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Disparity in the management of iron overload between patients with sickle cell disease and thalassemia who received transfusions

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Abstract

BACKGROUND—Transfusion therapy is frequently used to prevent morbidity in sickle cell disease (SCD), and subsequent iron overload is common. The objective of this study was to evaluate the current standard of care in monitoring iron overload and related complications in patients with SCD compared to thalassemia (Thal).

STUDY DESIGN AND METHODS—A cross-sectional study was conducted at 31 hematology clinics in the United States, Canada, or the United Kingdom. Patients who received transfusions with a mean serum ferritin level of least 2000 ng per mL were eligible. A total of 199 patients with SCD (113 female; 24.9 ± 13.2 years) and 142 with Thal (66 female; 25.8 ± 8.1 years) were recruited, and data were collected between 2001 and 2003 by interview and medical record review.

RESULTS—Although both groups were recruited on the basis of significant iron overload, the likelihood of performing a liver biopsy for routine iron monitoring was significantly higher (odds ratio [OR], 3.4; 95% confidence interval [CI], 2.2–5.3) in Thal than SCD. Thal patients were also more likely to be screened for iron-related organ injury including an echocardiograph for cardiomyopathy (OR, 2.6; $p < 0.001$; 95% CI, 1.6–4.2), alanine aminotransferase for liver function (OR, 8.3; CI, 1.05–64.4), and thyroid-stimulating hormone for hypothyroidism (OR, 12.3; CI, 7.0–21.5). For adult SCD patients, those maintained on simple transfusion with a serum ferritin level of greater than 2500 ng per mL were the least likely to have a liver biopsy ($p < 0.03$).

CONCLUSIONS—These data highlight the unsystematic monitoring of iron and related organ injury in SCD. Until the relationship between iron and related comorbidities is better understood, routine monitoring of iron overload in SCD patients who receive transfusions should be considered a standard part of clinical care.

Chronic red blood cell (RBC) transfusion has been used for decades to prevent the classical bone changes and life-threatening anemia in patients with homozygous β -thalassemia (Thal).¹ More recently, transfusion therapy has also been used to minimize disease-specific morbidity in patients with sickle cell disease (SCD).^{2,3} Long-term transfusion therapy without adequate chelation, however, results in iron overload–associated organ failure.^{4–7} Consensus documents have been developed for patients with Thal^{8–10} and adopted for use in SCD,^{11,12} to provide clinicians guidance in the monitoring and treatment of chronically transfused patients. Quantitative iron assessment by percutaneous liver biopsy, the most viable clinical option at the time of this study, was recommended to be performed every 2 years, in addition to quarterly assessment of serum ferritin. Details for annual monitoring of cardiac, endocrine, and hepatic function were also provided. In 2002, the National Institutes of Health (NIH) released a consensus document for the care of patients with SCD receiving transfusion therapy.¹³ The document summarized that “there is no evidence that SCD patients are spared the fatal consequences of iron overload. Therefore a comprehensive program to monitor and treat iron overload is necessary.” To date, there have been no studies directly comparing the adequacy of care provided in these two similarly transfused patient populations.

Disparity in the delivery of health care has gained attention over the past decade.^{14–16} In its report of racial and ethnic disparities in health care, the Institute of Medicine (IOM) concluded that there were significant disparities in the quality and quantity of health care received by minority groups in the United States.¹⁷ In 1994, the Sickle Cell Treatment Act was passed designed to improve funding and resources for specialized SCD centers. Despite significant advances in the treatment of SCD, a 2006 report suggests that major funding gaps remain when support is compared between patients with SCD and cystic fibrosis, a chronic disease affecting far fewer Americans who are primarily Caucasian.¹⁸ This report highlights federal and philanthropic research support; however, the quality of clinical care provided is undoubtedly impacted. Although solutions remain elusive, it is clear that health care disparity is a complex issue that cannot be explained solely on the basis of research support, a patient’s race, socioeconomic status, access to health care, behavior, or physician knowledge or pre-paredness. The objective of this article is to evaluate the adequacy in the assessment of iron overload and management of iron-related organ toxicity in two similarly transfused but distinct patient groups.

