Identification and Management of Transfusion-Related Iron Overload in Childhood Cancer Survivors - Pediatric - Ambulatory Clinical Practice Guideline

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Introduction

Transfusion-related iron overload (TRIO) is a potential cause of morbidity and mortality in survivors of childhood cancer who received multiple packed red blood cell (PRBC) transfusions during treatment.\textsuperscript{1,2} Excess iron causes tissue damage through chronic formation of free radicals, which can cause significant organ damage resulting in liver, cardiac, and endocrine dysfunction, as well as death.\textsuperscript{3} The prevalence of iron overload among childhood cancer survivors who did not receive hematopoietic stem cell transplantation (HSCT) ranged from 3-14%,\textsuperscript{2} compared to as high as 32% among adult recipients of HSCT.\textsuperscript{1}

Very high levels of ferritin (eg, ≥3000 ug/L) are reported to be an independent risk factor for treatment-related mortality.\textsuperscript{4,5} Older age at oncologic diagnosis has been reported to be associated with higher risk of iron overload, due to decreased growth potential and iron needs.\textsuperscript{6,7} Several studies have also demonstrated that the total volume of blood transfused is correlated with iron overload, where >1000 mL of PRBCs transfused has been recommended as a cutoff for TRIO screening.\textsuperscript{2,7,8}

While liver biopsy is the gold standard for confirming iron overload and predicting total iron body stores, radiographic imaging has become an important clinical tool to noninvasively quantify liver iron concentration (LIC) in patients with significant iron overload who may require iron-reducing therapy.\textsuperscript{9-11} There is no consensus on the serum ferritin threshold to be used as an indicator of significant overload in pediatric patients, though a range of >500 ng/mL to >1000 ng/mL has been used in studies.\textsuperscript{1,2} A serum ferritin threshold of 637 ng/mL has recently been shown to exclude clinically-significant iron overload of LIC >7 mg/g.\textsuperscript{11}

For patients who require treatment of TRIO, therapeutic phlebotomy is a safe, rapid and effective method of iron removal in patients for whom need for transfusions has ceased.\textsuperscript{12} Iron-chelating therapy has dramatically improved event-free survival and quality of life for patients with TRIO resulting from treatment of thalassemia,\textsuperscript{13} but chelators are not without potential side effects and their use in the setting of TRIO among childhood cancer survivors is less well studied.

While long-term follow-up guidelines by the Children’s Oncology Group (COG) recommend obtaining a baseline serum ferritin for patients who underwent HSCT, there are no recommendations for routine screening for iron overload in pediatric oncology patients who received repeated PRBC transfusions during treatment for their cancer diagnoses. The absence of TRIO screening among pediatric cancer survivors can lead to unrecognized and untreated cases of iron overload in this population. This guideline outlines the early identification and management of transfusion-related iron overload during surveillance follow-up for childhood cancer survivors.
Scope

Intended Users: Physicians, Advanced Practice Providers, Pharmacists, Nurses, Technical Support

Objectives: To guide the identification and management of transfusion-related iron overload (TRIO) in childhood cancer survivors with the goal of promoting early identification of at-risk patients and appropriate evidence-based interventions

Target Population: Pediatric patients in the ambulatory setting with prior oncologic diagnoses who are not receiving active therapy

Clinical Questions Considered:
- What assessments should occur when screening a pediatric cancer survivor for TRIO?
- What assessments should occur when confirming and quantifying the degree of iron overload in these patients?
- When should phlebotomy be used for the treatment of TRIO?
- When should chelation be used for the treatment of TRIO?

Definitions
1. LIC: Liver Iron Concentration
2. Pediatric cancer survivor: Pediatric patient with a prior oncologic diagnosis who is not receiving active therapy
3. Patients at high risk for TRIO include any of the following:
   a. Patients who have received ≥10 PRBC transfusions
   b. Patients whose serum ferritin is >500 ng/mL or transferrin saturation >50%
   c. Patients who are >14 years of age
4. TRIO: Transfusion-Related Iron Overload
Recommendations

