Complications of β-thalassemia major in North America

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for the Thalassemia Clinical Research Network *

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ABSTRACT

Treatment of patients with beta thalassemia major has improved dramatically during the past 40 years; however, the current clinical status of these patients remains poorly characterized. We performed a cross-sectional study of 342 patients in the Registry of the NIH-sponsored Thalassemia Clinical Research Network. Evidence of hepatitis C exposure was present in 35% of tested patients, was associated with age, and had a rate of spontaneous viral clearance of 33%. Ferritin levels ranged from 147 to 11,010 ng/mL (median 1696 ng/mL). Median hepatic iron content was 7.8 mg/g dry wt and 23% had values ≥ 15 mg/g dry wt. No patients 15 years or younger and 5% of patients 16-24 years had heart disease requiring medication. Ten percent had cirrhosis on biopsy. Endocrinologic complications were common among adults. Seventy-four (22%) patients had recent implantable central venous access devices (CVAD). Among 80 episodes of bacteremia in 38 patients, 90% were attributable to CVAD. Among 330 patients who had received deferoxamine chelation therapy, 224 (68%) reported no complications. We conclude that Hepatitis C, iron-related organ dysfunction and complications of iron chelation are strongly age-dependent in North American β-thalassemia patients.
INTRODUCTION

To assess the present clinical status of North American patients with transfusion dependent thalassemia major, to define the complications that appear in this group of complex patients and to lay the groundwork for future clinical trials, the Thalassemia Clinical Research Network of the National Heart, Lung and Blood Institute created a registry. This includes relevant data on more than 700 patients, 342 of whom have severe transfusion dependent beta-thalassemia. This is the largest group of North American patients with this disease ever assembled. Among transfusion-dependent patients with beta thalassemia, a wide spectrum of complications arise from obligatory lifelong transfusions of packed red blood cells. These include blood-borne infections, iron overload, toxicities of iron chelation, and bacterial infections.\textsuperscript{1-4} While the clinical management of thalassemia has changed dramatically, the results of these changes, as reflected in the current clinical status of patients in North America, are poorly characterized. In the current study we report on the largest cohort of North American patients to date.
METHODS

The Thalassemia Clinical Research Network (TCRN) is an NIH-funded clinical research network composed of 5 core centers in North America, 13 clinical satellites, and a data-coordinating center [See Appendix 1]. The TCRN developed a registry to characterize demographic and clinical features of North American patients with thalassemia, to highlight areas requiring clinical research, and to identify candidates eligible for clinical research protocols. Only living patients were enrolled into the TCRN Registry. Analysis of the Registry data provides a cross-sectional view of the current state of thalassemia in North America. Registry data were assembled by retrospective chart review and in some instances by patient self-report (e.g., when events occurred at other institutions) using a case report form with 14 sections covering demographic, genetic, infectious, endocrine, cardiac, hepatic, iron-related, and DFO-related complications. Specific questions regarding complications are included in appendix 2.

Current and retrospective data for this report were entered once for each subject during the time period from May 2000 through April 2003. Ages reported here are the ages at Registry enrollment or at the time of particular events in the Registry dataset. Institutional review boards approved the protocol at each site and each subject or a parent or guardian gave informed consent.
**Genotype:** The Registry inquired if alpha and beta globin genotypes were available, and if so, documented the specific alpha and beta alleles. In this retrospective review from more than 40 years of data, many different methods were used. A manuscript describing this is in preparation.

**Definitions:** For the purposes of this report, beta thalassemia major (TM) was defined as homozygous (or compound heterozygous) beta thalassemia requiring eight or more transfusions in the 12 months prior to enrolling in the Registry. Patients with Hb E/beta thalassemia and non-transfused thalassemia variants were excluded from this analysis, as were patients with successful engraftment of transplanted stem cells. By the TCRN definition, patients with beta thalassemia who required fewer than eight transfusions annually are considered to have thalassemia intermedia and are not considered in the present analysis. This included several patients who might otherwise have been considered TM but had suspended regular transfusions prior to enrolling in the Registry (e.g., due to transfusion reactions or use of alternative therapies).

