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Pediatric Hematology Providers on Referral for Transplant Evaluation for Sickle Cell Disease: A Regional Perspective

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Summary

Hematology referral for evaluation is a key step for hematopoietic stem cell transplantation for sickle cell disease (SCD). Pediatric SCD providers in the US Northeast (New York-Mid-Atlantic and New England regions) were surveyed anonymously for perspectives and practices regarding transplant referral and compared by whether they practiced at SCD transplant centers. Data were analyzed using the Fisher exact test, χ^2 test, and logistic regression. Half of the respondents practiced primarily at transplant sites. Most (79%) were enthusiastic about transplant for SCD and 78% had recently referred 1 child for evaluation. Overall, 77% limited referral to certain sickle hemoglobinopathies and 44% preferred referral for β -thalassemia to SCD. Indications selected for referral resembled current transplant criteria, plus family request or poor response to therapy. Referral for children on chronic transfusions predicted enthusiasm and prior referral. Many (66%) referred children with multiple SCD complications, even without matched sibling donors, 37% with sibling donors despite limited disease. Practitioners at transplant centers more commonly accepted event-free survival rates of 90% ($P = 0.002$). North-eastern providers expressed varying enthusiasm for referral for evaluation based on eligibility, donor availability, and acceptable risk, with modestly more interest from practitioners at transplant centers. Differing provider perspectives may affect patient referral for transplant consideration.

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Keywords

sickle cell disease; transplantation; provider perspectives

Hematopoietic stem cell transplantation (HSCT) is the only curative treatment option for sickle cell disease (SCD).^{1–14} Transplantation for hemoglobinopathies was first explored in 1981 for patients with β -thalassemia, for which improved regimen and management strategies have led to current overall survival (OS) rates of 92% to 96% using matched sibling donors.^{1,3} The first HSCT for SCD was reported in 1984 using a myeloablative regimen.⁷ Since then, improvements in supportive care and treatment regimens for transplanted patients have increased OS, with rates comparable to those for β -thalassemia.^{1–2,6,9,11–14} Approximately 300 children with SCD have undergone HSCT in the United States.¹⁵ Results of HSCT suggest that transplantation in children may stabilize, prevent, or even reverse some of the cumulative disease-related morbidity.^{1–2,8,10–12,16–17}

Referral from the primary hematologist for transplant evaluation is often a key step toward HSCT. Despite a much larger affected population,^{18,19} significantly fewer patients in the United States with SCD have been referred to transplant centers for consultation compared with patients with β -thalassemia major.¹ Factors contributing to this difference may include the more varied clinical course of SCD, onset of disease complications for meeting standard transplant eligibility criteria,^{1,17} the option of hydroxyurea therapy, and the relative paucity of related matched donors. The highest rates of physician referrals for HSCT for β -thalassemia are for patients receiving treatment at facilities affiliated with a transplant center,³ suggesting that provider factors influence transplant referral.

Provider perspectives on HSCT for SCD may have evolved over the past 2 decades with accumulated experience and better outcomes.^{1,3,14,17} We hypothesized that pediatric SCD providers varied in their enthusiasm and referral practices for HSCT evaluation. Study aims were to assess: (1) current perspectives of pediatric hematology providers regarding eligibility for HSCT evaluation for children with SCD; and (2) whether perspectives of practitioners working at transplant centers differed from those who do not. Factors assessed included their self-reported history of referral for HSCT, perceived indications for referral, and acceptable rates of morbidity and mortality. Using a convenience sample in the US Northeast region extending from Virginia to Maine, the primary pediatric SCD practitioners at all 41 state-certified hemoglobinopathy treatment centers were contacted. Collectively, these 13 states annually diagnose over one third of all newborns with SCD in the United States and include 11 medical centers performing pediatric HSCT for SCD as of 2011.¹⁵

MATERIALS AND METHODS

Study procedures were approved by the institutional review boards of Columbia University and Albert Einstein College of Medicine.

This was a cross-sectional study from May to December 2011 of all hematology providers identified as responsible for follow-up care at the hemoglobinopathy centers accredited by newborn screening programs within 2 (of 7) federally designated regional Genetic Service

Collaboratives: the New York-Mid-Atlantic (NYMAC) and New England (NE) Regions.^{20,21} Twelve of the 41 centers performed pediatric HSCT for pediatric SCD during the survey period. Providers and their email contact were identified from their respective listservs (information for NYMAC provided by Katherine Harris²⁰ and for NE by S.O.O.). A survey was created and piloted among providers at Columbia University, then emailed using Survey Monkey to these providers by the listserv. Five emailed reminders were sent monthly. For the preferred age for transplantation, age ranges were assessed across childhood. Responses were collected anonymously, with descriptive statistics and data analyses performed using SAS 9.2 software. A χ^2 test or the Fisher exact test was used when comparing answers based on whether respondents practice at transplant centers, by self-report. Logistic regression analysis was carried out to assess the indication for transplantation. A *P*-value of 0.05 was considered as significance level.