1. Screening for TRIO
   1.1. Pediatric cancer survivors who received ≥10 PRBC transfusions should be screened for TRIO by obtaining a serum ferritin and a transferrin saturation level.1,2,7,8 (UW Health GRADE moderate quality evidence, C recommendation)
   1.2. If the serum ferritin is >500 ng/mL and/or the transferrin saturation is ≥50%:
      1.2.1. Proceed with confirming and quantifying degree of TRIO as outlined in Confirnmg and quantifying the degree of TRIO.1,2,7,8 (UW Health GRADE high quality evidence, C recommendation)
   1.3. If the serum ferritin is >500 ng/mL and transferrin saturation <50%:
      1.3.1. Consider repeating a serum ferritin level at least one month apart along with iron studies and CRP and/or ESR to help rule out ferritin elevation as an acute phase reactant.1,2,6,7,8,12 (UW Health GRADE moderate quality evidence, C recommendation)
      1.3.2. If repeat serum level remains elevated and there is no other evidence of infection or inflammation, proceed with confirming and quantifying degree of TRIO as outlined in Confirnmg and quantifying the degree of TRIO.1,2,6,7,8,12 (UW Health GRADE high quality evidence, C recommendation)
   1.4. If the serum ferritin is ≤500 ng/mL and transferrin saturation <50%:
      1.4.1. Further TRIO work-up is not recommended.1,2,6,7,8,11,12 (UW Health GRADE high quality evidence, C recommendation)

2. Confirming and quantifying the degree of TRIO
   2.1. If the serum ferritin is >500 ng/mL and/or transferrin saturation is >50% as described in Screening for TRIO, then obtain an R2*MRI (rapid fat-iron protocol) for quantification of liver iron concentration.9,10,11,14 (UW Health GRADE moderate quality evidence, C recommendation)
   2.2. If patient has existing cardiac dysfunction, then consider cardiac MRI without contrast (specify “iron quantification”) for quantification of heart and liver iron content.9,10,11 (UW Health GRADE moderate quality evidence, C recommendation)

3. Management of TRIO
   3.1. Close monitoring of patients with radiographic evidence of iron overload is recommended (i.e., LIC ≥1.8 mg Fe / gram dry liver tissue).1,2,6,7,8,12 (UW Health GRADE very low-quality evidence, C recommendation for 3.1 and each sub-item below)
      3.1.1. Continue serial monitoring of serum ferritin and/or transferrin saturation every 3-6 months
      3.1.2. Repeat radiographic quantification of LIC every 12-18 months until LIC has normalized
   3.2. Treatment intervention is recommended for patients with greater than “Borderline LIC”13 TRIO (i.e., LIC ≥3.2 mg Fe / gram dry liver tissue).1,2,6,7,8,12 (UW Health GRADE very low-quality evidence, C recommendation for 3.2 and each sub-item below)
      3.2.1. Special Considerations
         3.2.1.1. If the patient is a menstruating female or ≤10 years of age, consider continued close monitoring. If labs and/or imaging are persistently abnormal after 6-12 months, recommend treatment intervention to reduce iron burden.
         3.2.1.2. If the radiographic quantification of iron deposition has normalized but the serum ferritin and/or transferrin saturation remains elevated, discontinue therapeutic intervention but continue to monitor relevant laboratory parameters every 3 to 6 months.
3.2.2. Therapeutic Interventions: the choice between therapeutic phlebotomy and oral chelation therapy should be individualized based on patient-specific factors, as there are no informative trials comparing these interventions for pediatric TRIO to guide selection. In general, therapeutic phlebotomy should be avoided in patients with underlying anemia or in those who are transfusion-dependent. The choice of oral chelation therapy with deferasirox is generally guided by patient preference for available formulations and potential differences in cost. Dosing guidance is as follows:1,2,6,7,8,12

3.2.2.1. **Therapeutic phlebotomy:** Phlebotomize 10 mL/kg whole blood monthly for 6 months, then 5 mL/kg monthly (as tolerated without signs or symptoms of anemia) until there is radiographic evidence of normalized LIC.

3.2.2.2. **Oral chelation therapy (Table 2)**

3.2.2.2.1. Jadenu® (deferasirox) 14 mg/kg/day (rounded to nearest whole tablet or sprinkle sachet); may increase by 3.5 or 7 mg/kg/day every 3-6 months based on serum ferritin up to 28 mg/kg/day

3.2.2.2.2. Exjade® (deferasirox) 20 mg/kg/day; may increase by 5-10 mg/kg/day increments every 3-6 months based on serum ferritin up to 40mg/kg/day

3.2.2.2.3. Consider dose reduction if serum ferritin is between 500 to 1000 ng/mL and stop chelation therapy if ferritin <500

3.2.2.2.4. Consider obtaining baseline creatinine, serum transaminases, bilirubin, and baseline auditory and ophthalmic examinations (as described in FDA-approved labeling, March 2019; Table 2).
Figure 1: Screening and Management of TRIO

