A Tool for Monitoring, Managing and Preventing Iron Deficiency in Intestinal Failure Patients

**Presentation Overview/Summary**
Iron deficiency is common and problematic for patients with intestinal failure (IF) receiving long-term parenteral nutrition. Determining and evaluating appropriate iron parameters for the management of iron supplementation and deficiency can present several challenges to the nutrition support healthcare professional. No standardized protocols or guidelines exist to steer the prevention, management and monitoring of iron deficiency in long-term parenteral nutrition patients. This roundtable session aims to address this gap in competence by discussing a tool (specifically a flowchart) to be used for patients with intestinal failure who are at risk for iron deficiency, and will provide a forum for shared experiences that will help healthcare professionals manage iron deficiency in these patients. The session moderators will provide a brief overview of iron deficiency, identify the key issues to consider when developing preventative, management, and monitoring strategies, and present patient cases which will guide discussion. Specific topics will include: supportive labs associated with iron deficiency (including soluble transferrin receptor (sTfR), ferritin, iron level, iron saturation, total iron binding capacity (TIBC)) to determine if iron deficiency is present, strategies for maintenance iron dosing (to avoid deficiency), guidance for ongoing monitoring of iron deficiency and toxicity, and some potential challenges facing the nutrition support healthcare professional in administering intravenous and oral iron doses in this patient population. Participants will have the opportunity to share experiences specific to their patient populations and institutions. Participants will be able to learn from these shared experiences and bring back strategies to apply to their daily nutrition support practices.

**Learning Objectives**
At the conclusion of the presentation, the learner will be able to:
1. Identify iron deficiency based on supporting laboratory monitoring parameters
2. Understand the benefits of using soluble transferrin receptor in the setting of intestinal failure
3. Design and apply a strategic plan for management of iron deficiency in intestinal failure patients

**Key Takeaways/Fast Facts**
- Iron deficiency (ID) can exist without anemia and should be treated as early as possible to avoid negative life-long cognitive and developmental effects, especially in pediatric patients
- Soluble transferrin receptor is an important monitoring tool to trend ID in the intestinal failure population
- Patients who receive a high percentage of their calories via parenteral nutrition (PN) are more susceptible to iron deficiency, especially infants and children
- Lab values are helpful in identifying iron deficiency, but there are many confounders in the most commonly used labs.
- There are no standard guidelines to treat iron deficiency in pediatric intestinal failure patients (eg. treating with IV iron 3- days per week is not feasible for our patients in the out-patient setting)
Learning Assessment Questions

1. True or False: In the development of ID, decreased ferritin occurs before decreased hemoglobin

2. An intestinal failure patient has severe anemia, an elevated sTfR, low ferritin, with a normal CRP, and a normal MCV. This patient most likely has:
   A. only an iron deficiency
   B. anemia of chronic disease (ACD) plus several nutrient deficiencies (iron, vitamin B12, folate)
   C. aplastic anemia
   D. an ID, but possibly other causes of anemia, such as nutrient deficiencies or blood loss.

3. The patient on TPN with the highest risk for iron deficiency is most likely:
   A. the 25yo male who is on 50% of his calories parenterally and the rest of his calories by mouth
   B. the 17yo girl with her menses who is on 60% of her calories from parenteral nutrition.
   C. the 1 month (full-term newborn) with small gastroschisis whose abdomen was recently closed awaiting bowel function
   D. the 9mo with 20cm of small bowel, who is on 90% of his calories by parenteral nutrition, but starting to advance his GT feedings by 1mL/hr weekly.