RESULTS

Demographics

A total of 104 pediatric SCD providers responded from the 197 contacted through the merged listservs. As email addresses used to contact practitioners could not be independently verified, some providers may not have received the requests for survey completion. Hence, survey response rate was at least 53%. Of the 197 targeted providers, 85 (43%) were primarily affiliated with transplant centers and only 5 (2.5%) serve as attending physicians on transplant services. Nonrespondents of this anonymous survey could not be individually identified. Virtually all respondents (95%) confirmed that they practiced primarily at academic medical centers or at university-affiliated hospitals (Table 1).

The sample was divided into 2 groups by whether respondents practiced primarily at a site performing HSCT for pediatric SCD (Table 1). Half of respondents (52.9%) practiced primarily at a transplant site. An additional 18% reported an affiliation with a transplant center, for a total of 71% of respondents being affiliated with a transplant center. Nearly all (90.1%) providers were physicians. Nonphysicians comprised a significantly lower proportion of practitioners in the group who were primarily at transplant centers (18% vs. 0%; *P* = 0.007). No other differences were found between provider groups based on the following demographics: sex (*P* = 0.750), age distribution (*P* = 0.380), board certification (*P* = 0.985), or years since training (*P* = 0.381). Of all respondents, most (74.4%) had practiced for at least 11 years and 47.6% for over 20 years. Nearly all of the physicians (97%) were board certified or board eligible in Pediatric Hematology/Oncology, with just a few in General Pediatrics, Hospice and Palliative Medicine, or Medical Genetics. Overall, hematology providers practicing at transplant centers cared for larger pediatric SCD patient populations (comparing <100, 100 to 300, and 300 or more; *P* < 0.001; Table 1). In all, 33.7% of respondents worked at sites with 300 SCD patients.

Statistically significant differences existed between providers based on whether or not they practiced at a transplant site, only where noted below.

Overall Perspective

The majority of respondents (78%) viewed HSCT as able to achieve disease improvement. Similarly, 79% thought that more patients should be considered for referral but not significantly more of those practicing at transplant centers compared with the others (84% vs. 73%, $P = 0.241$).

Referral History

Most respondents (89.2%, 91 of 102) reported referring at least 1 child with SCD for transplant. Of the 11 providers who never referred a patient for HSCT evaluation, 6 (5.9%) practiced at a transplant center and 5 (4.9%) did not ($P = 0.965$). More providers at transplant center had previously referred at least 3 patients, 42 (84%) versus 23 (53%; $P = 0.001$), but there was no difference after adjusting for clinic size ($P = 0.11$).

Providers were asked about their recent referrals for transplant evaluation, defined as during the previous 2 years. In all, 78% of all respondents had made at least 1 recent referral. Of the 20 who had not, 8 (8.8%) practiced at a transplant center and 12 (13.2%) did not ($P = 0.164$). Significantly more providers practicing at transplant centers had recently referred at least 3 patients, 28 (56%) versus 9 (21%; $P = 0.001$). Among all respondents, providers who had trained 20 years ago were more likely to have made at least one recent referral compared with those completing training over 20 years ago: 90.7% versus 71.1% ($P = 0.023$).

Patient Demographics for Referral

Primary hematology providers were asked about characteristics that qualified patients for referral for transplant evaluation.

Hemoglobinopathy

Of all respondents, 44% stated that they were *less* likely to refer a child with SCD than with β -thalassemia (Table 2), 38% claimed that they considered these 2 as equivalent, and 13% were *more* likely to refer a child with SCD. Among respondents, a majority (66%) would limit referral and transplant to children with hemoglobin SS (Hb SS) and/or HbS- β^0 -thalassemia, whereas few others would include HbSC and/or HbS combined with certain other hemoglobin variants. No significantly different preferences were found between provider groups.

Optimal Age

Both provider groups preferred patients aged between 6 and 16 years for transplant referral, followed in decreasing order by age groups: between 3 and 5 years, older than 16 years, and younger than 3 years. More providers at transplant centers selected age between 6 and 16 years as their ideal patient age for referral (100% vs. 84.8%; $P = 0.004$). Survey responses to age brackets 6 to 10 years and 11 to 16 years were identical and thus merged.

