Effective Iron Chelation Practice for Patients With β-Thalassemia Major

Susan M. Carson, RN, MSN, CPNP, and Marie B. Martin, RN

Chronic blood transfusion is the only treatment for severe anemia in patients with β-thalassemia major. However, red blood cell transfusions lead to iron overload and subsequent organ damage because of the toxic effects of iron. The heart is particularly vulnerable to iron toxicity, and heart failure is the leading cause of death among these patients. Iron chelation therapy prevents or reverses iron loading, thereby reducing the risk of complications from excess iron. Serum ferritin and liver iron concentration often are used to gauge the risk of organ iron overload, but these measurements may not correlate well with cardiac iron load. Magnetic resonance imaging (MRI) is a noninvasive diagnostic tool that can provide a more direct measure of iron concentration in both the heart and liver. Cardiac iron determined by MRI is expressed as a function of T2*, in which higher values represent lower concentrations. Changes in T2* are used to assess the effectiveness of iron chelation and to adjust therapy. Early treatment and compliance are keys to successful therapy. Nursing strategies to optimize chelation therapy include identifying patients who are at risk for developing organ damage, developing chelation plans, promoting compliance, and educating patients. The efficacy and safety of iron chelators, as well as nursing best practices, are reviewed.

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halassemia is an inherited disorder characterized by the inability or reduced ability to produce adult hemoglobin (Hb). The various thalassemias are named according to the subunit of the Hb molecule, or globin chain, affected by a genetic defect. Thus, α-thalassemia is named for altered α-globin production and β-thalassemia for altered β-globin production (Cunningham, 2008).

β-thalassemia major is caused by the inheritance of two β-thalassemia alleles, resulting in reduced synthesis of Hb (Hoffman et al., 2008). The disorder has a prevalence of about 1,000 cases in the United States (Centers for Disease Control and Prevention, n.d.). The symptoms of β-thalassemia major appear at age 4–6 months of life, coinciding with the replacement of fetal Hb by adult Hb, which requires β-globin chains (Hoffman et al., 2008). The disease causes clinically severe anemia, as opposed to β-thalassemia intermedia or thalassemia minor, which are less severe diseases.

β-thalassemia major requires lifelong blood transfusions and likely is fatal in early childhood if untreated; however, treated patients who also remain compliant with chelation therapy can approach normal life expectancy (Cunningham, 2008). Thalassemia is detected in newborn screening, and the thalassemia clinical team is able to determine exactly when to begin chronic red blood cell transfusions. The requirement for chronic transfusion places patients at risk for organ damage from iron overload, a predictable and preventable side effect of transfusion. Each unit of blood contains 200–250 mg of iron, yet the human body has no mechanism for excreting excess iron (Andrews, 1999). Therefore, the heavy iron influx from transfusion leads to rapid iron loading of vital tissues. The liver is one of the major storage sites for excess iron (Kohgo, Ikuta, Ohtake, Torimoto, & Kato, 2008). However, in the presence of a large excess iron pool, the pituitary gland, pancreas, and heart also store iron (Kohgo et al., 2008). With iron accumulation, the
fraction of free iron in these tissues increases, causing damage to cells within these organs (Kohgo et al., 2008).

Cardiac toxicity from iron overload is the leading cause of death in patients with β-thalassemia major (Borgna-Pignatti et al., 2004). However, adequate chelation therapy has been shown to increase survival (Gabutti & Piga, 1996). A retrospective study by Olivieri et al. (1994) showed that the chance of being cardiac disease-free after 10 years depended on maintaining serum ferritin levels less than 2,500 ng/ml. Similarly, a more recent study showed that patients with serum ferritin levels greater than 1,000 ng/ml were at 2.6 times increased risk of early death (Borgna-Pignatti et al., 2004). However, caveats apply. Studies have shown disparity between measures of cardiac and of total body iron load (e.g., serum ferritin, liver iron concentration [LIC]), suggesting that the heart is susceptible to iron loading despite other indicators of good control (Aessopos et al., 2007; Anderson et al., 2001, 2006; Kolnagou, Economides, Eracleous, & Kontogiorghes, 2006; Tanner et al., 2006; Wood, 2007; Wood, Tyszka, Carson, Nelson, & Coates, 2004). Those studies emphasized the importance of adequate chelation and adherence to therapy to minimize the risks of iron overload.