MATERIALS AND METHODS

The Multi-Center Study of Iron Overload was a natural history comparative study of adolescents and adults with transfusional iron overload and Thal or SCD. Patients were recruited from 31 clinical hematologic centers in the United States, Canada, and the United Kingdom. Before study initiation, a meeting was held with study investigators to review the study protocol, chart abstraction, and interview techniques. The protocol and consenting

documents were developed at the coordinating center (CHRCO) and full institutional approval was obtained at each participating center. Informed written consent was obtained from all patients and/or parents for patients less than 18 years of age, and assent was obtained from child participants in accordance with each institution's policy. After enrollment, each subject's medical history was reviewed, and subject interview and medical record review were performed on an annual basis as described previously.¹⁹ Data from the 12-month period preceding the baseline visit are the primary focus of this report.

Patients

Patients maintained on transfusion therapy either currently, or previously, who were 12 years of age or older, with Thal (β - or E- β -Thal) or SCD (Hb SS-type or Hb S β^0 -Thal) were screened at each center for eligibility between April 2001 and 2003. Chronic transfusion was defined as at least eight times per year or one transfusion at least every 7 weeks. Eligibility was initially based on a liver iron concentration of at least 10 mg per g dry weight by percutaneous biopsy within 2 years of screening. For many patients, biopsy was not available; therefore, those maintained on simple RBC transfusions with three serum ferritin values within the previous 12 months, which averaged at least 2000 ng per mL were also eligible.

Procedures

Only anthropometric and pubertal development data were directly assessed in the patients. No specific laboratory or clinical procedures performed in the patients were required by the study, and results were collected only if completed as part of standard clinical care. The subject interview questionnaire included sections on demographics, medical and surgical history, recent hospitalizations, fracture history, and medication history. Race was defined by the subject and reported according to US Census 2000 definitions. The medical record review included documentation of transfusion and chelation history, recent laboratory values, and specific procedures (when available): echocardiograph (ECHO), electrocardiogram, liver biopsy for iron quantitation, and bone densitometry. The three most recent pretransfusion serum ferritin values obtained within 12 months of the baseline visit were also collected. Liver biopsy results were collected if they were performed within 2 years of the baseline assessment. For patients who had more than one liver biopsy within this time period, the most recent biopsy was used for analysis. Mean yearly transfusion volume was determined by a calculation of mean transfusion frequency (e.g., every 3 weeks) $\times$ mean volume per transfusion (e.g., 500 mL). Although there may be significant variability in unit volume depending on how it is prepared for transfusion, for purposes of this report, 1 unit of RBCs was assumed to be 250 mL. For patients who received transfusion every 4 to 6 weeks, a mean of every 5 weeks was used for the calculation. At the time of this study, the participating centers were almost exclusively using leukodepleted blood products. Both filtration (leukodepletion) and washing of units may have effects on the amount of iron within a unit of RBCs. Unfortunately, details regarding the type of blood transfused were not collected at baseline for each subject and therefore were not included in these volume calculations.

To explore center specific differences in the management of iron overload, hematology centers within the United States were categorized according to type: those which were part of an NIH-funded Sickle Cell Center Grant or part of the NIH-funded Thalassemia Clinical Research Network were categorized as “research-type centers” and all others were categorized as “clinical-type centers.” There were two international centers located in the United Kingdom (London) and Canada (Toronto), which recruited a total of 82 patients; the London site only enrolled patients with Thal.

Statistical analysis

Data were analyzed using computer software (STATA version 9.0, Stata Corp., College Station, TX). Differences in continuous variables between groups (Thal vs. SCD) were analyzed by Student’s t test. For categorical outcomes, differences between groups were analyzed using Pearson chi-squared tests. Fisher’s exact tests were used when expected cell counts are low. The ferritin data were skewed and therefore log-transformed before performing statistical tests. Logistic regression techniques were used to develop models to describe variables related to performance of liver biopsy and management of iron-related organ dysfunction. Only variables that yielded p values of less than 0.1 in univariate analyses were entered into the models. Descriptive data were presented as percentages or mean $\pm$ standard deviation (SD). Significance was defined as a p value of less than 0.05.