Donor Availability and Extent of Clinical Disease

Most respondents would offer HSCT to a child with multiple disease complications and a matched sibling donor (95%), or who had complications but no sibling donor (66%) (Table 3). Over one third (37%) of providers would offer transplant to children with a sibling match, despite limited disease. No statistical difference was found between the 2 provider groups regarding these characteristics.

Clinical Indications for Referral for Evaluation

Most respondents cited clinically apparent multiple disease complications or central nervous system involvement as main indicators for transplant, comparable to current standard indications.^{1,17} The most commonly cited *single* clinical indications for referral were stroke (76%), acute chest syndrome (42%), and family request (53%) (Table 3). Providers not practicing at transplant centers more often favored referral for family request (63% vs. 45%; $P = 0.085$) but were not significantly different from the other group. Only a modest proportion (31%) of all providers would offer transplantation for an abnormal transcranial Doppler or clinically silent stroke (Table 3).

Indications for referral based on previous treatments commonly included lack of response to hydroxyurea (71%), a new stroke despite transfusion therapy (82%), or chronic transfusion therapy (66%) (Table 3), but not iron overload (22%) or hydroxyurea noncompliance (12%).

Perceived Transplant Outcomes Affecting Referral

Referring providers consider the perceived probability of improved health from HSCT and the acceptable risk for serious adverse outcome. The majority of all providers identified an acceptable minimal OS rate as 90% to 100%, evenly divided between 90% and 95% to 100% (Fig. 1). Providers at transplant centers were more likely to accept a lower event-free survival (EFS) rate of 75% to 90% (87% vs. 63%; $P = 0.002$), rather than 95% to 100% (Fig. 1).

Hematology providers considering referral may also weigh the likelihood of an actual HSCT stemming from the referral, along with the potential barriers. Among providers who had referred patients for evaluation, 75% had 1 patient undergo HSCT. Providers most consistently identified the major barriers to transplant referral as the risk of mortality or lack of sibling match. Practitioners most commonly identified the most significant barrier for *families* as the risk of mortality, followed by concerns about transplant-related medical complications.

Provider Referral History and Enthusiasm for HSCT: Logistic Regression

We asked which provider characteristics were associated with a history of any referral for transplant evaluation, and whether those same factors were associated with provider enthusiasm for the procedure. By univariate logistic regression analysis, provider age, sex, years after completion of training, profession type, types of board certification, and practice center type were neither associated with ever having made a transplant referral, nor was highly rating a family request for transplant. In contrast, providers identifying “chronic transfusion therapy” as an indication for referral were significantly more likely to have

referred a patient for evaluation (odds ratio 19.4; 95% confidence interval [CI], 2.4–158; $P = 0.006$), compared with those who had not referred a patient. For the 79% who had expressed enthusiasm for HSCT for pediatric SCD, these same factors were examined by univariate logistic regression analysis. Here too, only providers selecting “chronic transfusion therapy” as a qualifying characteristic yielded a significantly higher likelihood of enthusiasm (odds ratio 3.4; 95% CI, 1.1–10; $P = 0.029$), compared with the other providers.

In response to questions about the potential utility of clinical guidelines and more research, respondents consistently identified their desire for guidelines from their professional society and for additional outcomes research to support increasing referral of children with SCD for transplant evaluation.

DISCUSSION

As more children with SCD undergo transplantation and EFS are improving,^{1,6,14,17} their hematology providers increasingly may consider this option for long-term health. Understanding providers’ recent referrals and perspectives on indications for referral based on perceived outcomes, risks, patient eligibility, and alternatives are important for treatment planning. To our knowledge, this is the first report on this topic for pediatric hematology providers, albeit a convenience sample that was limited to the Northeast US. Many centers in the Northeast performed HSCT for children with SCD, such that half of respondents primarily worked at a transplant site. We describe characteristics of those enthusiastic for HSCT referral and those who referred children for evaluation, and compared respondents by whether their primary practice site was a transplant center.

Overall, most respondents viewed HSCT as a therapeutic option for qualified patients and supported an increase in referrals for evaluation. Respondents in the 2 provider groups shared many of the perspectives on acceptable OS and on the appropriate demographic and clinical indications for referral, similar to current transplant standards.^{1,17} After accounting for their larger patient populations, providers at nontransplant centers had comparable numbers of referrals to those at transplant centers. The major difference was that a higher rate of EFS was deemed as acceptable, reflecting a higher outcome standard in that group. Despite similarly favorable OS rates,^{1,17} overall a large portion of providers preferred transplant for β -thalassemia over SCD. Our findings suggest mixed provider perspectives about referral for HSCT for pediatric SCD, irrespective of type of practice site. In general, those who had completed their specialty training within the past 2 decades were more likely to recently have referred at least 1 patient for evaluation but were only modestly more enthusiastic about referring a patient for evaluation. The majority of respondents reported limited eligibility for referral to children with severe clinical disease and only certain sickle types. Nonetheless, many respondents favored transplant evaluation for some patients, even if lacking a sibling donor. Such patients were those experiencing multiple disease complications, and those on chronic transfusion therapy.

