Transfusion Related Iron Overload: Improving the evaluation and management in pediatric cancer survivors.

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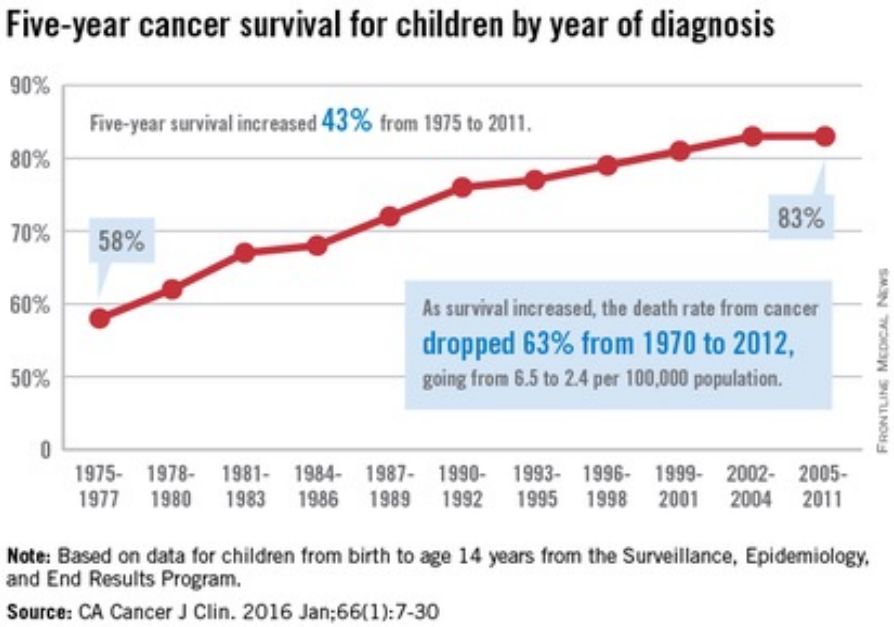
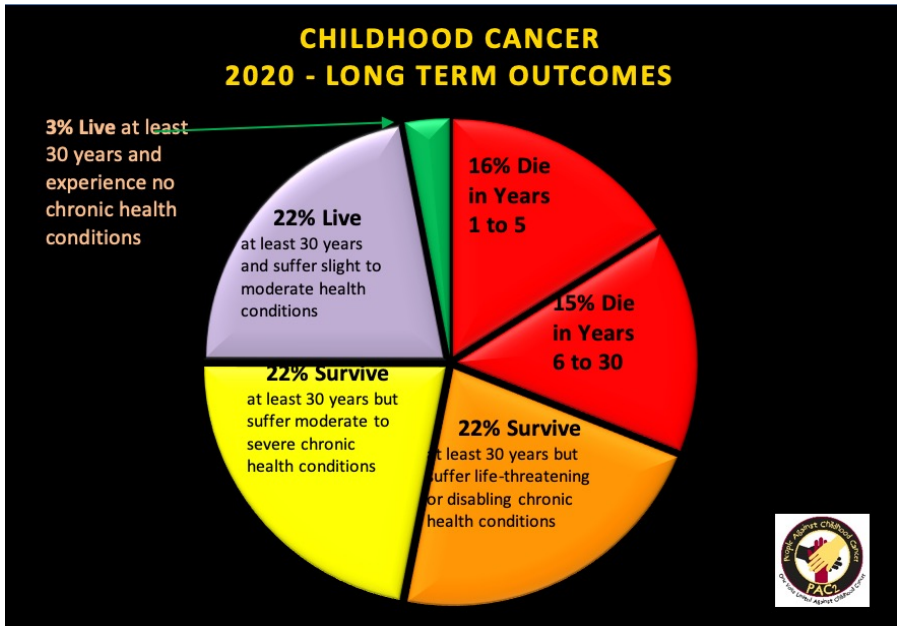
Objectives:

- To review and discuss the evidence of transfusion-related iron overload (TRIO) in pediatric hematology and oncology (PHO) patients.
- To highlight the lack of consistent practice in screening and treating TRIO in PHO patients.
- To educate on advances in TRIO quantification
- To identify risk factors that predispose patients to TRIO.
- To create a new clinical guideline that promotes early TRIO identification and appropriate evidence-based interventions.
- Assess adherence to guideline and identify changes in patient outcomes before and after algorithm implementation