RESULTS

A total of 352 patients were initially eligible and enrolled, including 149 with Thal and 203 with SCD. Within this original group, there were a total of 11 sibling pairs enrolled: 7 pairs in the Thal group and 4 pairs in the SCD group. Given that siblings are likely to have the same health insurance and hematologists, and may have similar opinions regarding assessments and treatments, the potential for interdependence within a sibling pair for many of the outcome variables presented was considerable. Therefore, the youngest subject within each pair was dropped from the analysis resulting in a total of 341 patients: 142 with Thal (76 male; 25.8 ± 8.1 years) and 199 with SCD (86 male; 24.9 ± 13.2 years). A total of 46.9 percent of the total sample were not more than 21 years at study entry. There were proportionally more adults in the Thal group (67.6%) versus SCD group (42.7%, $p < 0.001$). As reported previously,¹⁹ the groups were racially distinct: 92.0 percent of the SCD group were black and the remainder categorized themselves as other or mixed race, whereas the Thal group was 35.2 percent white, 26.1 percent Asian, 23.9 percent Middle Eastern, 7 percent black, and 7.8 percent other.

Transfusion therapy

The majority (89.7%) of patients were currently on a chronic transfusion regimen, although all enrolled patients had received some transfusion therapy in the past (Table 1). Transfusion was initiated at an earlier age for patients with Thal compared to those with SCD ($p < 0.001$),¹⁸ whereas SCD patients started chelation therapy slightly sooner after transfusion initiation (4.1 ± 5.0 years after) than patients with Thal (5.5 ± 5.3 years; $p = 0.04$). Thirty-three of the iron-overloaded SCD patients had never received chelation therapy, in contrast to one Thal subject. These SCD patients naïve to chelation therapy were older than those

who had received chelation (38.8 ± 14.7 years vs. 22.2 ± 11.0 years); however, there was no difference with regard to the duration of transfusion therapy (naïve 9.5 ± 10.4 vs. chelated 10.0 ± 6.8 years), nor the average serum ferritin (naïve 3361 ± 1302 µg/L vs. chelated 4533 ± 3236 µg/L; $p = 0.11$). Additionally, none of the SCD patients who were naïve to chelation therapy were currently maintained on exchange transfusion. The most frequently utilized chelation therapy was deferoxamine; only 6 patients, all with a Thal diagnosis, were maintained on oral chelators alone (deferiprone or deferasirox).

As expected given the recruitment criteria, indices of iron storage were elevated in both Thal and SCD patients: 65.0 percent of Thal and 75.5 percent of SCD patients had mean serum ferritin values of more than 2500 ng per mL. No relationship was observed between transfusion duration and serum ferritin or liver iron concentration.

Management of iron overload

Subjects within this study received transfusions on average 13.3 ± 5.0 times per year. Owing to the risk for transfusion-related iron toxicity, patients were routinely assessed for iron load and screened for iron-related organ injury; however, the frequencies of these assessments varied considerably between and within subject groupings (Table 2). Subjects with Thal had a 3.4 times higher odds of receiving a liver biopsy within the previous 2 years compared to SCD patients ($p < 0.001$; 95% confidence interval [CI], 2.2–5.3). Pediatric and adult patients with Thal were equally likely to have received a liver biopsy, whereas adults with SCD had far fewer biopsies compared to adolescent SCD patients ($p = 0.001$). Thal patients were also more likely to have received routine monitoring for cardiac dysfunction (ECHO exam odds ratio [OR], 2.6; 95% CI, 1.6–4.2), liver abnormalities (alanine aminotransferase [ALT] OR, 8.3; 95% CI, 1.05–64.4), hypothyroidism (thyroid-stimulating hormone [TSH] OR, 12.3; 95% CI, 7.0–21.5), and osteoporosis (dual-energy x-ray absorptiometry [DXA] OR, 36.7; 95% CI, 19.2–70.0; Table 2). The only routine clinical tests for which no differences were observed between Thal and SCD were for serum ferritin, blood glucose, and hepatitis C virus (HCV) antibody. Given that serum ferritin was used as primary study entry criterion for many subjects, it was not assessed further.

Some centers may delay performing some of these monitoring procedures until patients have had significant iron exposure, therefore, these comparative analyses were repeated for patients who had been chronically transfused for at least 5 years ($n = 155$ SCD and $n = 135$ Thal). In this subgroup, patients with Thal remained more likely to have had a liver biopsy ($p < 0.001$; OR, 3.38; 95% CI, 2.15–5.31), an ECHO examination (OR, 3.10; 95% CI, 1.9–5.2), an ALT level (OR, 10.2; 95% CI, 1.3–80.3), and monitoring for hypothyroidism (TSH OR, 14.9; 95% CI, 8.2–27.1). Similar to the larger group, there were no differences between Thal and SCD patients in the likelihood of monitoring blood glucose.