Screening and Management of Transfusion-Related Iron Overload in Childhood Cancer Survivors
From: Identification and Management of Transfusion-Related Iron Overload in Childhood Cancer Survivors - Pediatric - Ambulatory Clinical Practice Guideline

Pediatric cancer survivor who has received 10 or more PRBC infusions

Serum ferritin >500 and/or Tsat ≥50%

Yes

Obtain R2*MRI

Assess LIC

LIC 1.8 <3.2 mg/g dw

Close monitoring with serial labs every 3-6 months and imaging every 12-18 months until LIC normalized

LIC 3.2 <7 mg/g dw

Where risk of treatment outweighs benefit

Consider Patient-Specific Factors (Preference for therapeutic intervention)

Monitoring and Follow-up

Start therapeutic phlebotomy or oral chelation therapy

No

Ferritin ≤500

Ferritin >500

If the serum ferritin is ≤500 ng/mL and transferrin saturation <50%:

Further TRIO work-up is not recommended

• Consider repeating a serum ferritin level at least one month apart along with iron studies and CRP and/or ESR to help rule out ferritin elevation as an acute phase reactant
• If repeat serum level remains elevated and there is no other evidence of infection or inflammation, proceed with confirming and quantifying degree of TRIO

If the serum ferritin is >500 ng/mL and transferrin saturation <50%:

LIC ≥ 7 mg/g dw

Abbreviations: PRBC, packed red blood cells; dw, dry weight; LIC, liver iron concentration; Tsat, transferrin saturation. LIC is measured in mg Fe/g dw; serum ferritin is measured in ng/mL.
Table 1: Clinical Relevance of Radiographic Quantification of LIC

<table>
<thead>
<tr>
<th>LIC Range (mg Fe/g dw)</th>
<th>( R_2^* ) at 1.5T (s(^{-1}))</th>
<th>( R_2^* ) at 3T (s(^{-1}))</th>
<th>Clinical Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.17-1.8</td>
<td>&lt;67</td>
<td>&lt;124</td>
<td>Normal range</td>
</tr>
<tr>
<td>1.8-3.2</td>
<td>67-119</td>
<td>124-223</td>
<td>Borderline LIC</td>
</tr>
<tr>
<td>3.2-7.0</td>
<td>120-266</td>
<td>224-495</td>
<td>Suggested optimal range of LIC for chelation therapy in TRIO</td>
</tr>
<tr>
<td>7.0-15.0</td>
<td>267-573</td>
<td>496-1066</td>
<td>Increased risk of complications</td>
</tr>
<tr>
<td>&gt;15.0</td>
<td>&gt;574</td>
<td>&gt;1067</td>
<td>Greatly increased risk of cardiac disease and early death in patients with TRIO</td>
</tr>
</tbody>
</table>

Table 2: Oral Chelation Therapy\(^a\)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Generic</th>
<th>How Supplied</th>
<th>Baseline Monitoring</th>
<th>Dosing</th>
<th>Adjustments</th>
<th>Max</th>
<th>Periodic Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jadenu</td>
<td>deferasirox</td>
<td>Tablets, Granules</td>
<td>Consider obtaining baseline creatinine, serum transaminases, bilirubin, and baseline auditory and ophthalmic examinations</td>
<td>14 mg/kg/day (rounded to nearest whole tablet or sprinkle sachet)</td>
<td>may increase by 3.5 or 7 mg/kg/day every 3-6 months based on serum ferritin</td>
<td>28 mg/kg/day</td>
<td>Consider dose reduction if serum ferritin is between 500 to 1000 ng/mL, and stop chelation therapy if ferritin &lt;500. See Full Prescribing information for information regarding monitoring, administration, and dose-reductions for organ impairment</td>
</tr>
<tr>
<td>Exjade</td>
<td>deferasirox</td>
<td>Tablets for oral suspension</td>
<td>Consider obtaining baseline creatinine, serum transaminases, bilirubin, and baseline auditory and ophthalmic examinations</td>
<td>20 mg/kg/day</td>
<td>may increase by 5-10 mg/kg/day increments every 3-6 months based on serum ferritin</td>
<td>40 mg/kg/day</td>
<td>Consider dose reduction if serum ferritin is between 500 to 1000 ng/mL, and stop chelation therapy if ferritin &lt;500. See Full Prescribing information for information regarding monitoring, administration, and dose-reductions for organ impairment</td>
</tr>
</tbody>
</table>