The majority of providers sampled indicated that multiple complications and/or central nervous system involvement were strong indications for transplant referral, comparable to with current standards for HSCT.^{1,17} Overlapping clinical conditions may complicate the

interpretation of how single indications would influence a referral to transplant. For example, a child with a stroke likely will be on chronic transfusion therapy. Some transplant experts consider as eligible for transplant those patients with matched sibling donors and stroke, multiple acute chest syndromes, frequent pain crises, elevated transcranial Doppler or red cell alloimmunization.^{16–17} As HLA-matched related donors may not be available, many of these clinical indications form the basis of the ongoing BMT CTN 0601 trial using unrelated donors for patients with SCD²² and BMT CTN 0603 utilizing related haploidentical donors.²³ In contrast, the hematology providers surveyed varied in their support of transplant for indications other than stroke, consistent with their heterogeneous perspectives. Patient perspectives may also be evolving.^{24–26}

Overall, there was tepid enthusiasm for referring patients with limited disease complications for HSCT despite an available matched sibling donor. In a French report of HSCT using a matched sibling donor, a subset of patients (14/50) had been clinically asymptomatic.⁹ Event-free and OS of that subgroup were higher than those with symptomatic disease. Although needing replication, those findings suggest a possible lower transplant risk for asymptomatic patients with matched sibling donors.

Impact of other therapies for SCD also influenced indications for transplant referral among those surveyed. Chronic transfusion therapy was strongly associated with provider referral and enthusiasm for transplant evaluation. Effects from hydroxyurea initiated in childhood on disease morbidity in adults are not yet available, precluding direct comparisons of long-term treatment outcomes to those of transplant. Interestingly, only a small proportion identified noncompliance as an indication. Our survey suggests that concerns about transplant-related mortality, infertility and graft-versus-host disease remain the primary barriers for providers. In contrast, surveys of adolescents with SCD and/or their parents reported that some would be willing to accept these risks if transplant offered a cure.^{24–27}

Limitations of our survey include the Northeastern US regional focus of our sampling frame, comprising 2 of the 7 federally defined regions covering maternal-child genetic services. Although these primary SCD providers collectively care for a large proportion of children with SCD in the United States, our results may not be generalizable to other regions, especially where there are fewer transplant centers. Nonetheless, sampling based on geography rather than affiliation with a professional organization may have reduced bias. Actual referrals and provider demographics could not be verified in this anonymous survey, nor could referral outcomes. Despite the large number of sites surveyed and the wide range of responses obtained, bias may have been introduced by using a nonrandom sample with multiple responders from single sites. Bias may also have been introduced through the higher proportion of respondents at transplant sites (43% of all those emailed vs. 53% of respondents). The response rate is consistent with results of other published physician surveys²⁸ and may have been underestimated because of possible inaccuracies in email addresses or recent personnel changes. Provider demographics, perspectives, or practice patterns of respondents may have differed from those of nonresponders^{28–30} but were not discernible.³¹ Nonetheless, survey response rates and the general homogeneity of our respondents in professional and educational background may have reduced the likelihood of nonresponse bias.^{29,32–34}

This survey did not explore potential influences on provider perspectives such as knowledge about specific HSCT procedures or current outcomes, why many providers preferred transplantation of β -thalassemia, perspectives on HSCT for adults with SCD, views of transplant experts and families,^{24–25} perceived influence of payer mixes, or other patient demographics. For example, preference for β -thalassemia may reflect perceived differences in transplant outcomes, donor availability, or disease course. Such queries could be informative for further health services research. Transplant teams may also consider factors not assessed here for making decisions to offer transplantation to patients, such as the resources available to families for decision making and patient factors such as medication adherence, social support systems, and reluctance to participate in clinical trials involving transplantation.³⁵

Benefits of transplant must be weighed taking into account the short-term and long-term complications and the risk of mortality. The initiation of hematology referrals may be facilitated by the formulation of national professional guidelines regarding HSCT. Although only a small proportion of children referred for evaluation actually undergo the procedure because of the lack of a suitable donor, contraindication, or family decision,^{24–26} the pediatric hematology provider is a critical conduit for ushering families to transplant evaluation to expand treatment options. Varied provider perspectives may affect patient referral for the procedure and the potential for access to this treatment option.