The primary goals of iron chelation therapy are preventing iron overload and minimizing organ damage in patients with iron overload. Prevention should be emphasized because it may take years of good adherence with chelation therapy to reverse cardiac iron loading (Davis, O’Sullivan, Jarritt, & Porter, 2004). Because clinical symptoms lag far behind organ damage (Ault & Jones, 2009), it is critical that nurses understand the pathophysiology of iron accumulation, how to identify patients at risk, and how to optimize chelation therapy. The current article reviews the outcomes of chelation therapy studies measuring cardiac iron in patients with β-thalassemia major and nurses’ role in effective chelation practice.

Iron Physiology and Pathophysiology

Dietary iron is absorbed from the gut and circulates in the blood bound to the protein transferrin (Andrews, 1999) (see Figure 1). Transferrin-bound iron is transported into cells and stored in the protein ferritin. Each ferritin protein shell holds up to 4,500 iron ions for release when the body requires more iron, such as in red blood cell production (Kohgo et al., 2008). Trace amounts of ferritin can be found in the blood and is known as serum ferritin. The level of serum ferritin is an indirect indicator of total body iron stores because additional ferritin is synthesized when excess iron accumulates in cells (Kohgo et al., 2008).

Non-transferrin bound iron (NTBI) is a toxic form of iron found in the blood when all available transferrin is saturated (Kohgo et al., 2008). This toxic iron is readily absorbed by organs, where it converts hydrogen peroxide to free radical ions, which damage cell membranes, proteins, and DNA (Andrews, 1999; Wood, Enriquez, Ghugre, Otto-Duessel, et al., 2005). That damage can play a role in the development of heart failure, cirrhosis, diabetes, and other endocrine diseases (Borgna-Pignatti et al., 2004).

Note. Based on information from Andrews, 1999; Borgna-Pignatti et al., 2004; Fleming & Ponka, 2012.

FIGURE 1. Normal and Pathologic Iron Storage
### TABLE 1. Outcomes in Iron Chelation Trials Measuring Cardiac Iron

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Groups</th>
<th>Groups(a)</th>
<th>Dose</th>
<th>Cardiac Iron Measurements, T2* (ms)(b)</th>
<th>Cardiac Function (LVEF)</th>
<th>Other Iron Measurements(b)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ha et al., 2011</td>
<td>2.5-year observational study</td>
<td>Patients aged 5–34 years with (\beta)-thalassemia major and mild-to-severe cardiac iron who were previously chelated</td>
<td>Deferoxamine (n = 10)</td>
<td>On-study dose: Standard or intense (40–60 mg/kg per day)</td>
<td>Baseline: 35 2.5 years: 31</td>
<td>Baseline: 62.8% 2.5 years: 63.7%</td>
<td>LIC T2*</td>
<td>Baseline: 7 ms 2.5 years: 6 ms</td>
<td>–</td>
</tr>
<tr>
<td>Pathare et al., 2010 (NCT00171171)</td>
<td>18-month extension of ESCALATOR trial</td>
<td>Patients aged 10–29 years with (\beta)-thalassemia major and mild-to-severe cardiac iron who previously failed chelation therapy for intolerance or noncompliance</td>
<td>Deferasirox (n = 19)</td>
<td>On-study dose: 40–60 mg/kg per day + 75–100 mg/kg per day</td>
<td>Baseline: 16 2.5 years: 23</td>
<td>Baseline: 60.6% 2.5 years: 63.8%</td>
<td>LIC T2*</td>
<td>Baseline: 3 ms 2.5 years: 5 ms</td>
<td>–</td>
</tr>
<tr>
<td>Pennell et al., 2006 (NCT00105495)</td>
<td>One-year randomized head-to-head trial</td>
<td>Adults with (\beta)-thalassemia major and mild-to-moderate cardiac iron who were previously chelated</td>
<td>Deferoxamine (n = 32)</td>
<td>On-study dose: 43 mg/kg for 5.7 days per week</td>
<td>Baseline: 13.3 12 months: 15</td>
<td>Baseline: 68% 12 months: +0.5% 12 months: +0.3%</td>
<td>LIC (mg Fe/g dw)</td>
<td>Baseline: 24.2 18 months: 17.6 Ferritin (ng/ml)</td>
<td>Baseline: 5,497 18 months: 4,235</td>
</tr>
<tr>
<td>Pennell et al., 2010 (NCT00171821)</td>
<td>One-year prospective, open-label, multi-center study (subanalysis of EPIC study)</td>
<td>Patients older than 10 years with (\beta)-thalassemia major and normal or mild-to-severe cardiac iron who were previously chelated</td>
<td>Deferasirox for prevention (normal cardiac iron) (n = 78)</td>
<td>On-study dose: 28 mg/kg per day</td>
<td>Baseline: 32 12 months: 32.5</td>
<td>Baseline: 67.7% 12 months: 69.6%</td>
<td>LIC (mg Fe/g dw)</td>
<td>Baseline: 28.8 12 months: 21.6 Ferritin (ng/ml)</td>
<td>Baseline: 4,367 12 months: −1.048</td>
</tr>
</tbody>
</table>