4. True or False: Soluble Transferrin Receptor level increases in the setting of iron deficiency without anemia, and it is increased in thalassemia, blood loss, or hemolysis

5. Patients with all the following are likely to have an elevated ferritin level, EXCEPT:
   A. Malignancy
   B. CLABSI, UTI, influenza or with 6 month vaccinations resulting in a fever
   C. chronic microscopic lower GI bleed
   D. intestinal failure associated liver disease who is listed for transplant

Learning Assessment Answers:

1. Answer = True; Rationale: reduced Hg concentration is a late clinical marker for ID
2. Answer = D; Rationale: elevated sTfR, low ferritin, normal CRP indicates ID. MCV is typically low in ID so an additional cause of anemia may be present (B12 or folate deficiency). In ACD ferritin and CRP are often elevated. sTfR is normal in aplastic anemia.
3. Answer = D; Rationale: Adult patients require less iron than growing pediatric patients. Patients who receive a larger percentage of calories from TPN are at higher risk for iron deficiency. Full term babies commonly have sufficient iron until 4-6 months of age
4. Answer = True; Rationale: sTfR increases when there is increased erythropoiesis which occurs in thalassemia, active bleeding and hemolysis
5. Answer = C; Rationale: Ferritin is an acute phase reactant and is commonly elevate in the setting of malignancy, infections, fever, chronic disease and inflammation making it less reliable in IF patients

References

1 Definitions
   a. **Iron deficiency**: a state in which there is insufficient total body iron to maintain normal physiologic functions (normal physiologic functions include storing iron as ferritin)
   b. **Anemia**: Hemoglobin concentration that is 2 or more standard deviations below the mean for a healthy population of the same gender and age
      i. Nutritional deficiencies responsible for anemia: iron, cobalamin (Vit B12), folate, copper, zinc
      ii. May result from blood loss, hemolysis, aplastic anemia, genetic conditions sickle cell, thalassemia etc
   c. **Ferritin**: a protein that contains iron and is the primary form of iron storage and transport
d. **Soluble Transferrin Receptor (STR, sTfR)**: a quantitative measure of erythropoietic activity; in iron deficiency, cell membrane transferrin receptor density increases, and truncated forms of sTfR increase in the serum

2 Determination of Iron Deficiency
   a. Effect of Evolving Iron Deficiency on Clinical Markers
   
<table>
<thead>
<tr>
<th>Biochemical Marker</th>
<th>Early Phase ID</th>
<th>Mid phase with Compensation</th>
<th>Late Phase Established ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Iron</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>%Saturation</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Ferritin</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Total iron binding capacity</td>
<td>Normal</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Mean corpuscular volume</td>
<td>Normal</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Red blood cell distribution width</td>
<td>Normal</td>
<td>Normal</td>
<td>↓</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Normal</td>
<td>Normal</td>
<td>↓</td>
</tr>
</tbody>
</table>

   b. Differentiation of iron deficiency (ID) anemia and anemia of chronic disease (ACD)

<table>
<thead>
<tr>
<th>Ferritin Anemia (IDA)</th>
<th>Anemia of Chronic Disease(ACD)</th>
<th>IDA and ACD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>High</td>
<td>Normal or High</td>
</tr>
<tr>
<td>TIBC</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Serum Iron</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>sTfR</td>
<td>High</td>
<td>Normal</td>
</tr>
</tbody>
</table>

3 Benefits of soluble transferrin receptor level
   a. Not an acute phase reactant
   b. Detects iron deficiency, regardless of the presence of anemia of chronic disease, acute inflammation, infection or malignancy
c. sTfR also quantitatively evaluates the absolute rate of erythropoiesis
   i. False elevation (False POSITIVE)
      1. Hemolysis
      2. Thalassemia and sickle cell
      3. Gastrointestinal bleeding
   ii. False low (False NEGATIVE)
      1. Aplastic anemia
      2. Chronic renal failure
4 Equations to calculate iron deficit (Goal Iron Dose)
   a. Pinsk 2008
      Calculate iron Deficit (total replacement dose)
      <13 kg: mg of iron = 0.6 x weight (kg) x [100 – (actual Hg/12 x 100)]
      >13 kg: mg of iron = 0.6 x weight (kg) x [100 – (actual Hg/14.8 x 100)]
   b. Ganzoni formula
      \[ \text{Body wt (kg) x (Target Hb – Actual Hb in g/L) x 0.24} \] + iron depot (mg)
      \( \text{Iron depot (mg) = \text{< 35kg is 15mg/kg or \geq 35kg = 500mg}} \)