**Data Validation:** Over 80% of all Registry forms have been partially reviewed with sites, targeting data of specific interest, including: diagnoses, genotyping, endocrinopathies, hepatitis C testing, ferritin concentrations, and biopsy results. One hundred percent of the positive diabetes data was validated. Independent source document verification was conducted for selected variables on approximately 20% of Registry forms.
Statistical Methods: Age-trends in incidence rates were tested by Cochran-Armitage trend tests. Associations of categorical variables were tested by Fisher’s exact test. Differences of medians for continuous measures were tested by exact Wilcoxon-Mann-Whitney rank-sum tests. Locally-weighted regressions of proportions of patients with elevated iron stores were fit using generalized additive models for binomial data with a logit link function (S-Plus 6.1). Significance was accepted at alpha = 0.05 for two-tailed tests.

RESULTS

Three hundred forty-two patients with TM were enrolled in the Registry. Seventy-four percent of patients reported beta-globin genotyping. The five most common genotypes, reflecting combinations of three common haplotypes, are shown in Table 1. The median patient age was 20 years (range 1 to 51 years). The pre-transfusion hemoglobin level was maintained between 9 and 11 g/dL in 86% of patients. Additionally, 2% were less than 8 g/dL, 9% were 8-9 g/dL and 3% 11-12g/dL. The proportion below 9 g/dL was not different between main and satellite sites (9.7% vs. 11.5%) or by age. Fifty-five percent of patients had undergone splenectomy at a median age of 9 years (range 1 to 31 years).

Transfusion-transmitted infections

Of 334 patients tested for hepatitis C (HCV), 35% were seropositive or positive for HCV RNA. Laboratory evidence of HCV exposure was significantly associated with age (Table 2), occurring in 5% of patients less than 16 years old,
23% of patients 16 through 24 years old and 70% of patients 25 years or older (p<.001 by Cochran-Armitage trend test). Among patients tested for both HCV antibody and RNA, 26 of 75 seropositive patients (35%) were subsequently HCV RNA negative. This includes 20 of 61 patients (33%) with no report of treatment who apparently cleared virus spontaneously. Three of nine (33%) treated with interferon monotherapy and three of five (60%) treated with interferon and ribavirin had cleared virus. Eight of 311 (2.5%) patients tested for hepatitis B surface antigen were positive. Two percent of TM patients in the Registry were HIV positive.

Iron Overload

Hepatic iron content (HIC), assessed by biopsy (93%) or magnetic susceptibility (7%), and serum ferritin levels were tested within two years of Registry entry in 166 and 330 patients, respectively. Median serum ferritin level was 1710 ng/mL (range 147 to 11,010 ng/mL; Figure 1A). Median HIC was 7.8 mg/g dry weight (range 0.9 to 43 mg/g dry weight; Figure 1B). Twenty-three percent of the patients had HIC greater than or equal to 15 mg/g dry weight (ages 2 to 39 years), a level at which more aggressive chelation has been recommended because of increased risk of morbidity and mortality. Of 35 patients with a report of heart disease, 15 have HIC data within 2 yrs of Registry entry. Two of these 15 patients have HIC ≥ 15 mg/g, the other 13 (87%) have HIC <15 mg/g. There is a suggestion of higher body iron stores in patients from 10 to 25 years of age and lower iron stores in older patients (Figure 2A and 2B).
documents the poor association of ferritin and HIC and total body iron previously reported.\textsuperscript{2,7}