\(a\) Deferiprone is indicated for second-line treatment of transfusional iron overload; deferoxamine is indicated for first-line treatment of chronic iron overload from transfusion dependence; deferasirox is indicated for first-line treatment of chronic iron overload from transfusion dependence.

\(b\) Longer T2* indicates lower iron concentration. Risk stratification: T2* greater than 20 ms indicates relatively normal cardiac iron; T2* from 10–20 ms indicates iron deposition but no immediate risk; T2* less than 10 ms indicates immediate risk of decompensation.

dw—dry weight; EPIC—Evaluation of Patients’ Iron Chelation With Exjade®; Fe—iron; LIC—liver iron concentration; LVEF—left ventricular ejection fraction; ms—milliseconds

(Continued on the next page)
### TABLE 1. Outcomes in Iron Chelation Trials Measuring Cardiac Iron (Continued)

<table>
<thead>
<tr>
<th>Study</th>
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<th>Participants</th>
<th>Groups</th>
<th>Dose</th>
<th>Cardiac Iron Measurements, T2* (ms)b</th>
<th>Cardiac Function (LVEF)</th>
<th>Other Iron Measurementsb</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pennell et al., 2010 (NCT00171821)</td>
<td>One-year prospective, open-label, multicenter study (subanalysis of the EPIC study)</td>
<td>Patients older than 10 years with β-thalassemia major and normal or mild-to-severe cardiac iron who were previously chelated</td>
<td>Deferasirox for iron reduction (mild-to-severe cardiac iron) (n = 114)</td>
<td>On-study dose: 33 mg/kg per day</td>
<td>Baseline: 11.2 12 months: 12.9</td>
<td>Baseline: 67% 12 months: 67%</td>
<td>LIC (mg Fe/g dw) Baseline: 28.2 12 months: 21.4 Ferritin (ng/ml) Baseline: 5,235 12 months: −1,257</td>
<td>–</td>
</tr>
<tr>
<td>Pennell et al., 2011 (NCT00171821)</td>
<td>Two-year extension of EPIC subanalysis</td>
<td>Patients older than 10 years with β-thalassemia major and mild-to-severe cardiac iron who were previously chelated</td>
<td>Deferasirox for iron reduction (mild-to-moderate cardiac iron) (n = 62)</td>
<td>On-study dose: 35.3 mg/kg per day</td>
<td>Baseline: 14.7 Two years: 20.1</td>
<td>Baseline: 68% Two years: 68%</td>
<td>LIC (mg Fe/g dw) Baseline: 28.1 Two years: 15.8 Ferritin (ng/ml) Baseline: 4,893 Two years: 2,565</td>
<td>Significant improvements in T2* were seen at two years in both groups (mild-to-moderate and severe cardiac iron) requiring iron reduction (p &lt; 0.001 for both).</td>
</tr>
<tr>
<td>Pennell, Porter, Cappellini, et al., 2012 (NCT00171821)</td>
<td>Three-year extension of EPIC subanalysis</td>
<td>Patients older than 10 years with β-thalassemia major and mild-to-severe cardiac iron who were previously chelated</td>
<td>Deferasirox for iron reduction (severe cardiac iron) (n = 39)</td>
<td>On-study dose: 37.5 mg/kg per day</td>
<td>Baseline: 7.3 Two years: 8.7</td>
<td>Baseline: 66% Two years: 67%</td>
<td>LIC (mg Fe/g dw) Baseline: 28.4 Two years: 20.9 Ferritin (ng/ml) Baseline: 7,185 Two years: 3,614</td>
<td>–</td>
</tr>
<tr>
<td>Pennell, Porter, Cappellini, et al., 2012 (NCT00171821)</td>
<td>Three-year extension of EPIC subanalysis</td>
<td>Patients older than 10 years with β-thalassemia major and mild-to-severe cardiac iron who were previously chelated</td>
<td>Deferasirox for iron reduction (mild-to-moderate cardiac iron) (n = 47)</td>
<td>On-study dose: 31.9 mg/kg per day</td>
<td>Baseline: 15 Three years: 22.3</td>
<td>Baseline: 68% Three years: 69%</td>
<td>LIC (mg Fe/g dw) Baseline: 27.4 12 months: 15 Ferritin (ng/ml) Baseline: 4,869 12 months: 2,037</td>
<td>Significant improvements in T2* were seen at three years in both groups (mild-to-moderate and severe cardiac iron) requiring iron reduction (p &lt; 0.001 for both).</td>
</tr>
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aDeferiprone is indicated for second-line treatment of transfusional iron overload; deferoxamine is indicated for first-line treatment of chronic iron overload from transfusion dependence; deferasirox is indicated for first-line treatment of chronic iron overload from transfusion dependence.