5 Flowchart
   a. Guideline #1: Identify if patient has iron deficiency
   b. Guideline #2: Differentiate between patient who need
      1. IV iron maintenance dose
      2. IV iron replacement dose
      3. Enteral iron +/- IV iron replacement dose or IV maintenance dose
   c. Guideline #3: IV iron maintenance dose
   d. Guideline #4: IV iron replacement dose

CASE #1

JP, is a 3-year-old male, former 25-week premature infant with a history of gastroschisis and necrotizing enterocolitis resulting in extensive small bowel resection (length remaining 30 cm at 30 weeks GA) and subsequent intestinal failure and malabsorption syndrome. JP receives minimal enteral nutrition via G-J tube, and he is primarily home parenteral nutrition (HPN) dependent for complete nutritional support. (10% EN, 90% PN)

Current weight: 9.8 kg, Vital signs are normal and he is healthy appearing

Recent pertinent laboratory parameters:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>7.9 g/dl</td>
<td>(normal 11-14 g/dL)</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>24 %</td>
<td>(normal 34-42%)</td>
</tr>
<tr>
<td>MCV</td>
<td>73%</td>
<td>(normal 75-102%)</td>
</tr>
<tr>
<td>MCHC</td>
<td>30.5%</td>
<td>(normal 30.5-36%)</td>
</tr>
<tr>
<td>RDW</td>
<td>15.4%</td>
<td>(normal 11.5-15%)</td>
</tr>
<tr>
<td>Ferritin</td>
<td>65 ng/ml</td>
<td>(normal 6-155 ng/ml)</td>
</tr>
<tr>
<td>sTfR</td>
<td>14.5 mg/L</td>
<td>(normal 1.8-4.6 mg/L)</td>
</tr>
<tr>
<td>CRP</td>
<td>3.2 mg/dL</td>
<td>(normal 0.0-0.6 mg/dL)</td>
</tr>
</tbody>
</table>

Using the case provided above and the flowchart, answer the following questions:

1. Does JP have an iron deficiency?
2. What labs help determine iron deficiency?
3. The best approach for managing JP’s iron deficiency is:
   a. Administer pRBC
   b. Calculate and give repletion dose of intravenous iron
   c. Give maintenance dose of intravenous iron
   d. Continue to monitor laboratory parameters
   e. Start enteral iron
ASSEN EDUCATION PROGRAM OUTLINE

JP received 70 mg x 3 doses of replacement IV iron over the course of one month. Repeat laboratory parameters were drawn 4 weeks after the last IV iron infusion and are as follows:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>10.4 g/dL</td>
<td>11-14 g/dL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>32%</td>
<td>34-42%</td>
</tr>
<tr>
<td>MCV</td>
<td>76%</td>
<td>75-102%</td>
</tr>
<tr>
<td>MCHC</td>
<td>32.6%</td>
<td>30.5-36%</td>
</tr>
<tr>
<td>RDW</td>
<td>17%</td>
<td>11.5-15%</td>
</tr>
<tr>
<td>Ferritin</td>
<td>41 ng/ml</td>
<td>6-155 ng/ml</td>
</tr>
<tr>
<td>sTfR</td>
<td>8.6 mg/L</td>
<td>1.8-4.6 mg/L</td>
</tr>
<tr>
<td>CRP</td>
<td>1 mg/dL</td>
<td>0.0-0.6 mg/dL</td>
</tr>
</tbody>
</table>

4. At this time the patient appears to remain iron deficient. The best approach for managing JP’s iron deficiency now is:
   a. Administer pRBC
   b. Screen for other nutrient causes of anemia (copper, zinc, folate)
   c. Recalculate IV iron replacement dose with new labs
   d. Give IV iron maintenance dose and repeat labs one month later