Organ dysfunction due to iron overload was common in young adults with TM (Table 2). Twenty-three percent of patients 25 years or older had heart disease requiring medication. No patients $\leq 15$ years and 5\% of patients 16-24 years were reported to have heart disease requiring medications. Of 232 patients with pathology results from liver biopsy, twenty-four (10\%) had cirrhosis. Of these, 11 (46\%) did not report clinical findings of liver failure or cirrhosis. The prevalence of cirrhosis by biopsy increased significantly with age (Table 2, $p = .03$). Three percent of patients $\leq 15$ years and 6\% of patients 16-24 years had evidence of liver failure or cirrhosis. The range of ferritin and LIC values in this group of patients was 221 ng/mL to 9456 ng/mL and 1.3 mg/g to 36.4 mg/g, respectively. However, these data do not necessarily correspond with the onset of the complication since this is a one-time data collection. Of 130 patients 25 years or older, 17\% were receiving treatment for thyroid disease, 9\% for parathyroid disease, and 21\% for diabetes. Sixty-two percent had received hormone replacement therapy for hypogonadism. Endocrinopathies were approximately half as prevalent among patients 16 through 24 years old as those older than 25 years. No endocrinopathies were reported in patients $\leq 15$ years. There was no influence of gender on prevalence of endocrinopathies. Eleven pregnancies occurred in 8 of 101 female TM patients age 18 years or older (7.9\%). Seven were carried successfully to term. Two miscarriages and two terminations were
reported. Twelve of 94 males age 18 years or older (13%) were reported to have fathered pregnancies.

**Complications of Iron Chelation Therapy**

Among 328 patients who had ever received chelation therapy with deferoxamine (DFO), 105 (32%) reported complications requiring modification of the dose or route of administration of the chelator. Twenty percent of 309 patients using DFO at the time of enrollment in the Registry reported current complications. Table 3 identifies specific complications associated with therapy with DFO and their frequencies. Complications of chelation therapy with DFO were more common in older patients (Table 4; \( p<.001 \) by Cochran-Armitage trend test). Sixty of 129 patients (47%) age 25 years or older ever reported complications versus 16 of 106 (15%) of patients less than 16 years of age.

Twenty patients reported stopping DFO, while 14 young patients had not initiated therapy. Of the 20 who reported stopping DFO, the median age was 26 years after a median of 15 yrs using DFO. Of these patients, 3 (15%) had heart disease when enrolled in the Registry (vs. 10% of DFO users, \( p = 0.46 \)); however, the temporal relationship between cessation of DFO use and the date of development of heart disease is not known. The single-time data collection, precludes knowing with certainty whether the patients stopped DFO temporarily or permanently. By report, 10 patients stopped due to non-compliance, 1 due to possible toxicity and 1 for unknown reason. The other 8 patients discontinued for reasons more likely to be temporary: 1 pregnancy, 1 oncologic surgery, 2
decreased iron stores, and 4 participants in an oral chelator trial. Severe local reactions at infusion sites were associated with stopping DFO. Eight of 28 patients (29%) with past severe local reactions stopped DFO compared with 12 of 299 patients (4%) without significant local reactions (Table 3 p < .001 by Fisher’s exact test). Higher ferritin level within two years of enrollment (median 3026 vs. 1634 ng/mL, p < .001 by exact Wilcoxon-Mann-Whitney rank-sum test), but not HIC, was associated with past history of local reactions (Table 4).

Implantable vascular access devices, used for transfusions or for intravenous DFO infusion, are common among the thalassemia population. Seventy-four (22%) had surgically placed central vascular access devices (CVAD) within five years of Registry entry. Patients using CVADs within five years of enrollment were generally older than those not using CVADs (median age 26 yrs vs. 19 yrs, p = 0.02 by signed rank test). CVAD placement was significantly associated with history of local reactions (Table 3; p < .001 by Fisher’s exact test). Among 80 episodes of sepsis or bacteremia occurring in 38 patients, 90% were attributable to CVAD. Among CVAD-associated infections, Staphylococcal infections predominated, causing 75% of the infections. Stenotrophomonas, Escherichia coli, Candida and Enterococcus each caused 3 to 4% of the infections. Forty-three percent of patients with CVAD developed infections related to the device.
DISCUSSION

We have defined the current status of complications among 342 patients with thalassemia major in North America. Complications can be grouped as (i) transfusion-transmitted infections, (ii) transfusional iron overload, (iii) toxicities of iron chelation therapy and, (iv) bacterial infections. Age is directly related to the prevalence of most of these complications. This paper is the first attempt to compile such data on North American patients. Several of the network sites and satellites are known to be among the largest providers in the US and Canada. It is possible that the data for Registry patients are biased by age or severity, but the magnitude and sign of any bias are unknown.