These same comparative analyses were then performed in patients who were cared for at 8 of the 31 hematology centers in this study that routinely treat both Thal and SCD patients who received transfusions ($n = 248$). For these patients, ECHOs were performed on a similar percentage of SCD and Thal patients (63.9% vs. 70.3%, respectively). Additionally, glucose was assessed in a similar proportion of SCD and Thal patients (60.7% vs. 61.0%, respectively); however, the differences observed in the monitoring of iron overload by

biopsy, and the assessment of thyroid function and osteoporosis remained significant in this smaller cohort of patients.

For patients with SCD, the likelihood of receiving a liver biopsy was related to the age of the subject, his or her serum ferritin level, the age at which he or she began transfusion, and transfusion type (Table 3). Whether or not a subject had a liver biopsy was not, however, related to gender, years of transfusion, or chelation therapy. For the Thal group, there was no difference in any of the factors noted above in the likelihood of receiving a biopsy.

Finally, center-specific differences in the performance of liver biopsy were also explored. No differences were observed between those subjects with SCD who were cared for primarily at a research-type versus clinical-type hematology center.

DISCUSSION

This study is unique in that it is the first to compare a large group of transfusional iron-overloaded SCD and Thal patients. These two groups of patients have distinct genetics and racial profiles; however, chronic transfusion regimens are similar. One of the most striking observations in this study was the significant difference in monitoring between these two groups of transfused patients. Although both groups were recruited on the basis of significant iron overload, patients with Thal were more likely to have routine iron assessments and screening for iron-related organ injury such as diabetes, cardiac, endocrine, and hepatic disease. Close to two-thirds of the patients with Thal had a biopsy to assess liver iron concentration within 2 years of the baseline examination. During this same time interval, only 37 percent of the SCD patients had a biopsy, a percentage that dropped to less than one-quarter when adult patients were analyzed separately. These discrepancies in monitoring between-subject diagnoses remained apparent when the analyses were limited to patients who had received at least 5 years of chronic transfusion therapy or who were cared for primarily at a research-type versus a clinical-type institution.

For patients with SCD, there were some data that indicated that a liver biopsy was performed on patients perceived to be at greater risk of iron overload, such as those who began transfusion therapy at an earlier age and, therefore, were theoretically at greater risk for iron overload, due to the length of time on transfusion. Counter to this hypothesis, however, adult patients with SCD, those maintained on simple transfusion therapy, or those with a serum ferritin level of greater than 2500 ng per mL were least likely to have a biopsy for iron assessment. Neither duration of transfusion or chelation therapy had any relationship to whether or not a biopsy was performed. Additionally, those patients who were maintained on simple transfusion were less likely to receive a biopsy compared to those on exchange transfusion, a finding that could not be explained by age differences or severity of iron overload. This unsystematic monitoring was not apparent in the Thal patients.

The only similarities in clinical assessment between groups was monitoring of serum ferritin, glucose, and hepatitis serology testing. Given that serum ferritin was used as one of the entry criteria, it was expected that we found the majority of patients with at least one serum ferritin test within the 12 months preceding enrollment. Although serum ferritin is

frequently used to monitor iron burden in patients who received transfusions, it has been shown repeatedly that a single serum ferritin value is an unreliable predictor of whole-body iron stores.^{20–22} A second quantitative assessment of iron load is particularly important in SCD patients, because serum ferritin is an acute-phase reactant and, therefore, highly variable in diseases with chronic inflammation, such as SCD.²³ Liver iron concentration assessed either by biopsy or via noninvasive measures such as superconducting quantum interference device (or liver biosusceptometry) or quantitative magnetic resonance imaging techniques^{24,25} remain the optimal tools for monitoring iron load. Although noninvasive measures for hepatic iron assessment are becoming more available, at the time of this data collection (2001–2003), access to these devices at the participating centers was quite limited and therefore not a viable clinical option for most patients.

Published guidelines for monitoring patients who receive chronic transfusion are available for patients with Thal^{8–10,26} and more recently for SCD;^{11,12,13} however, for hematologists who specialize in SCD, patients who receive transfusions typically constitute approximately 10 percent of their entire clinic population. The primary focus for these patients continues to be acute and chronic pain management.²⁷ The lack of easily available material to guide hematologists in the care of these unique patients may contribute to the differences in iron monitoring. Additionally, the paucity of clinical studies focused on iron overload in iron-related organ injury in SCD patients provides little evidence to support the importance of similar monitoring.