Background and Significance

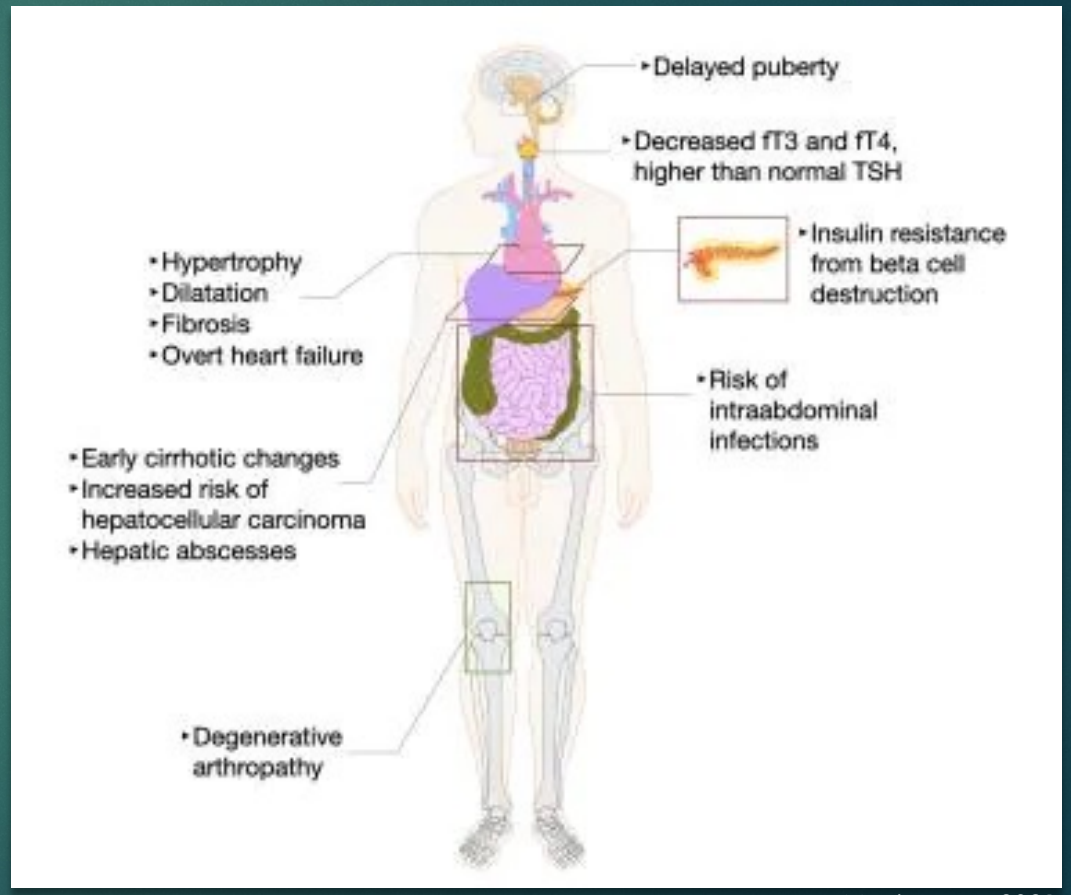
- >80% 5 year-survival rate when diagnosed with cancer < 20 years old (Hayat, M.J., et al., 2007).
- 62% – 95.5% of childhood cancer survivors will develop at least 1 chronic health condition (Hudson, M.M., et al. 2013, Nathan, P.C., et al., 2008) .