Transfusion-related infections: Hepatitis C and HIV are no longer major threats in the North American blood supply. However, transfusion-acquired HCV remains one of the most important problems among patients with thalassemia, largely due to transfusions given before 1990. The 33% rate of spontaneous clearance in our patient population is favorable compared to the 10-20% rate reported in the general literature, is also higher than the rate of 25% in patients with hemophilia exposed to blood products and substantially higher than the 0% remission reported in hemophilia patients co-infected with HIV. This clearance is only surpassed by infants with vertically transmitted HCV who demonstrate the highest rate of spontaneous resolution at 75%. A multicenter trial to address the efficacy of current HCV therapy with interferon and ribavirin in this patient population has been initiated. Reports of malaria and West Nile virus in
the US blood supply suggests that blood safety cannot be completely ensured and that despite sensitive and specific testing, transfusion-related infections are still a concern.

*Iron overload—Endocrinopathies:* Hypogonadism, hypothyroidism, diabetes mellitus, low bone mass and hypoparathyroidism\(^5,^{23-27}\) are still common in young adults with thalassemia major. Our data are consistent with the Italian cohort in which no diabetes was reported in the subgroup of patients at the age of 15 years, born between 1980 and 1984.\(^{27}\) Our overall diabetes rate of 10% is higher than their overall reported rate of 5.6% but less than the 20% reported in Brittenham’s cohort of 59 patients, aged 7-31 years.\(^5\) An analysis of low bone mass in thalassemia syndromes using data from the Registry will be reported elsewhere (Manuscript in preparation).

*Iron overload—Heart disease:* Cardiac failure and rhythm disturbances remain the main cause of death among young adults with thalassemia major.\(^2,^{28,29}\) In our cohort, no patients 15 years or younger and 5% of patients 16-24 years had heart disease requiring medication. In an earlier cohort of 1,146 patients born from 1960 through 1987, Borgna-Pignatti and her co-workers found the incidence of heart failure by 15 years of age to be 5% in patients born between 1970 and 1974 and 2% in those born between 1980 and 1984.\(^{27}\) Further, in a cohort of 97 patients born before 1976, 37% had heart disease as defined by need for
inotropic or antiarrhythmic medications. This can be compared to the 23% rate in patients > 25 years of age in the present cohort who were born before 1978.

Hepatic iron concentration greater than 15 mg/g dry weight is considered to be a risk factor for heart disease. Available data support the use of more intensive iron chelation (i.e. higher dose per day or chelation more days per week) for patients with values in excess of this level.

Because the Registry data are not longitudinal, neither changes in dose over time, nor the resulting effects on HIC or heart disease are available. The exact relationship between HIC and heart disease is not well understood. Some patients have heart failure and arrhythmias at HIC substantially less than 15 mg/g dry weight. Conversely, some patients with HIC > 15 mg/g dry weight do not have heart disease. Because the Registry contains data from only one clinical time point, we cannot judge whether historical HIC’s predicted risk of cardiac complications. However, the data from our study show that a single HIC < 15 mg/g dry weight does not preclude the presence of significant iron-induced cardiac disease.

Iron-overload—Liver disease: The Registry findings in regard to liver iron may reflect secular trends in chelation compliance, but other possible contributing factors include: survival bias (the patients with worst iron by age 30 may die and be lost to the dataset; the patients with best iron may preferentially survive) and presence of cirrhosis (less iron per gram of liver if more fibrosis/cirrhosis). In addition, since fewer than 50% of the patients have undergone a liver biopsy
within 2 years of enrollment, this raises the possibility that only the most compliant patients have agreed to this procedure (or the very worst ones who are forced to by their physician). Older patients might be more compliant with their chelation, or might have genetic resistance to iron loading, promoting survival.