\(^a\) Adapted from FDA-Approved Labeling, March 2019

Disclaimer
Clinical practice guidelines assist clinicians by providing a framework for the evaluation and treatment of patients. This guideline outlines the preferred approach for most patients. It is not intended to replace a clinician’s judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.
Methodology

Development Process
Each guideline is reviewed and updated a minimum of every 3 years. All guidelines are developed using the guiding principles, standard processes, and styling outlined in the UW Health Clinical Practice Guideline Resource Guide. This includes expectations for workgroup composition and recruitment strategies, disclosure and management of conflict of interest for participating workgroup members, literature review techniques, evidence grading resources, required approval bodies, and suggestions for communication and implementation.

Methods Used to Collect the Evidence:
The following criteria were used by the guideline author(s) and workgroup members to conduct electronic database searches in the collection of evidence for review.

Literature Sources:
- Electronic database search (e.g., PubMed)
- Databases of systematic reviews (e.g., Cochrane Library)
- Hand-searching journals, external guidelines, and conference publications

Time Period: All published articles through 2019

Search Terms:
- ("iron overload") AND ["pediatric") or ("childhood") AND ("cancer")

Methods to Select the Evidence:
Searches were limited to clinical trials, review articles, case series, human subjects, and articles available in English. Expert opinion and clinical experience were also considered during discussions of the evidence.

Methods Used to Formulate the Recommendations:
The workgroup members agreed to adopt recommendations developed by external organizations and/or created recommendations internally via a consensus process using discussion of the literature and expert experience/opinion. If issues or controversies arose where consensus could not be reached, the topic was escalated appropriately per the guiding principles outlined in the UW Health Clinical Practice Guideline Resource Guide.

Methods Used to Assess the Quality of the Evidence/Strength of the Recommendations:
Recommendations developed by external organizations maintained the evidence grade assigned within the original source document and were adopted for use at UW Health.

Internally developed recommendations, or those adopted from external sources without an assigned evidence grade, were evaluated by the guideline workgroup using an algorithm adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (see Figure 1). Screening and imagining recommendations were assessed using appropriate frameworks for diagnostic interventions in addition to GRADE methodology (see Figure 2).
Figure 1. GRADE Methodology adapted by UW Health

Rating Scheme for the Strength of the Evidence/Recommendations:

GRADE Ranking of Evidence

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>We are confident that the effect in the study reflects the actual effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.</td>
</tr>
<tr>
<td>Low</td>
<td>The true effect may differ significantly from the estimate.</td>
</tr>
<tr>
<td>Very Low</td>
<td>The true effect is likely to be substantially different from the estimated effect.</td>
</tr>
</tbody>
</table>

GRADE Ratings for Recommendations For or Against Practice

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>The net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.</td>
</tr>
<tr>
<td>C/conditional</td>
<td>Recommendation may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.</td>
</tr>
</tbody>
</table>

Figure 2. Frameworks for the Evaluation of Screening and Diagnostic Imaging

Stages of Technical Efficacy: Journal of Magnetic Resonance Imaging Style

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Technical Efficacy</td>
</tr>
<tr>
<td>2</td>
<td>Diagnostic Accuracy, Considered by Most as Clinical Efficacy</td>
</tr>
<tr>
<td>3</td>
<td>Diagnostic Thinking</td>
</tr>
<tr>
<td>4</td>
<td>Therapeutic Efficacy</td>
</tr>
<tr>
<td>5</td>
<td>Improvements in Patient Care</td>
</tr>
<tr>
<td>6</td>
<td>Cost Effectiveness</td>
</tr>
</tbody>
</table>

(Fryback & Thornbury, The Efficacy of Diagnostic Imaging, 1991), (Gazelle, et al., 2011)

Evidence Level, Journal of Magnetic Resonance Imaging

<table>
<thead>
<tr>
<th>Evidence Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Prospective studies with an excellent reference standard. This reference standard(s) should be determined before the study begins.</td>
</tr>
<tr>
<td>2</td>
<td>Prospective studies with a reference study determined during the course of that study or prospective cohort studies</td>
</tr>
<tr>
<td>3</td>
<td>Nonconsecutive cohort studies, usually retrospective with an imperfectly applied reference standard</td>
</tr>
<tr>
<td>4</td>
<td>Observational retrospective case series.</td>
</tr>
<tr>
<td>5</td>
<td>Case reports, commentaries and editorials.</td>
</tr>
</tbody>
</table>

(Schweitzer ME, 2016)
References