The progression of iron loading in SCD patients may also contribute to the disparity between SCD and Thal in terms of the vigilance of monitoring for iron overload and subsequent organ toxicity. Given that, in adult patients with SCD, iron overload may result not only from prescribed, physician-monitored, chronic transfusion therapy, but also from the cumulative lifetime effects of potentially unindicated, episodic transfusions that patients receive in community hospitals perhaps unfamiliar with the treatment of SCD. Transfusion therapy is the greatest contributor to iron overload in SCD; each unit of blood supplies roughly 200 mg of iron so that a regularly transfused adult patient accumulates 20–30 mg per day from transfusion. Normal dietary iron absorption of about 1 mg per day is not characteristically increased in SCD so that dietary iron absorption is matched by insensible losses. Hereditary hemochromatosis is quite rare²⁸ and there are no reports of iron-overload in patients with SCD who did not receive transfusions. By contrast, iron absorption is on average three times that of healthy controls in anemic patients with Thal syndromes.²⁹ Increased iron absorption in Thal is most likely due to ineffective erythropoiesis leading to inhibition of hepcidin synthesis in the liver.³⁰ Given this, even patients with Thal who did not receive transfusions should be monitored on a regular basis and treated when necessary to avoid iron-related organ dysfunction (Table 4).

Regardless of cause, iron overload is pervasive in patients with SCD who received transfusion. In transfusional iron overload, the majority of excess iron is stored in the liver but iron distribution to tissues that possess uptake mechanisms for plasma non-transferrin-bound iron, such as the myocardium, is known to occur.³¹ While the frequency of cardiac dysfunction from myocardial iron overload in SCD is less well defined than in thalassemia major, myocardial iron loading has been noted at postmortem in multiply transfused SCD

patients³² and overt cardiac failure has been observed in iron-overloaded SCD patients. Although iron-associated endocrinopathy is rare in transfused patients with SCD,⁷ there is a growing body of evidence that suggests the role of iron in other comorbidities of SCD including pulmonary hypertension and cirrhosis.^{33,34} Until the relationship between iron and these or other comorbidities is better understood, routine monitoring of iron overload in these patients should be considered a standard part of their clinical care.

Other factors may also influence the decision regarding iron risk assessment. For a subject residing in the United States, insurance coverage could be a limiting factor. Subject responsibility and choice must also be considered, particularly with regard to the liver biopsy procedure. Missed appointments and noncompliance are common in patients with chronic illness, likely related to understanding of the disease and its consequences, family stresses, and perceived satisfaction with personal health.^{35,36} Additionally, the perceived importance of the procedure by either the practitioner or the patient likely plays a significant role. Patients with SCD have far more acute and unpredictable clinical crises compared to patients with Thal; therefore, iron risk assessment is not perceived as having high priority in clinical care management. Finally, the availability of treatment options may also contribute to the iron risk assessment decision process. At the time of this report, subcutaneous chelation therapy was the only therapeutic option for patients residing in the United States. Clinicians deciding between the effects of iron overload versus painful and/or expensive diagnostic procedures and therapy might well opt to minimize intervention altogether in poorly compliant, underinsured patients who do not advocate strongly. Deferasirox, a recently approved oral chelation therapy in the United States, has been shown to be effective in Thal and SCD.^{37,38} Although side effects such as gastrointestinal disturbances, skin rash, and mild increases in serum creatinine are not uncommon,³⁹ this new oral treatment option may improve adherence and perhaps overall care^{40,41} (Table 5).

Patients with Thal major begin transfusion therapy within the first few months to years of life, due to severe anemia, significant ineffective erythropoiesis, and the desire to prevent long-term orthopedic deformities, whereas patients with SCD typically begin transfusion therapy somewhat later, primarily to reduce stroke risk. In this study on average, patients with Thal began transfusion at 4 years of age, whereas SCD patients began at 13 years. Despite the longer estimated duration of transfusion in the Thal patients, a similar degree of iron burden was observed and thus potential for iron-related comorbidities. Guidelines available for transfused patients with Thal are primarily focused on iron-related organ dysfunction, and thus comprehensive management is imperative, whereas guidelines prepared for patients with SCD who receive transfusions have been mainly concerned with the provision of transfusion therapy itself and less about the resulting iron overload. Routine, quantitative assessment of iron in the body is stressed, but little attention is directed at comprehensive care management. It is suggested that patients with SCD who receive transfusions would benefit from a team approach, similar to that seen at many comprehensive thalassemia centers in the United States and abroad, where patients meet with gastroenterologists, endocrinologists, nutritionists, psychologists, and social workers in addition to their primary hematologist.