Background and Significance

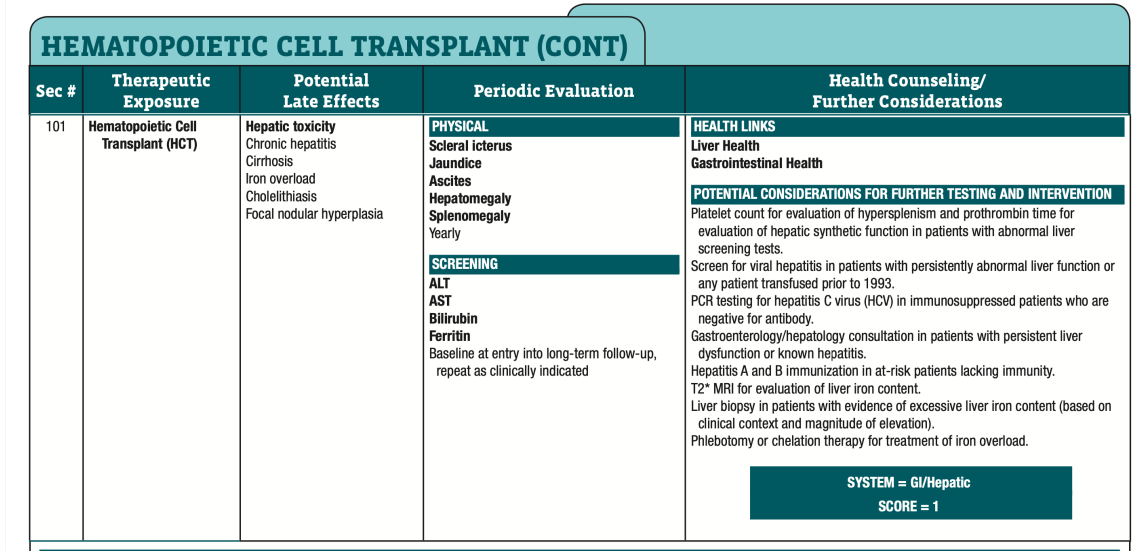
- TRIO is a potential cause of morbidity and mortality in CSS who receive multiple pRBC transfusions (Trovillion et al., 2018, Schempp 2016).
- Iron is known to accumulate in the heart, liver, pancreas and spleen resulting in oxidative stress -> tissue damage
- Growth alone does not normalize moderate-to-severe iron overload in pediatric patients (Majhail, N.S., et al., 2008).
- Current chemotherapy regimens have increased transfusion reliance and potential for iron overload (Ruccione, K.S., et al., 2012)
  i. Non-HSCT patients:
     - 3% (Trovillion et al., 2018)
     - 14% (Halonen et al., 2003)
     - 24% (Nair, et al,. 2018)
     - 38% (Olcay et al., 2014)
  ii. HSCT patients: 40% (Chotsampancharoen, T., et al., 2009)



Medscape, 2021

Background and Significance

- Currently, COG only recommends serum ferritin for HSCT patients.
- No recommendations exist for non-HSCT TRIO screening or treatment.
- Innovations in imaging and pharmacology provide new tools for TRIO assessment and management.



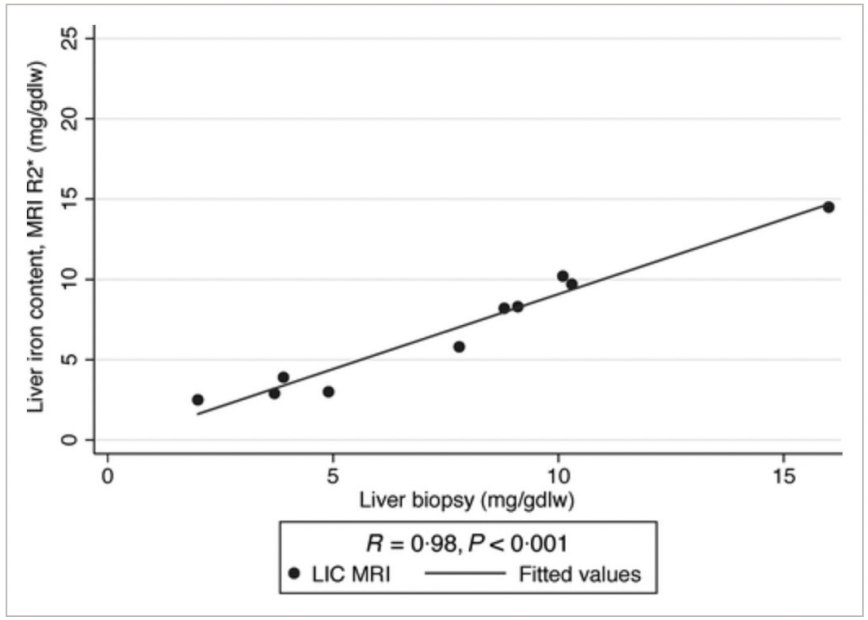
HEMATOPOIETIC CELL TRANSPLANT (CONT)