bLonger T2* indicates lower iron concentration. Risk stratification: T2* greater than 20 ms indicates relatively normal cardiac iron; T2* from 10–20 ms indicates iron deposition but no immediate risk; T2* less than 10 ms indicates immediate risk of decompensation.

dw—dry weight; EPIC—Evaluation of Patients’ Iron Chelation With Exjade®; Fe—iron; LIC—liver iron concentration; LVEF—left ventricular ejection fraction; ms—milliseconds

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<th>Cardiac Function (LVEF)</th>
<th>Other Iron Measurements\b</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pennell, Porter, Piga, et al., 2012</td>
<td>One-year randomized, open-label, multicenter, noninferiority trial</td>
<td>Patients aged 10 years and older with (\beta)-thalassemia major and mild-to-severe cardiac iron who were previously chelated (N = 197)</td>
<td>Deferasirox</td>
<td>On-study dose: 36.7 mg/kg per day</td>
<td>Baseline: 11.4 One year: +12%</td>
<td>Baseline: 67% One year: 66%</td>
<td>LIC Baseine: 29.8 One year: -8.9 Ferritin (ng/ml) Baseline: 5,062</td>
<td>The trial demonstrated noninferiority of deferasirox to deferoxamine for cardiac iron removal, with a trend toward superiority</td>
</tr>
<tr>
<td>--</td>
<td>--</td>
<td>Deferoxamine</td>
<td>On-study dose: 41.5 mg/kg per day for seven days per week</td>
<td>Baseline: 11.4 One year: +7%</td>
<td>Baseline: 66% One year: 66%</td>
<td>LIC Baseine: 30.3 One year: -12.7 Ferritin (ng/ml) Baseline: 4,684</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Tanner et al., 2007 (NCT00103753)</td>
<td>One-year randomized, placebo-controlled, double-blind trial</td>
<td>Adults with (\beta)-thalassemia major and mild-to-moderate cardiac iron who were previously chelated (n = 32)</td>
<td>Deferoxamine + deferiprone</td>
<td>On-study dose: 35 mg/kg per day + 75 mg/kg per day</td>
<td>Baseline: 11.7 Six months: 14.7 12 months: 17.7</td>
<td>Baseline: 66% 12 months: 68%</td>
<td>LIC T2* Baseine: 4.9 ms Six months: 9.5 ms 12 months: 10.7 ms Ferritin (mcg/l) Baseline: 1,574 12 months: 598</td>
<td>Combined treatment group had superior improvement in T2* at study end (p = 0.02).</td>
</tr>
<tr>
<td>--</td>
<td>--</td>
<td>Deferoxamine + placebo (n = 33)</td>
<td>On-study dose: 43 mg/kg per day</td>
<td>Baseline: 12.4 Six months: 14.5 12 months: 15.7</td>
<td>Baseline: 64.7% 12 months: 65.3%</td>
<td>LIC T2* Baseine: 4.2 ms Six months: 4.9 ms 12 months: 5 ms Ferritin (mcg/l) Baseline: 1,379 12 months: 1,146</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Tanner et al., 2008 (NCT00103753)</td>
<td>Subanalysis of one-year trial by Tanner et al. (2007)</td>
<td>Adults with (\beta)-thalassemia major, severe cardiac iron, and left ventricular dysfunction who were previously chelated (n = 15)</td>
<td>Deferoxamine + deferiprone</td>
<td>End-of-study dose: 20 mg/kg for 4.5 days per week + 66 mg/ kg per day</td>
<td>Baseline: 5.7 Six months: 7.1 12 months: 7.9</td>
<td>Baseline: 51.2% 12 months: 65.6%</td>
<td>LIC T2* Baseine: 3.7 ms Six months: 8.8 ms 12 months: 10.8 ms Ferritin (mcg/l) Baseline: 20,571 12 months: 666</td>
<td>T2* improved at study end (p &lt; 0.001).</td>
</tr>
</tbody>
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\a Deferiprone is indicated for second-line treatment of transfusional iron overload; deferoxamine is indicated for first-line treatment of chronic iron overload from transfusion dependence; deferasirox is indicated for first-line treatment of chronic iron overload from transfusion dependence.

