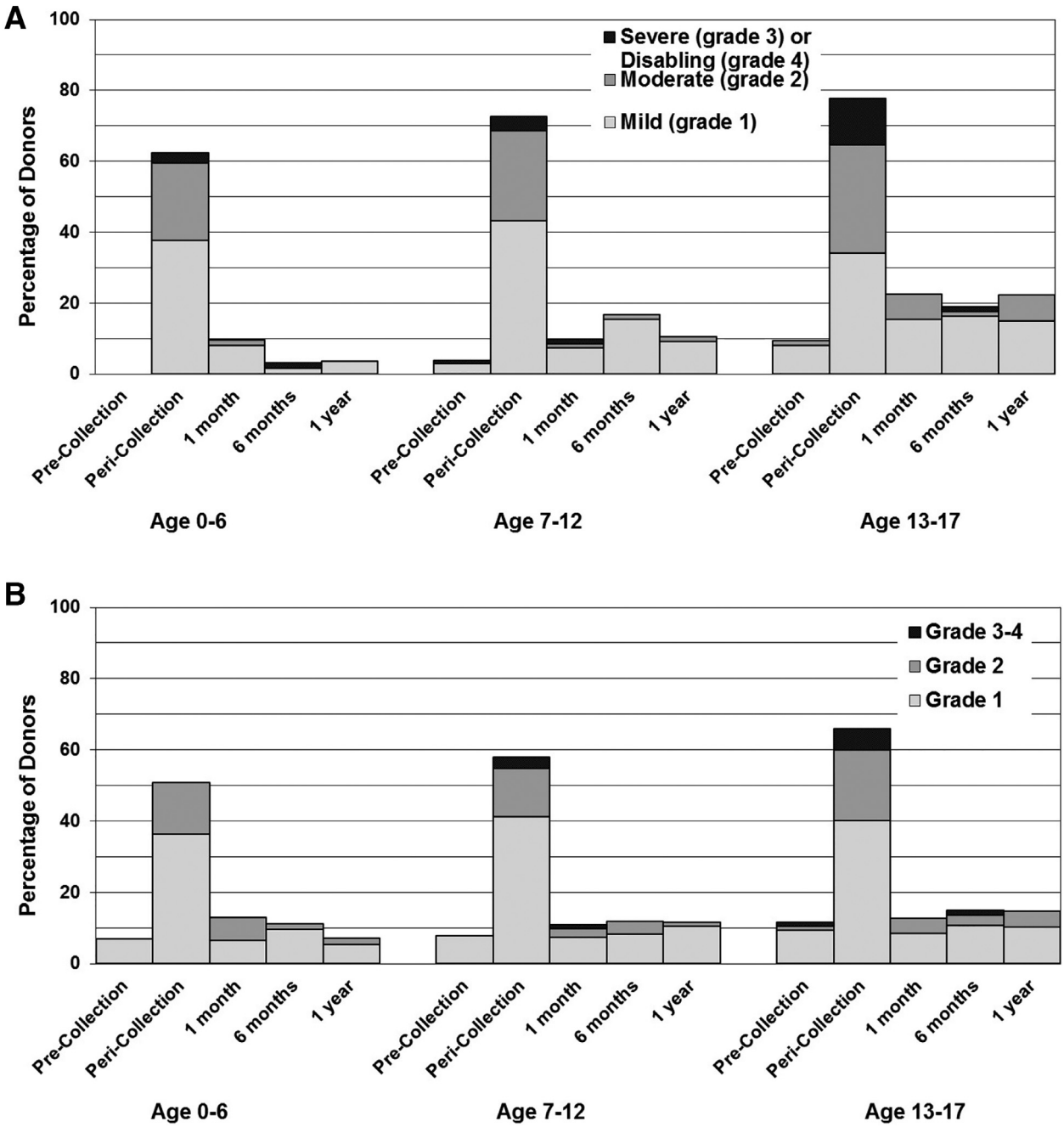


**Figure 2.** Overall highest reported grade of pain and symptoms by age at pre-BM collection, within 48 hours of BM collection, and at 1 month, 6 months, and 1 year post-BM collection. (A) Skeletal pain experienced by BM donors, by age, at predonation, during the peridonation period, and postdonation. Skeletal pain comprises pain in at least 1 of the following sites: back, bone, headache, hip, limb, joint, and neck. The severity of skeletal pain is defined as the maximum grade among these pain sites. (B) Max MTC. Symptoms experienced by BM donors, by age, at predonation, during the peridonation period, and postdonation. Max MTC comprises fatigue, insomnia, site reaction, dizziness, anorexia, nausea, vomiting, skin rash, fever, and syncope. The severity of max MTC is defined as the maximum grade among these symptoms.

describe in much more detail a general observation made by other studies [3] that as children age, higher percentages of them report pain and symptoms, such that by the time they are teenagers they report levels of pain similar to those previously published for adult NMDP donors [14]. However, different from previous reports, even the youngest donors in our study reported pain >60% of the time, >20% of which was grade 2-4 pain. This should serve as a reminder to practitioners involved in pediatric BM donation procedures that the large majority of patients will experience pain, and some will experience significant pain. Therefore, measures should be in place to minimize this (eg, long-acting local analgesics to collection sites, prophylactic pain medications). We note that reported pain levels within 24 to 48 hours of collection decreased over the course of the study, possibly as a result of increased attention focused on related donors during the study period.

Of note, this study is the first to demonstrate that sex differences in pain experienced during the BM donation process start early, and that young female donors age 13 to 17 years

**Table 4**
Classification of Comorbidities in Related Pediatric BM Donors by Age at Donation