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
101	**Hematopoietic Cell Transplant (HCT)**	**Hepatic toxicity** Chronic hepatitis Cirrhosis Iron overload Cholelithiasis Focal nodular hyperplasia	**PHYSICAL** **Scleral icterus** **Jaundice** **Ascites** **Hepatomegaly** **Splenomegaly** Yearly **SCREENING** **ALT** **AST** **Bilirubin** **Ferritin** Baseline at entry into long-term follow-up, repeat as clinically indicated	**HEALTH LINKS** **Liver Health** **Gastrointestinal Health** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Platelet count for evaluation of hypersplenism and prothrombin time for evaluation of hepatic synthetic function in patients with abnormal liver screening tests. Screen for viral hepatitis in patients with persistently abnormal liver function or any patient transfused prior to 1993. PCR testing for hepatitis C virus (HCV) in immunosuppressed patients who are negative for antibody. Gastroenterology/hepatology consultation in patients with persistent liver dysfunction or known hepatitis. Hepatitis A and B immunization in at-risk patients lacking immunity. T2* MRI for evaluation of liver iron content. Liver biopsy in patients with evidence of excessive liver iron content (based on clinical context and magnitude of elevation). Phlebotomy or chelation therapy for treatment of iron overload. **SYSTEM = GI/Hepatic** **SCORE = 1**

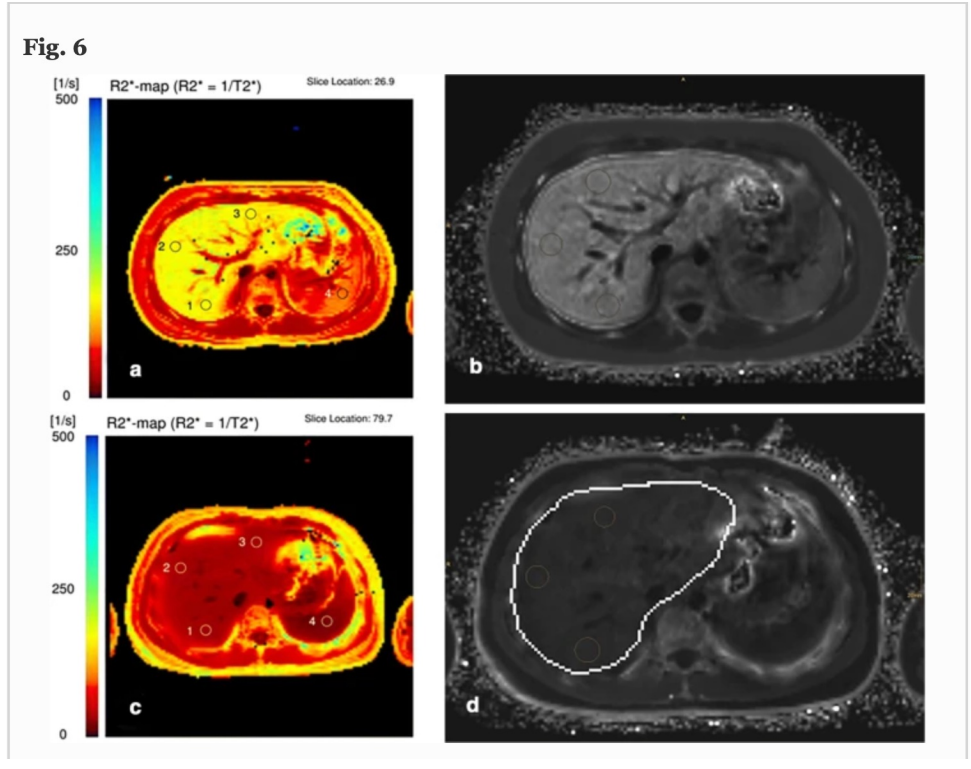
Quantifying TRIO

- CT scanning has limited sensitivity (63%) for assessing hepatic iron overload (Guyader D. et. al., 1989).
- Liver iron content estimated by R2 MRI was found to be strongly correlated to that measured by liver biopsy (Badawy S. et al. , 2016).