Published liver cirrhosis data bound our results. In an Italian cohort of 86 thalassemia major children age 15 years or younger and biopsied between 1976 and 1981, cirrhosis was evident in 19%.31 Among 73 thalassemia major patients from Hong Kong age 1.5 and 22.5 years (mean 11.7 years) and biopsied from 1992 to 1999, none had evidence of cirrhosis and 30% had liver fibrosis.7

DFO complications: The majority of patients receiving DFO had no complications despite the fact that patients must administer the chelator by infusion for decades and at cumulative doses of several kilograms. Sixty-eight percent of all patients and more than 50% of patients 25 years and older have not reported complications of DFO. DFO-related problems are more common in older patients. While this may reflect the fact that younger recipients had less time to develop DFO complications, the alternative and more likely explanation is that clinicians over time have learned to adjust the dose of DFO to prevent dose-related toxicity. Despite the excellent overall tolerability of DFO, some patients have stopped the drug, and those with severe local reactions have poor compliance and are at high risk of iron-related toxicity.
Local reactions to DFO: Local reactions to subcutaneous DFO are common among patients with thalassemia and, as noted above, are a risk factor for cessation of chelation therapy. Pain and erythema at injections sites do not appear to be allergic in nature.

Implantable venous access devices: Our data demonstrate that implantable CVAD are a major cause of bacteremia and risk of sepsis in this patient population. CVAD are commonly placed in younger patients for reliable transfusion access, and in older patients to allow 24-hour chelation for heart disease, or because of severe local reactions to DFO. Some limitations are inherent in this retrospective dataset. First, the cross-sectional methodology across a wide age range establishes a survival bias. For example, patients who previously succumbed to infections or to iron-induced heart disease are not part of the Registry and therefore are not included in this report. Second, age-related complications are confounded by advances in therapy and diagnostics. For example, very few young patients are infected with hepatitis C not only because they are young, but because of the advent of hepatitis C screening in 1990. Similarly, patients over age thirty-five precede the deferoxamine treatment era, and it is possible that this contributes to their iron-related complications. Third, the cross-sectional methodology does not allow an evaluation of the clinical response to abnormal laboratory studies, particularly elevated hepatic iron concentration. For example, high liver iron concentrations
usually prompt more intensive iron chelation therapy. Fourth, patient self-report (when data were not available at the network center) may be biased, but the direction and magnitude of this bias are indeterminate. Finally, not every patient underwent every study. Therefore, a potential for selection bias exists. This may be most problematic for liver biopsies. Ascertainment of serious cardiac or endocrine abnormalities is less likely to be incomplete. With these limitations in mind, the present data still demonstrate a high prevalence of complications, some improvement when compared to older cohorts in the DFO era, and the need for further improvement in the management of these complex patients.

Improvements over the last 15 years include, blood screening for HCV, individualization of DFO dosing and less aggressive hypertransfusion (pretransfusion Hb 9-11 g/dL rather than 10-12 g/dL). Treatment of this profound disorder has also greatly improved in other ways during the last four decades. In the 1960’s most neonates with this disorder were infrequently transfused and destined to develop severe deformities and growth retardation followed by the lethal consequences of iron overload. Their life expectancy was less than 20 years. Today, as consequences of improved red cell transfusion schedules and the safe and effective use of subcutaneous DFO, children with thalassemia avoid serious deformities and have an improved life expectancy. But compliance is a problem in any disease that requires life long treatment, and subcutaneous DFO delivered by pump is not an easy therapeutic program with which to comply. Furthermore, complications in addition to iron overload, such as
blood borne infections, may arise from obligatory life-long transfusions of red blood cells. Differences between the current study and previous studies in regard to patient populations, definition of specific complications and types of analyses make comparisons of outcomes inexact. However, the present data suggest that some age-related complications may now occur less frequently in younger patients with thalassemia major.

Acknowledgement

The authors thank Drs. Nancy Oiivieri and David Nathan for critical comments on the manuscript.
Figures and Legends:

**Table 1: Genotypes for beta-thalassemia major patients (of 254 with beta-globin genotyping)**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codon 39 (C-&gt;T) β^0 / IVS-I-110 (G-&gt;A) β^+</td>
<td>29 (11.4%)</td>
</tr>
<tr>
<td>IVS-I-110 (G-&gt;A) β^+ / IVS-I-110 (G-&gt;A) β^+</td>
<td>26 (10.2%)</td>
</tr>
<tr>
<td>Codon 39 (C-&gt;T) β^0 / Codon 39 (C-&gt;T) β^0</td>
<td>15 (5.9%)</td>
</tr>
<tr>
<td>Codon 39 (C-&gt;T) β^0 / IVS-I-6 (T-&gt;C) β^+</td>
<td>12 (4.7%)</td>
</tr>
<tr>
<td>IVS-I-6 (T-&gt;C) β^+ / IVS-I-110 (G-&gt;A) β^+</td>
<td>11 (4.3%)</td>
</tr>
</tbody>
</table>