\b Longer T2* indicates lower iron concentration. Risk stratification: T2* greater than 20 ms indicates relatively normal cardiac iron; T2* from 10–20 ms indicates iron deposition but no immediate risk; T2* less than 10 ms indicates immediate risk of decompensation.

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<th>Design</th>
<th>Participants</th>
<th>Cardiac Iron Measurements, T2* (ms)</th>
<th>Other Iron Measurements†</th>
<th>Dose</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wood, Kang, et al. (2010) (NCT00447694)</td>
<td>Prospective, open-label, multicenter study</td>
<td>Patients aged 10 years and older with β-thalassemia major and severe cardiac iron who were previously chelated</td>
<td>Baseline: 9.2</td>
<td>LIC (mg Fe/g dry weight)</td>
<td>Deferasirox (n = 27)</td>
<td>T2* improved by 18 months: 10.5 %, 18 months: 62.7%</td>
</tr>
<tr>
<td>Wood, Glynos, et al. (2015) (NCT00447694)</td>
<td>Six-month extension of trial of monthly treatment of patients with β-thalassemia major and severe cardiac iron who were previously chelated</td>
<td>Patients aged 10 years and older with β-thalassemia major and severe cardiac iron with LIC &gt; 50 mg Fe/g dry weight</td>
<td>Baseline: 7.8</td>
<td>LIC (mg Fe/g dry weight)</td>
<td>Deferasirox (n = 10)</td>
<td>T2* improved by 2 years: 10.7 %, 2 years: 63.7%</td>
</tr>
</tbody>
</table>

**Note:** T2* information is reported for first-line treatment of chronic iron overload from transfusion dependence; deferasirox is indicated for chronic iron deposition but no immediate risk; T2* less than 10 ms indicates immediate risk of decompensation and require intense chelation therapy.

### Iron Monitoring

Serum ferritin levels and LIC, measured by biopsy, have been the traditional assessments for cardiac risk from iron loading. Thresholds for the initiation of chelation therapy in patients with β-thalassemia major have been established based on these measurements (Porter, 2001). Because the liver is one of the normal storage sites for iron, its iron uptake is mediated by transferrin.

The heart and endocrine organs also take up transferrin-bound iron under normal conditions. However, during iron overload, they absorb NTBI, which can form anytime transferrin becomes saturated. Therefore, chronically elevated iron levels are not necessary for heart and endocrine organ loading. The ability of organs to take up NTBI whenever available explains why low serum ferritin levels and LIC can be misleading.

Magnetic resonance imaging (MRI) is a noninvasive tool that provides direct determination of cardiac iron load and LIC (Ghugre et al., 2006; Wood, Enriquez, Ghugre, Tyzka, et al., 2005). MRI is based on the transmission of radio waves that excite protons in water molecules. As the protons relax from the excited state, they emit radio waves detected by the MRI scanner, providing information about the microenvironment of tissue including iron concentration. In general, protons in organs relax faster than those in surrounding tissue, and organs appear darker. Organs containing iron darken even faster because iron disrupts the local magnetic field.

T2* is the echo time for tissue to become twice as dark as reference measurements, and is expressed in milliseconds (ms) (Wood, 2011). The inverse of T2* (R2*) provides a signal decay rate that is directly proportional to iron load and is expressed in hertz (Hz) (Wood, 2007). Although not every MRI machine is equipped to measure iron, those with specialized software and calibration can provide accurate measurements (Anderson et al., 2001; Chavhan, Babyn, Thomas, Shroff, & Haacke, 2009).