(Badawy S. et al. , 2016)

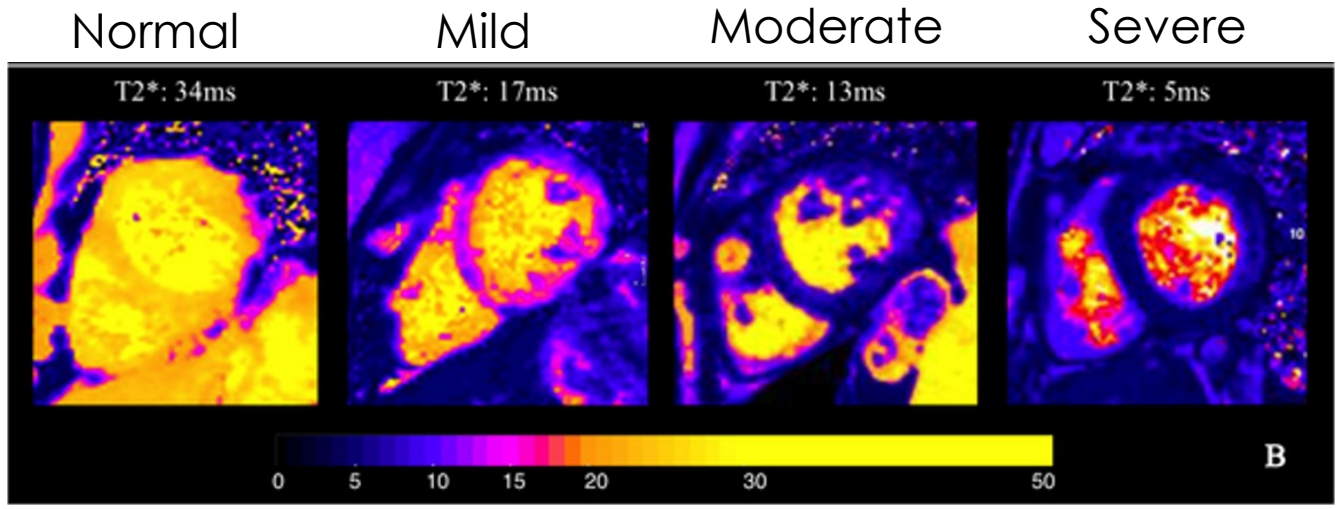


Henninger et al., 2020



Quantifying TRIO

- T2 cardiac MRI can be used for initial diagnosis and treatment monitoring of myocardial iron overload (Aronow W. S. et al., 2018).
- Significantly shorter myocardial T2 time in patients with cardiac iron overload (Krittayaphong R et al 2019).



TRIO Risk factors

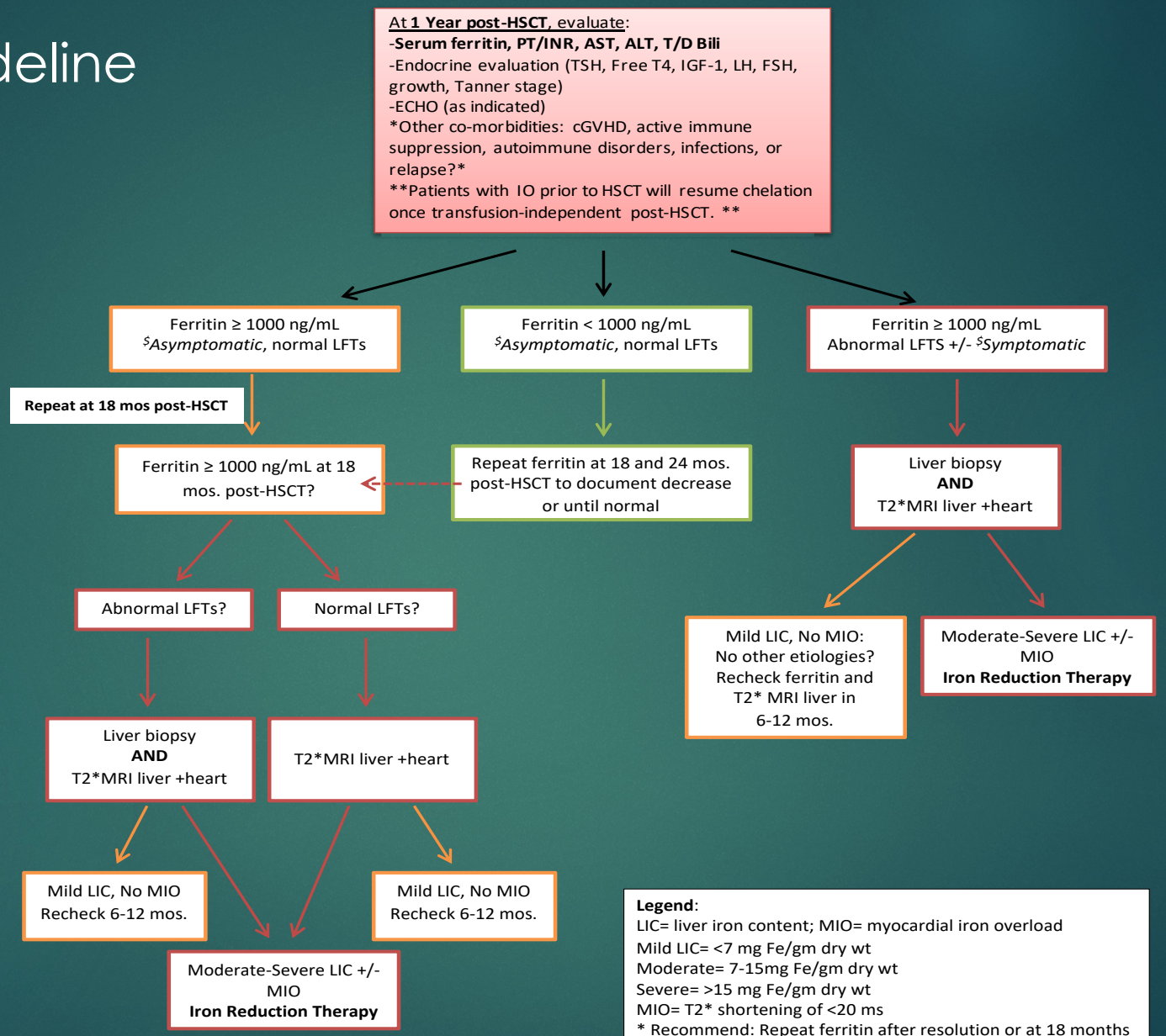
Major consideration:

- >10 pRBC transfusions or >1000mL pRBC (Trovillion EM et al., 2018, De Goyet MD et al., 2013, Ruccione, K.S., et al., 2012)
  - Sensitivity = 70%, specificity = 75%, AUC 76.6
- Minor considerations:
- Male
- Increased age (>14 years) (Trovillion et al., 2018)
- Significant GVHD (Sirvent et al., 2017)
- Allogeneic transplant from non-sibling (Sirvent et al., 2017)
- Elevated pre-transplant ferritin (Barba et al., 2013)

HSCT

Texas Transplant Physician Group Guideline

Screening Algorithm for Iron Overload (IO) after Allogeneic HSCT©



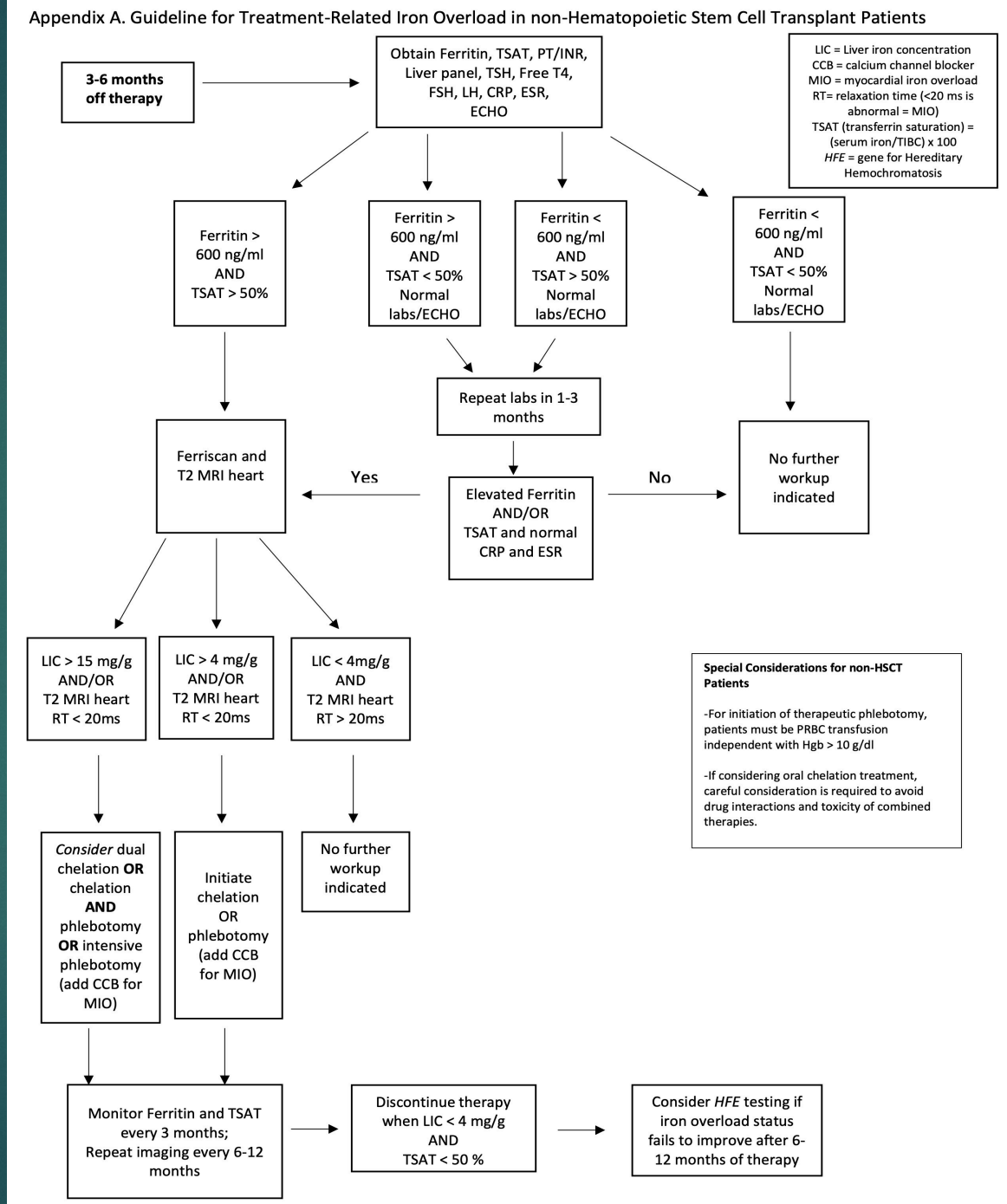
Texas Transplant Physician Group
Methodist Physicians

Legend:
LIC= liver iron content; MIO= myocardial iron overload
Mild LIC= <7 mg Fe/gm dry wt
Moderate= 7-15mg Fe/gm dry wt
Severe= >15 mg Fe/gm dry wt
MIO= T2* shortening of <20 ms
* Recommend: Repeat ferritin after resolution or at 18 months post-HSCT.
**Sickle cell disease, thalassemias, SAA, DBA, other where PRBC-dependent prior to HSCT.
$*Symptomatic* patients may include patients with cardiac, endocrine, or growth dysfunction.

Troy Quigg, DO, MS
Lisa McDonald, DNP
2013

Clinical Pathway

Implemented (6/1/23)



BMT** - 100 days post-transplant

Inclusion Criteria

Cohort 1 (CAYA Cancer Survivors): Any patients treated by PHO providers who are > 3 months status post completion of oncology therapy AND not receiving ongoing PRBC transfusions.

Cohort 2 (HSCT): Any patients treated by Pediatric BMT providers who are >100 days post-HSCT AND not receiving ongoing PRBC transfusions.

Exclusion Criteria

1. Patients with prior history of TRIO or history of iron chelation treatment prior to starting chemotherapy or bone marrow transplant will be excluded from the post-implementation cohort only.

2. Patients who were treated with surgery or observation alone.

3. Patient >25 years of age.

4. Patients with no history of PRBC transfusions during oncology or HSCT treatment.

Variables to be collected

- Demographic information (Name, age, sex, weight, diagnosis, etc)
- Treatment methods (Surgery, chemo, radiation)
- Dosing/duration of therapy
- BMT variables (Transplant donor source/recipient, conditioning modality, transplant type, Number of transplants, etc)
- Outcomes and complications of therapy (BMT/Onc)
- Transfusional burden (Number pRBCs/cumulative volume)
- Chelation therapy and complications
- Clinical guideline components (CBC, Echo, Ferriscan, Hemochromatosis testing, etc)

Questions

- What associations can be drawn between age, diagnosis, treatment and the level/location of iron overload?
- Do certain diagnostic or prognostic factors place patients at greater risk of iron overload?
- How can screening guidelines be adjusted to account for differences in TRIO risk?

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