These represent the five most common genotypes.
Table 2: Complications of thalassemia major by age group

<table>
<thead>
<tr>
<th>Age</th>
<th>0-15 years</th>
<th>16-24 years</th>
<th>25+ years</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infectious complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis C exposure (Ab+ or RNA+)</td>
<td>5% (6/115)</td>
<td>23% (21/91)</td>
<td>70% (90/128)</td>
<td>35% (117/334)</td>
</tr>
<tr>
<td>Chronic Hepatitis C (Ab+ and RNA+)(^1)</td>
<td>100% (3/3)</td>
<td>56% (9/16)</td>
<td>66% (37/56)</td>
<td>65% (49/75)</td>
</tr>
<tr>
<td>Spontaneous Clearance (Ab+ and RNA neg)(^2)</td>
<td>0% (0/3)</td>
<td>43% (6/14)</td>
<td>32% (14/44)</td>
<td>33% (20/61)</td>
</tr>
<tr>
<td><strong>Heart Disease Requiring Medication</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Disease Requiring Medication</td>
<td>0% (0/120)</td>
<td>5% (5/93)</td>
<td>23% (30/128)</td>
<td>10% (35/341)</td>
</tr>
<tr>
<td><strong>Cirrhosis by biopsy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis by biopsy</td>
<td>4% (3/70)</td>
<td>10% (6/62)</td>
<td>15% (15/100)</td>
<td>10% (24/232)</td>
</tr>
<tr>
<td><strong>Liver failure/cirrhosis by clinical findings</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver failure/cirrhosis by clinical findings</td>
<td>0% (0/119)</td>
<td>5% (5/93)</td>
<td>6% (8/125)</td>
<td>4% (13/337)</td>
</tr>
<tr>
<td><strong>Endocrine disorders</strong></td>
<td>(n=120)</td>
<td>(n=93)</td>
<td>(n=129)</td>
<td>(n=342)</td>
</tr>
<tr>
<td>Thyroid Disease</td>
<td>0%</td>
<td>8%</td>
<td>17%</td>
<td>9%</td>
</tr>
<tr>
<td>Hypoparathyroidism</td>
<td>0%</td>
<td>1%</td>
<td>9%</td>
<td>4%</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>0%</td>
<td>9%</td>
<td>21%</td>
<td>10%</td>
</tr>
<tr>
<td>Hypogonadism Requiring Meds</td>
<td>0%</td>
<td>41%</td>
<td>62%</td>
<td>35%</td>
</tr>
<tr>
<td>&gt; 0 endocrinopathies</td>
<td>0%</td>
<td>45%</td>
<td>67%</td>
<td>38%</td>
</tr>
<tr>
<td>&gt; 1 endocrinopathy</td>
<td>0%</td>
<td>10%</td>
<td>27%</td>
<td>13%</td>
</tr>
<tr>
<td>&gt; 2 endocrinopathies</td>
<td>0%</td>
<td>3%</td>
<td>12%</td>
<td>6%</td>
</tr>
<tr>
<td>&gt; 3 endocrinopathies</td>
<td>0%</td>
<td>0%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>DFO complications</strong></td>
<td>(n=106)</td>
<td>(n=93)</td>
<td>(n=129)</td>
<td>(n=328)</td>
</tr>
<tr>
<td>Ever experienced</td>
<td>15%</td>
<td>31%</td>
<td>47%</td>
<td>32%</td>
</tr>
<tr>
<td>Currently experiencing</td>
<td>5%</td>
<td>22%</td>
<td>33%</td>
<td>20%</td>
</tr>
</tbody>
</table>

In this cross sectional methodology, not every patient is screened for every test. The denominator represents the number tested. Evidence of Hepatitis C by liver biopsy was not queried by the database.