Typically, T2* information is reported for cardiac iron measurements, and R2* information is reported for LIC. Biopsy studies have shown that MRI data accurately reflect iron content in the human liver and heart. A plot of R2* versus LIC from biopsy showed a linear relationship (Wood, Enriquez, Ghugre, Tyzka, et al., 2005). Linear relationships also have been shown in the heart (Ghugre et al., 2006). Therefore, patients can be risk-stratified by T2* results, in which those with T2* greater than 20 ms have relatively normal cardiac iron levels and are not considered to be at risk, those with T2* from 10–20 ms have iron deposition but are not at immediate risk, and those with T2* less than 10 ms are at immediate risk of decompensation and require intense chelation therapy (Wood, 2007).

MRI studies also have shown that the heart and liver accumulate iron at different rates, which could explain the lack of good correlation between LIC and actual cardiac iron load (Anderson et al., 2004; Wood et al., 2004). That is, a patient with high LIC may not have cardiac iron overload, but is at risk of developing it (Brittenham et al., 1994). The converse is also true in certain circumstances. A patient with cardiac iron overload may not have high LIC if they have been chelated because iron is cleared from the heart more slowly than from the liver (Noetzi, Carson, Nord, Coates, & Wood, 2008). Patients with these disparate patterns of iron loading will require different treatment approaches (Wood, 2007). For example, the patient with high
TABLE 2. Common Adverse Events in Iron Chelation Therapy

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Deferiprone (%)</th>
<th>Deferasirox (%)</th>
<th>Deferoxaminea (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>10.4</td>
<td>21.3</td>
<td>14.1</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>7.5</td>
<td>2.4b</td>
<td>8.4b</td>
</tr>
<tr>
<td>Appetite increased</td>
<td>4</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>ChromaturiaSa</td>
<td>14.6</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>–</td>
<td>11.1</td>
<td>–</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>11.8</td>
<td>7.2</td>
</tr>
<tr>
<td>Nausea</td>
<td>12.6</td>
<td>10.5</td>
<td>4.8</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6.2</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Neutrophil count increased</td>
<td>7.3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Rash</td>
<td>–</td>
<td>8.4</td>
<td>3.1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9.8</td>
<td>10.1</td>
<td>9.7</td>
</tr>
</tbody>
</table>

a Other possible adverse events include systemic allergic reactions, injection site reactions (e.g., localized irritation, pain, burning, swelling, induration, infiltration, pruritus, erythema, wheal formation, eschar, crust, vesicles, local edema), and loss of special senses at high doses or low ferritin levels (high-frequency sensorineural hearing loss and/or tinnitus and visual disturbances: decreased acuity, blurred vision, loss of vision, dyschromatopsia, night blindness, visual field defects, scotoma, retinopathy [pigmentary degeneration], optic neuritis, and cataracts).

b Greater than five times the upper limit of normal at two postbaseline visits

c Deferoxamine may cause rust-colored urine; deferasirox may cause orange-colored urine.

Note. Required monitoring for deferiprone includes weekly absolute neutrophil count, serum ferritin, serum transaminases, and plasma zinc; for deferoxamine, serum ferritin and serum creatinine; and for deferasirox, serum ferritin, serum creatinine, serum transaminases, and bilirubin.


LIC but no cardiac loading will require high-dose chelation to prevent cardiac loading. By contrast, the patient with cardiac iron overload but no liver loading will require continuous low-dose chelation to eliminate NTBI and reverse cardiac loading.

**Chelation Therapy and Cardiac Iron Magnetic Resonance Imaging**

Three iron chelation therapies have been approved: deferoxamine, deferasirox, and deferiprone. Deferoxamine is approved for first-line treatment of iron overload and typically is administered by slow subcutaneous administration over 8–24 hours via continuous infusion at a dose of 20–40 mg/kg per day (Novartis Pharmaceutical Corporation, 2010a). Deferasirox also is approved for first-line treatment and is administered as an oral liquid suspension once daily at a total dose of 20–40 mg/kg (Novartis Pharmaceutical Corporation, 2010b). Deferiprone is approved in the United States and Europe for second-line treatment of iron overload, and is administered orally three times daily at a total dose of 75–99 mg/kg (ApoPharma Inc., 2011).