One limitation of this study is that we did not collect information related to insurance coverage, which does have racial and regional differences. Approximately 15 percent of Americans have no health insurance, and various government agencies provide health insurance to more than 29 percent of Americans. It has been noted that patients residing in the west and south of the United States are more likely to be uninsured, which could have a significant impact on access to adequate care.⁴² Additionally, only those procedures that were conducted within the 12 to 24 months before the patient visit were recorded, and all visits were conducted before the initiation of the oral chelator studies in the United States. This time frame may have led to a conservative estimate of monitoring, but is unlikely to have resulted in the discrepancies between patient groups. Furthermore, when data from subsequent years of this study are assessed, the discrepancies observed between Thal and SCD remain surprisingly different. For example, in the 3 years following the baseline assessment, on average 15.3 percent of SCD patients had a liver biopsy to assess iron load compared to 38.0 percent of Thal patients, and 42 percent of SCD patients had an ECHO examination compared to 60.1 percent of Thal patients.

In conclusion, these data suggest that, despite both groups of patients exhibiting heavy total body iron burden, patients with Thal are monitored on a more frequent basis for iron-related organ damage compared to SCD patients. The reasons for these discrepancies are multifactorial and likely include a lack of supporting clinical evidence of iron-related disease and efficacy of monitoring in SCD, a paucity of readily available disease-specific clinical guidelines for physicians, limited treatment options for iron overload, subject nonadherence both to the assessment procedures and to chelation therapy, and specifically for US-residing patients, limited access to financial reimbursement for clinical services. What is clear from these preliminary baseline data is that the disparity in the care of SCD patients who receive transfusions requires further study and that guidelines for the assessment of this select group of patients should be supported by existing evidence and expert opinion, until the full effect of iron overload in this population is better understood.

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Appendix

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ABBREVIATIONS

DXA	dual-energy x-ray absorptiometry
ECHO(s)	echocardiograph(s)
SCD	sickle cell disease

Thal	thalassemia
TSH	thyroid-stimulating hormone

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TABLE 1

Transfusion and chelation characteristics among iron overloaded Thal and SCD patients

Characteristic (unit)	Thal (n = 142)	SCD (n = 199)	p Value [*]
Transfusion type ^{†‡}	Simple, 121 (95.3%); exchange, 6 (4.7%); both, 0	Simple, 133 (73.3%); exchange, 47 (25.7%); both, 2 (1.1%)	
Volume transfused (mL/kg/yr) ^{§¶}	181.2 (82.1)	149.7 (78.0)	0.002
Pediatrics [¶]	200.2 (93.7)	172.6 (74.2)	0.071
Adults [¶]	170.8 (73.6)	104.5 (64.9)	<0.001
Currently chelated [‡]	131 (92.3)	140 (70.7)	<0.001
Never chelated [‡]	1 (0.7)	33 (16.6)	<0.001
Chelation type (%) ^{//}	SubQ (77.1) IV (16.0) Both (2.3) Oral (4.6)	SubQ (74.2) IV (19.7) Both (6.1) Oral (—)	NS

^{*} p Values for differences between groups are based on Pearson's chi-square tests for categorical variables or two-sided Student's t tests for continuous variables.

[†] Transfusion type: exchange transfusion includes subjects who received transfusion by manual apheresis.

[‡] Data are reported as number (%).

[§] Volume transfused: mean volume of RBCs transfused in mL per kg per year. One unit of RBCs was considered to be 250 mL, regardless of hematocrit content.

[¶] Data are reported as mean (SD).

^{//} Chelation type: SubQ = subcutaneous; IV = intravenous; both = combination of both SubQ and IV.