\(^1\) These results reflect the subset of patients (n = 75) with a positive test for anti-HCV antibodies and a concurrent or subsequent positive HCV RNA assay.

\(^2\) These results reflect the subset of patients (n = 61) with a positive test for anti-HCV antibodies and a concurrent or subsequent negative HCV RNA assay who have never been treated for hepatitis C.
Table 3: DFO Complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>N (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High frequency hearing loss</td>
<td>59 (18%)</td>
</tr>
<tr>
<td>Vision/Retinal</td>
<td>19 (6%)</td>
</tr>
<tr>
<td>Allergy</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Other *</td>
<td>33 (10%)</td>
</tr>
</tbody>
</table>

**Severe Local Reactions**

- Stopped DFO (%): 28 (9% Yes, 299 (91%) No, P-value <.001
- Median Ferritin (ng/mL): 8 (29%) 12 (4%)
- Median HIC (mg/g dry wt liver): 9.8, 7.8, 0.27
- CVAD Placement (%): 16 (56%) 57 (19%), P-value <.001

*Among the ‘other’ category were six patients in whom poor growth was attributed to DFO therapy, four with gastrointestinal symptoms, three with Yersinia infections, and two each with tinnitus, metaphysial dysplasia, and renal complications (failure and calculus).

Table 4: Association between age and DFO complications

<table>
<thead>
<tr>
<th>AGE</th>
<th>0-15 years (n=106)</th>
<th>16-24 years (n=93)</th>
<th>25+ years (n=129)</th>
<th>Overall (n=328)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DFO complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever experienced</td>
<td>15%</td>
<td>31%</td>
<td>47%</td>
<td>32%</td>
</tr>
<tr>
<td>Currently experiencing</td>
<td>5%</td>
<td>22%</td>
<td>33%</td>
<td>20%</td>
</tr>
</tbody>
</table>

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FIGURE 1. Iron overload in TM patients.

Ferritin and hepatic iron concentration are shown as a function of age. Filled circles indicate patients with cirrhosis. No patients less than 13 years of age who had liver biopsy had evidence of cirrhosis. HIC and ferritin values are on a log scale.

A. Serum ferritin levels within two years of Registry entry are shown for 330 TM patients. Values greater than 2,500 ng/ml (shown by the dashed line) are associated with higher risk of long-term cardiac morbidity and mortality.2

B. Hepatic iron concentration by biopsy (93%) or magnetic susceptibility (7%) was performed within two years of Registry entry for 166 TM patients. The dashed horizontal at 15 mg/g dry wt is discussed in the text.
Figure 2: Measurements of Iron Overload

A

B

Fig 2. Proportion of patients with elevated iron stores estimated by locally-weighted regression versus age. Dotted lines are ±2 SE. A. Proportion of patients with ferritin >2500 ng/mL (p = 0.05 for dependence on age). B. Proportion with HIC >15 mg/g (p = 0.10 for dependence on age).
Figure 3: LIC vs. Ferritin

Fig 3. Scatterplot of HIC and serum ferritin concentrations measured within 180 days of each other (n = 85) with dotted lines at HIC = 15 mg/g and ferritin = 2500 ng/mL. The $r^2$ value is 0.19 ($p < .001$).
Reference List


20. Sibbald B. Canada will check donor blood for West Nile virus if test available. CMAJ. 2003;168:207.


Appendix I:

The following institutions and researchers contributed to the Thalassemia Clinical Research Network Registry data reported in this paper:

**Toronto General Hospital, Toronto, Canada (62 subjects)**

- Nancy F. Olivieri, MD, Principal Investigator
- Filip Kotynia, Study Coordinator
- Giulia M. Muraca, Study Coordinator

Satellites:
- Hospital for Sick Children (58 subjects)
  - Sergio Muraca, Study Coordinator
  - Chelsea M. Taylor, Study Coordinator

**The Children's Hospital of Philadelphia (37 subjects)**

- Alan Cohen, MD, Principal Investigator
- Janet Kwiatkowski, MD, Co-Investigator
- Catherine Manno, MD, Co-Investigator
- Marie Martin, RN, Co-Investigator
- Debbie Hillman, Study coordinator