T2* outcomes in deferoxamine and deferiprone treatment have been studied in small trials (see Table 1). A head-to-head trial of deferoxamine versus deferiprole showed that deferiprole treatment was associated with greater cardiac iron removal at one year (Pennell et al., 2006). Combination deferoxamine and deferiprole treatment showed superior cardiac iron removal compared with either treatment alone in mild-to-moderate cardiac iron overload at one year (Tanner et al., 2007). Patients with severe cardiac iron overload also benefited from combination treatment at one year (Tanner et al., 2008). An observational study in patients with mild-to-severe cardiac iron overload showed cardiac iron removal with combination treatment but not with either treatment alone at 2.5 years (Ha et al., 2011). Changes in LIC and serum ferritin mirrored cardiac iron outcomes in these studies.

**CORDELIA** is a one-year, head-to-head trial of deferasirox versus deferoxamine in patients with mild-to-severe cardiac iron overload (Pennell, Porter, Piga, et al., 2012). The trial showed equivalence of the two therapies, with a trend toward deferasirox superiority over deferoxamine. Subanalysis of the large EPIC trial provided prospective data for up to three years of deferasirox treatment in patients with mild-to-severe cardiac iron overload (Pennell et al., 2010; Pennell et al., 2011; Pennell, Porter, Cappellini, et al., 2012). Patients received either preventive therapy or iron reduction therapy. Those targeted for iron reduction showed a significant reduction in cardiac iron burden over the course of the study. Patients with severe cardiac iron overload received higher doses of deferasirox in the two- and three-year EPIC extension trials and achieved significant reductions in cardiac iron burden. Smaller studies have shown similar cardiac iron outcomes in patients with mild-to-moderate and severe iron overload treated with deferasirox (Pathare, Taher, & Daar, 2010; Wood, Glynos, et al., 2010; Wood, Kang, et al., 2010). LIC and serum ferritin generally mirrored cardiac iron burden in these trials.

The more commonly reported adverse events for deferoxamine, deferasirox, and deferiprole are shown in Table 2. All treatments are associated with gastrointestinal symptoms and the potential for increased liver transaminases. In addition, all treatments are associated with an increased risk of infection. Deferoxamine use may increase the risk of bacterial infection (Yersinia, mucormycosis) in rare cases; deferiprole use requires weekly absolute neutrophil counts because of its black-box warning for agranulocytosis and neutropenia; and deferasirox use requires monthly blood count monitoring for cytopenias (e.g., agranulocytosis, neutropenia, thrombocytopenia). Quarterly serum ferritin monitoring is required to prevent overtreatment in all cases. Treatment interruptions or dose reductions are warranted in the event of renal dysfunction, liver dysfunction, or infection.
The majority of the chelation trials summarized in the current article were performed in patients with normal left ventricular ejection fraction. Efficacy and safety may differ in patients who have developed cardiomyopathy. All patients receiving chelation therapy require assessment for adverse events and routine laboratory testing.

The Nurse Role in Patient Management

Identifying Patients at Risk

Regularly transfused patients may develop iron overload after 10–20 transfusions (Ault & Jones, 2009). Consequently, transfusion history should be closely tracked and assessments begun after one year of chronic transfusions or after the 10th transfusion for those patients yet to begin iron chelation therapy. In these patients, consistently elevated serum ferritin is the first indication of risk. The normal ranges for serum ferritin are 30–300 ng/ml for men and 15–200 ng/ml for women (Hoffman et al., 2008). Patients with serum ferritin levels greater than 1,000 ng/ml are candidates for iron chelation therapy (Angelucci et al., 2008). Put simply, the chronically transfused patient with β-thalassemia should require chelation therapy at or about two years of age.

For patients who have begun iron chelation therapy, nurses should assess iron burden quarterly. Trends in serum ferritin and other blood work, such as iron profile and liver enzymes, will provide information on the adequacy of iron chelation and patient compliance. That information can be communicated to the clinical team to facilitate discussion about the case. In addition, trends in serum ferritin can provide information on patient compliance with chelation therapy. If serum ferritin trends upward in a patient who was once well controlled, compliance may be an issue.

However, serum ferritin is an indirect measure of iron load and may be influenced by illness or nutritional deficiency (Ault & Jones, 2009). Serum ferritin typically is increased in the presence of inflammation or tissue damage, and may be depressed with low vitamin C levels (Porter, 2001). To minimize the influence of these factors, elevated serum ferritin should be confirmed by serial measurement. When at-risk patients are identified, the extent of organ iron overload should be determined by MRI (Aessopos et al., 2007; Anderson et al., 2001; Tanner et al., 2006; Wood et al., 2004). Some institutions assess heart iron load and LIC by MRI on any at-risk patient with β-thalassemia major (transfused for a year and older than two years of age). Young children may be sedated or secured with minor restraints prior to MRI to ensure image quality, but this is a center-specific decision.