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Outcomes Deemed Acceptable for Transplant Referral

Figure 1.

Acceptable outcomes for transplant referral. Most providers considered appropriate overall survival (OS) rates of 90% or 95%. Providers at transplant centers more commonly accepted lower event-free survival (EFS) for referring patients ($P = 0.002$).

TABLE 1

Demographics of Respondents

	At Transplant Center [*]	Not At Transplant Center [*]
	N=55 % (n)	N=49 % (n)
Age (y)		
20–39	23 (10)	10 (4)
40–49	25 (11)	30 (11)
50–59	34 (15)	30 (11)
60	18 (8)	30 (11)
Sex		
Female	59 (26)	55 (20)
Years since training		
0–10	32 (14)	18 (7)
11–20	25 (11)	29 (11)
21	43 (19)	53 (20)
Professional degree ^{**}		
MD	82 (36)	100 (37)
NP	18 (8)	0
Sickle cell clinic size ^{***}		
0–100	11 (6)	49 (24)
100–300	40 (22)	35 (17)
>300	49 (27)	16 (8)

* Not all providers responded to all questions, so N may vary for some questions.

** P -value <0.005.

*** P -value <0.001.

TABLE 2

Indications for Referral for Transplant Evaluation: Patient Demographics

	% (n)			<i>P</i>
	Respondents [*] N=101	At Transplant Center N=55	Not At Transplant Center N=46	
Comparability to β -thalassemia				0.509
Less likely to refer for sickle cell disease	44 (44)	38 (21)	50 (23)	
As likely to refer for sickle cell disease	38 (38)	38 (21)	37 (17)	
More likely to refer for sickle cell disease	13 (13)	16 (9)	9 (4)	
Uncertain	6 (6)	7 (4)	4 (2)	
Hemoglobinopathy	N=99	N=53	N=46	0.362
Hb SS only	11 (11)	11 (6)	11 (5)	
Hb SS and Hb S/ β^0 -thalassemia	66 (65)	62 (33)	70 (32)	
Hb SS, Hb S/ β^0 -thalassemia, Hb SC	7 (7)	11 (6)	1 (2)	
Any Sickle variant	16 (16)	15 (8)	17 (5)	
Optimal age of patients	N=99	N=53	N=46	
<3 y	46 (46)	47 (25)	46 (21)	0.880
3–5 y	75 (74)	75 (40)	74 (34)	0.860
6–16 y	93 (92)	100 (53)	85 (39)	0.004
>16 y	60 (59)	66 (35)	52 (24)	0.161

* Not all providers responded to all questions, so the overall N may vary between questions.
Hb SS indicates hemoglobin SS.

TABLE 3

Clinical Indications for Referral for Transplant Evaluation

	% (n)			<i>P</i>
	Respondents* N=90	At a Transplant Center N=47	Not At Transplant Center N=43	
Clinical complications [†]				
Clinical stroke	76 (68)	72 (34)	79 (34)	0.458
New stroke despite transfusion therapy	82 (76)	82 (40)	82 (36)	0.982
Family request	53 (48)	45 (21)	63 (27)	0.085
History of acute chest	42 (38)	43 (20)	42 (18)	0.947
Pulmonary hypertension	36 (32)	38 (18)	33 (14)	0.570
Silent stroke	34 (31)	38 (18)	30 (13)	0.421
>3 painful crises per year	33 (30)	36 (17)	30 (13)	0.551
Multisystem organ failure	32 (29)	30 (14)	35 (15)	0.605
Abnormal transcranial Doppler	31 (28)	30 (14)	33 (14)	0.777
Previous treatments	N=93	N=49	N=44	
Hydroxyurea nonresponsiveness	71 (66)	67 (33)	75 (33)	0.417
Hydroxyurea noncompliance	12 (11)	10 (5)	14 (6)	0.609
Chronic transfusion therapy	66 (61)	67 (33)	64 (28)	0.707
Iron overload	22 (20)	18 (9)	25 (11)	0.437
Donor and disease considerations	N=94	N=50	N=44	
Matched sibling and multiple/severe SCD complications	95 (89)	96 (48)	93 (41)	0.545
Matched sibling and limited SCD complications	37 (35)	42 (21)	32 (14)	0.308
No matched sibling and multiple SCD complications	66 (62)	72 (36)	59 (26)	0.188

* Not all providers responded to all questions, so the overall N may vary between questions.

[†] Additional indications asked about; listed are responses with >30% support.
SCD indicates sickle cell disease.