Satellites:
- St. Christopher’s Children’s Hospital (2 subjects)
  - Maureen Rockstein, Study Coordinator
- Children’s Memorial Hospital, Chicago, IL (21 subjects)
  - Alexia Thompson, MD, Principal Investigator
  - Dena Haddad, Study Coordinator

**Weill Medical College of Cornell University (57 subjects)**

- Patricia Giardina, MD, Principal Investigator
- Robert Grady, MD, Co-Investigator
- Karen Autio, Study Coordinator

Satellites:
- Columbia Presbyterian Medical Center (7 subjects)
  - Sergio Piomelli, MD, Principal Investigator
  - Sujit Sheth, MD, Co-Investigator
  - Dawn Haughey, Study Coordinator
- Schneider Children’s Hospital (5 subjects)
  - Carole Paley, MD, Principal Investigator
  - Eva Atsidaftos, Study Coordinator
- New York Methodist Hospital (1 subject)
  - Rita Bellvue, MD, Principal Investigator
- Long Island College Hospital (18 subjects)
  - Jolantha Kulpa, MD, Principal Investigator
- Hackensack University Medical Center (2 subjects)
Frances Flug, MD, Principal Investigator
Cheryl Falls, Study Coordinator

Winthrop University Hospital (2 subjects)
Mark Weinblatt, MD, Principal Investigator

**Children's Hospital at Oakland (26 subjects)**
Elliott Vichinsky, MD, Principal Investigator
Dru Foote, NP, Research Nurse
Sandie Edwards, Study Coordinator
Satellites:
Children’s Hospital of Los Angeles (10 subjects)
Thomas Coates, MD, Principal Investigator
Susan Carson, Study Coordinator
University of California San Francisco (9 subjects)
Bill Menzer, MD, Principal Investigator
Laura Quill, Study Coordinator

**Children’s Hospital, Boston (25 subjects)**
Ellis Neufeld, MD, PhD, Principal Investigator
Melody J. Cunningham, MD, Co-Investigator
Eric Nisbet-Brown, MD, Co-Investigator
Jennifer Braunstein, NP, Research Nurse
Eileen Irish, NP, Research Nurse

Network Steering and Publications Committee Chair, David Nathan, MD
NHLBI oversight, Charles Peterson, MD.
Data Coordinating Center: New England Research Institutes (Libby Wright, PhD)
Appendix 2:

<table>
<thead>
<tr>
<th>Complication</th>
<th>Registry Questions/specifs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Disease</td>
<td>Does the patient have heart disease requiring medications?</td>
</tr>
<tr>
<td>Liver Disease:</td>
<td>Does the patient have clinical findings of liver failure or cirrhosis?</td>
</tr>
<tr>
<td></td>
<td>Has the patient ever had a liver biopsy?</td>
</tr>
<tr>
<td></td>
<td>Cirrhosis by biopsy-yes/no?</td>
</tr>
<tr>
<td></td>
<td>The Registry recorded evidence of cirrhosis on liver biopsy but not specific data regarding active hepatitis C by biopsy, nor was the indication for biopsy recorded.</td>
</tr>
<tr>
<td>Endocrinopathies</td>
<td>Has the patient ever been on sex hormone replacement therapy for hypogonadism?</td>
</tr>
<tr>
<td></td>
<td>Does the patient have thyroid disease requiring treatment?</td>
</tr>
<tr>
<td></td>
<td>Does the patient have parathyroid disease requiring treatment?</td>
</tr>
<tr>
<td></td>
<td>Does the patient have diabetes requiring any of the following: Oral hypoglycemic agents and/or insulin?</td>
</tr>
<tr>
<td>DFO complications</td>
<td>Has the patient had any of the following considered to be related to DFO treatment, requiring adjustment of DFO dose or implementation of a different regimen of DFO or desensitization?</td>
</tr>
<tr>
<td></td>
<td>Following that question on the registry intake form was a yes/no past/present table for the each of the complications listed in table 3.</td>
</tr>
</tbody>
</table>
Complications of β-thalassemia major in North America

Melody J Cunningham, Eric A Macklin, Ellis J Neufeld and Alan R Cohen

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