| Comorbidity | Age 0-6 yr, n (%) | | | Age 7-12 yr, n (%) | | | Age 13-17 yr, n (%) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Absent | Present, Accept | Present, indeterminate | Absent | Present, Accept | Present, Indeterminate | Absent | Present, Accept | Present, Indeterminate |
| Overall comorbidities | 61(85) | 6(8) | 5(7) | 76(74) | 11(11) | 16(16) | 65(76) | 9(10) | 12(14) |
| Pulmonary | 66(92) | 1(1) | 5(7) | 89 (86) | 1(1) | 13(13) | 80(93) | 0 | 6(7) |
| Central nervous system/ psychiatric | 72(100) | 0 | 0 | 96(93) | 5(5) | 2(2) | 79(92) | 1(1) | 6(7) |
| Gastrointestinal | 72(100) | 0 | 0 | 99(96) | 4(4) | 0 | 82(95) | 3(3) | 1(1) |
| Hematologic | 70(97) | 2(3) | 0 | 101(98) | 1(1) | 1(1) | 85(99) | 1(1) | 0 |
| Cardiovascular | 71(99) | 1(1) | 0 | 101(98) | 2(2) | 0 | 85(99) | 1(1) | 0 |
| Endocrine | 72(100) | 0 | 0 | 102(99) | 1(1) | 0 | 86(100) | 0 | 0 |
| Genitourinary | 71(99) | 1(1) | 0 | 103(100) | 0 | 0 | 86(100) | 0 | 0 |
| Liver disease | 72(100) | 0 | 0 | 103(100) | 0 | 0 | 85(99) | 1(1) | 0 |

Comorbidities categorized based on NMDP guidelines for unrelated donors. Absent: no comorbidities present; present, acceptable: comorbidity(ies) present but acceptable for donation of product collected; present, need more information; comorbidity(ies) present but more information would be needed to evaluate whether the donor would have been accepted or deferred if evaluated as an unrelated donor for donation of the product collected; present, defer: comorbidity(ies) present that would have deferred the donor had he or she been evaluated as an unrelated donor for the type of product collected.
Note that a donor can have more than 1 comorbidity. All percentages are row percentage.

are particularly vulnerable to both pain and other toxicities. This finding is consistent with earlier studies of overall levels of pain in adolescents that have reported an approximate 2-fold greater rate of pain reported females compared with males [23,24]. However, our finding is even more striking, with multivariate analysis showing a 4-fold greater risk of grade 2-4 pain. Adolescent females would be an ideal population for prospectively planned interventions aimed at decreasing up-front discomfort associated with the procedure.