Providing Patient and Family Education

Nurses play a critical role in the management of patients who require chronic blood transfusions. Patients and family members need to understand why patients are at risk for iron overload and the dangers of accumulating iron in vital organs. As such, they need continuous education about the disease, iron chelation therapy, and the importance of maintaining a low iron burden. Reinforcement of these concepts at each office visit will keep patients and family members engaged in treatment. Helpful patient education materials are available for this effort (Centers for Disease Control and Prevention, n.d.; Cooley’s Anemia Foundation, n.d.; KidsHealth, 2012; Mayo Clinic, 2014; National Heart, Lung, and Blood Institute, 2012; Thalassemia International Federation, n.d.). It also is important to provide ongoing education about the importance of adhering to therapy. Patients who experience treatment-related adverse events also may be less likely to comply with therapy. Patients should be educated about the potential for adverse events and how to manage them. Adverse events may be transient or avoidable, and patients should understand how to minimize their occurrence.

The transfusion or infusion unit can serve as a forum for patient and family education, as well as interpatient support. Group meetings during transfusion can meet that need. Although nurses serve as advocates, it is helpful for younger patients and their families to speak with “veteran” patients about their experiences with life-altering disorders, transfusions, and chelation. Patients and families can offer one another practical advice about coping with disease and adhering to therapy.

Developing a Chelation Plan

Perhaps the most important element in successful chelation therapy is the development of a mutually agreeable chelation plan, which should include annual assessment at a thalassemia center of excellence. Patients and family members need to be involved in treatment decisions to ensure a good fit between treatment and lifestyle. The most appropriate chelation therapy for the individual patient and their family should be chosen, taking into account administration preferences and balancing safety, tolerability, and convenience to maximize adherence and efficacy. Because chelation therapy is not associated with immediate and tangible benefits to which patients and family members can relate, they need a meaningful way to track therapeutic benefits. Simple visual aids can fill that need by showing the impact of therapy on clinical measures. Graphs of serum ferritin, for example, can show a downward trend in iron levels, and MRI results can show progressive iron removal from the liver and heart. These tools also can reveal poor treatment adherence. If treatment nonadherence is suspected, medication shipment records from home care or specialty pharmacies can confirm nonadherence, thus highlighting the need for additional education. In cases in which patients may not have convenient access to care or are experiencing adverse events that limit compliance, the tools noted earlier can facilitate conversations about the importance of adherence to therapy and how to overcome adverse events.

Implications for Practice

- Implement iron chelation therapy at an appropriate early stage because cardiac damage from iron overload can occur in the absence of clinical symptoms.
- Use magnetic resonance imaging determination of T2*, which provides a direct indication of cardiac iron concentration, to assess cardiac iron load.
- Develop individual treatment plans with patient and family input and provide ongoing education to ensure they remain engaged.
Conclusion

β-thalassemia major causes clinically severe anemia early in life and typically is fatal if untreated. Chronic blood transfusion is the only treatment. However, chronic transfusion puts patients at risk of iron overload and eventual organ damage from iron toxicity. Iron chelation therapy prevents iron overload and can reverse iron loading in organs. It has proven effective in patients with mild-to-severe iron overload, although all available therapies carry the risk of adverse events and require monitoring for toxicity.

Well-chelated patients are at much less risk for heart failure, the main cause of early death in patients who are iron-overloaded. Specialized MRI protocols allow measurement of cardiac and liver iron load by noninvasive means, avoiding the pitfalls of traditional assessments. The adequacy of chelation therapy also can be monitored by MRI, which can track increasing T2* measurements that indicate iron removal. Successful iron chelation therapy requires engaged, adherent patients. Nursing strategies to ensure chelation therapy success include early identification of patients at risk for iron overload, the development of a mutually agreeable chelation plan, and ongoing patient education. These strategies allow nurses to play a key role in achieving the goals of iron chelation therapy, which are to prevent iron overload and minimize the risk of complications from iron loading. Optimal patient management will require patient and family involvement in treatment decisions, as well as education about the disease, iron chelation therapy, and adverse event management to help ensure adherence.

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