TABLE 2

Performance of the assessment of iron stores and iron overload–related comorbidities among patients with Thal or SCD*

Assessment	Thal (n = 142)	SCD (n = 199)	p Value [†]
Body iron stores assessment			
Liver iron concentration, biopsy performed [‡]	94/142 (66.2)	73/199 (36.7)	<0.001
LIC performed, pediatrics	32/46 (69.6)	53/114 (46.5)	0.008
LIC performed, adults	62/96 (64.6)	20/85 (23.5) [¶]	<0.001
Cardiac function [§]			
ECHO performed	103/137 (75.2)	106/197 (53.8)	<0.001
ECHO in pediatrics	34/44 (79.3)	61/113 (54.0)	0.007
ECHO in adults	69/93 (74.2)	45/84 (53.6)	0.004
Electrocardiogram (EKG) performed	81/135 (60.0)	79/192 (41.2)	0.001
Endocrine functions [§]			
Bone density examination for osteoporosis	73/137 (53.3)	13/192 (6.8)	<0.001
Bone density performed, pediatrics	19/46 (41.3)	5/111 (4.5)	<0.001
Bone density performed, adults	54/91 (59.3) [¶]	8/81 (9.9)	<0.001
Thyroid stimulating hormone assessed	122/142 (85.9)	66/199 (33.2)	<0.001
Fasting glucose assessed ^{//}	67/130 (51.5)	85/196 (43.4)	NS
Glucose assessed, pediatrics	31/44 (70.5)	42/113 (37.2)	<0.001
Glucose assessed, adults	36/86 (41.9) [¶]	43/83 (51.8)	NS
Liver function [§]			
ALT assessed	141/142 (99.3)	188/199 (94.5)	0.017
Hepatitis C antibody testing performed ^{**}	108/140 (77.1)	145/186 (78.0)	NS

* Data are presented as the number of patients with the noted assessment divided by the number of total patients for whom data are available (percentage of patients).

[†] p Values are determined using Pearson chi-square tests.

[‡] LIC = liver iron concentration: assessment defined as any liver biopsy recorded within 2 years of baseline data collection.

[§] Cardiac (ECHO/EKG), endocrine, and liver function tests were collected if performed within previous 12 months of data collection. ALT was collected if performed within previous 6 months of data collection.

[¶] Significantly differed from pediatric patients within the same group (LIC, p = 0.001; DXA, p = 0.046; glucose, p = 0.002).

^{//} Fasting glucose only in those patients who were not already diagnosed with diabetes.

^{**} Assessment for either HCV antibody or HCV RNA by polymerase chain reaction (PCR) within the previous 12 months.

NS = not significant.

TABLE 3

Factors related to performance of liver biopsy: unadjusted relationships for patients with SCD only who received transfusions

Patients with SCD who received transfusions	Liver biopsy (n = 73)	No biopsy (n = 126)	p Value *
Sex (male) [†]	33/73 (45.2)	53/126 (42.1)	NS [‡]
Age group (adults) [†]	20/73 (27.4)	65/126 (51.6)	0.001 [‡]
Transfusion type (simple) [†]	40/65 (61.5)	97/120 (80.8)	0.004 [‡]
High serum ferritin (> 2500 ng/mL) [†]	47/71 (66.2)	98/121 (81.0)	0.02 [‡]
Age (years) [§]	20.0 (9.0)	27.7 (14.4)	<0.001 [¶]
Average age of transfusion initiation (years) [§]	9.9 (7.1)	15.5 (14.6)	0.004 [¶]
Transfusion duration (years) [§]	9.6 (6.0)	10.1 (8.0)	NS [¶]
Chelation duration (years) [§]	5.5 (4.1)	6.4 (6.0)	NS [¶]
Average serum ferritin (ng/mL) [§]	4306 (3226)	4367 (2934)	NS [¶]

* There were no significant differences in any of these variables in the patients with Thal with and without liver biopsy assessment.

[†] Data are reported as number (%).

[‡] Chi-square p value.

[§] Data are reported as mean (SD).

[¶] Student's t test p value.