CASE #2

FM is a 25 y.o. female with chronic intestinal pseudo obstruction and intestinal dysmotility dependent on TPN. She cannot clamp her GT due to high output and therefore has not been able to use this for tube feedings. She is able to eat by mouth but the calories she absorbs enterally are uncertain. Her last iron infusion was 2 years ago
Current wt: 58.5 kg

Recent pertinent laboratory parameters:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>10.7 g/dl</td>
<td>11-14 g/dL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>34%</td>
<td>34-42%</td>
</tr>
<tr>
<td>MCV</td>
<td>76%</td>
<td>75-102%</td>
</tr>
<tr>
<td>MCHC</td>
<td>32.6%</td>
<td>30.5-36%</td>
</tr>
<tr>
<td>RDW</td>
<td>14.6%</td>
<td>11.5-15%</td>
</tr>
<tr>
<td>Ferritin</td>
<td>25 ng/ml</td>
<td>6-155 ng/ml</td>
</tr>
<tr>
<td>CRP</td>
<td>0.7 mg/dL</td>
<td>0.0-0.6 mg/dL</td>
</tr>
<tr>
<td>sTfR</td>
<td>unavailable</td>
<td></td>
</tr>
</tbody>
</table>

At this time the best approach for managing FM is:
   a. Administer pRBC
   b. Calculate and give repletion dose of IV iron
   c. Give maintenance dose of IV iron
   d. Continue to monitor
   e. Start enteral iron and repeat labs in 4 weeks including a sTfR
CASE #3

JS is a 12-year-old male with history of intestinal failure secondary to colonic atresia and small bowel volvulus s/p STEP with 100 cm of small bowel remaining. He has been on PN since birth now with evidence of IFALD. His caloric breakdown is: 24% EN: 76% PN. JS received replacement iron dose followed by maintenance dosing of 2 mg/kg every 2-3 months.

Recent pertinent laboratory parameter trend:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Prior to iron replaced</th>
<th>4 weeks post iron replaced</th>
<th>4 weeks post maintenance iron replaced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>8.1 g/dl</td>
<td>8.8 g/dL</td>
<td>9 g/dL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>24.9%</td>
<td>26%</td>
<td>26.3%</td>
</tr>
<tr>
<td>MCV</td>
<td>92.9%</td>
<td>93.5%</td>
<td>86.5%</td>
</tr>
<tr>
<td>MCHC</td>
<td>32.5%</td>
<td>33.5%</td>
<td>32%</td>
</tr>
<tr>
<td>RDW</td>
<td>17.5%</td>
<td>15.9%</td>
<td>17%</td>
</tr>
<tr>
<td>Ferritin</td>
<td>118 ng/ml</td>
<td>127 ng/ml</td>
<td>132 mg/ml</td>
</tr>
<tr>
<td>CRP</td>
<td>2 mg/dL</td>
<td>1.7 mg/dL</td>
<td>2.5 mg/dL</td>
</tr>
<tr>
<td>sTfR</td>
<td>10 mg/L</td>
<td>8.1 mg/L</td>
<td>7.8 mg/L</td>
</tr>
</tbody>
</table>

At this time the best approach for managing JS iron deficiency is:

a. Administer pRBC
b. Calculate and give another repletion dose of iron
c. Continue with maintenance dose of iron every 2-3 months
d. Screen for other nutrient causes of anemia
e. Add enteral iron to maintenance dose regimen

CASE #4

For each of the following IF scenarios, use the flowchart to determine the best management strategy:

- 26 year old with high ferritin, normal CRP, normal sTfR
- 18 year old with high sTfR, normal Hg, 80% calories EN, 20% PN
- 15 year old with normal ferritin but trending lower with each monthly lab, normal CRP
- 2 year old with normal sTfR
- Four month old with low Hg, low ferritin, normal CRP, no sTfR available