This is the first study in pediatrics to assess donation-associated symptoms at multiple time points after the procedure, and it is important to note that although the large majority of donors experienced a rapid and full recovery with no symptoms, some pediatric donors reported minor discomfort and/or persistent symptoms as late as 1 year after collection. A significant percentage of both males (22%) and females (23%) age 13 to 17 years had not fully returned to predonation levels at 1 year, and 11% of 13- to 17-year-old girls reported grade 2-4 pain (all grade 2), compared with 2% at predonation ($P = .01$). Why this low-grade discomfort persists in some donors is unclear; it is mostly back and hip pain, suggesting a relationship with the collection. Whether the pain was continuous over the year is also unclear, because the interviewers did not ask about perceived causes, whether the pain was persistent, or whether the pain was specifically localized the collection site. Further study into this issue is important; if persistent pain is noted to be due to local trauma or nerve damage, then interventions possibly could be designed to prevent this prolonged pain. In the meantime, it is important to inform parents and children that in a small percentage of cases, a child donor may experience mild persistent skeletal discomfort associated with the donation procedure.

It is notable that although the presence of comorbidities in children was associated with a slightly higher rate of predonation symptoms, there was no measurable effect of any of the reported comorbidities on the tolerability of the procedure or the time to recovery. As expected, the numbers of comorbidities reported by children were relatively small; therefore, further study with larger numbers could possibly identify specific comorbidities that may be important in informing whether pediatric donors with specific comorbidities are at increased risk. Until such data are available, a consensus panel from the Worldwide Network for Blood and Marrow Transplantation Association has recommended that potential pediatric HSC donors with chronic medical problems should be seen by a specialist who treats patients with that condition (eg, a child with diabetes should be seen by a pediatric endocrinologist), and donation should not proceed unless the specialist deems the child able to safely tolerate the anesthesia, temporary discomfort, and anemia associated with HSC donation [6].

It is also notable that 27% of children donating marrow received allogeneic blood transfusions in the EBMT study, compared with only .75% in our cohort. The EBMT study showed a higher risk of transfusions in BM donors who had >20 mL/kg collected and recommended that this amount not be exceeded [3]. A maximum of 20 mL/kg has long been standard practice at most US pediatric marrow donation centers, and our study demonstrates that using this approach, allogeneic blood transfusions after BM harvest in children can be minimized.

In conclusion, this is the most comprehensive study of pediatric HSC donation to date and the first to examine long-term recovery from pain and symptoms. Our data show that although the BM donation procedure is generally safe, almost all children experience pain or other collection-related symptoms, and teenage females are especially vulnerable to more

**Table 5**
Skeletal Pain Grade 2-4 at 2 Days Postcollection

| Variable | n (%) | OR (95% CI) | P Value |
|---|---|---|---|
| Age, yr/sex | | | .004 |
| 0-12, male | 87 (.25) | 1 | |
| 0-12, female | 84 (.30) | 1.25 (.63-2.47) | .519 |
| 13-17, male | 43 (.30) | 1.35 (.59-3.07) | .472 |
| 13-17, female | 42 (.57) | 4.05 (1.84-8.91) | <.001 |
| Year of collection | | | |
| 2010-2012 | 148 (.39) | 1 | |
| 2013-2014 | 108 (.25) | .52 (.29-.91) | .022 |

severe pain. In addition, a small percentage of child donors have incomplete recovery and persistent mild discomfort as late as 1 year after the procedure. The data presented here should serve as baseline data for informed consent and prospective trials aimed at improving comfort during and recovery after the pediatric HSC donation experience.

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*Corporate member.

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