TABLE 4

Recommendations for monitoring of iron overload–associated toxicity in patients with Thal and SCD on chronic transfusion therapy^{8–13}

Clinical assessments/tools	Suggested frequency*
Quantitative iron assessment	
Serum ferritin	Quarterly (monthly when on chelation therapy)
Hepatic iron assessment by quantitative MRI, SQUID, or liver biopsy [†]	Annually
Cardiac evaluation	
ECHO [‡] (>10 years)	Annually
Electrocardiogram	Annually
Cardiac iron assessment by MRI-T2 ^{*§}	Annually after 10 years' chronic transfusion
Endocrine function//	
Bone health	
Bone densitometry by DXA (>10 years)	Every 1–2 years
Diabetes	
Fasting blood glucose	Annually
Gonadal function (>10 years)	
Luteinizing and follicle-stimulating hormones	Annually
Testosterone (males)	Annually
Estradiol (females)	Annually
Growth, pubertal development	
Height, weight, and Tanner staging	Twice a year until Tanner 5
Insulinlike growth factor-1	Annually until mature height
Thyroid and parathyroid function (>6 years)	
TSH, free T4, parathyroid hormone	Annually
Liver function	
ALT, aspartate aminotransferase	Quarterly (monthly when on chelation therapy)
Hepatitis serology [¶]	Annually
Ophthalmology and audiology examinations	Annually
Transfusion and chelation monitoring ^{**}	Annually

* Most assessments should begin in patients within 1 year of chronic transfusion initiation unless specified. The frequency of testing is recommended for regularly transfused patients; however, they may also be performed as clinically indicated. Assessment by subspecialties (cardiology, endocrinology, hepatology) with some knowledge of the pathophysiology of Thal and SCD is assumed.

[†] Quantitative iron assessment by magnetic resonance imaging (MRI) or superconducting quantum interference device (SQUID) should begin 1 year after chronic transfusion therapy initiation or by age 4 in patients who begin transfusion therapy in infancy. Liver biopsy should be considered if evidence of hepatitis or when noninvasive techniques are not available.

[‡] Echocardiograms should include left ventricular ejection fraction, shortening fraction, and tricuspid jet velocity to assess pulmonary hypertension.

[§] Cardiac iron loading in SCD appears to be a late and inconsistent feature; nevertheless, periodic evaluation is recommended.

// Endocrine assessments in SCD, particularly gonadal function, may be performed as clinically indicated.

[¶]Hepatitis serology should include hepatitis B surface antibody (indicates immunity and does not require repeat after positive confirmation), hepatitis B surface antigen (does not require repeating after hepatitis B virus surface antibody confirmed), HCV antibody screen (HCV RNA by PCR if antibody positive), and human immunodeficiency virus testing.

^{**}Transfusion monitoring should include number of RBC units received, transfusion frequency, complications, and pretransfusion hemoglobin. Chelation monitoring should include effectiveness of chelation regimen, dose, and frequency as well as assessment of adherence.

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TABLE 5

Recommendations for chelation treatment of iron overload in chronically transfused patients with SCD

<i>Chelation initiation:</i>				
Age	>2 years of age*			
Timing	>1 year after the start of chronic transfusion therapy (may be later in patients on exchange transfusion)			
<i>Available chelators:</i>				
Chelator	Brand name	Administration	Dose	Licensed availability†
Deferoxamine	Desferal	IV or SubQ infusion 5×/week	20–40 mg/kg children 40–60 mg/kg adults/day	USA, Canada, Europe
Deferasirox	Exjade	Oral 1×/day	20–30 mg/kg/day	USA, Canada, Europe
Deferiprone	Ferriprox (L1)	Oral 3×/day	75 mg/kg/day	Europe
(with or without deferoxamine if poor control)				
<i>Chelation goals:</i>				
Ferritin <2500 ng/L and as close to 1000 ng/L as possible (normal values <300 ng/L)				
Liver iron concentration 3.0 to 6.0 mg/g dry weight				
Cardiac iron by T2* MRI normal values >20 ms (high risk if 8 ms, increased risk if <20 ms)				
<i>Additional chelator-specific toxicity monitoring:</i>				
Deferoxamine	Growth and skeletal development (>40 mg/kg/day may inhibit growth and induce bone changes)			
Deferasirox	Monthly creatinine (excess dosing associated with increased creatinine) Monthly liver function tests (occasional increases may require interruption)			
Deferiprone	Weekly complete blood counts (neutropenia and/or aganulocytosis in 1%–4%) Monthly liver function tests (occasional increases in first year of therapy sufficient to require interruption of therapy)			

* Only deferoxamine and deferasirox are licensed for children 2 to 6 years of age. Most patients with SCD do not initiate chronic transfusion therapy in infancy; therefore, timing of chelation initiation should include duration of transfusion therapy.

[†] Also generally licensed in South America, the Middle East, and Asia.