MEDICATION MANAGEMENT OF ANEMIA IN THE PEDIATRIC PATIENT

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April 4, 2019
DISCLOSURE

Jennifer Morris, PharmD has no conflicts of interest to disclose
OBJECTIVES

1. Identify the type of anemia

2. Develop a medication therapy plan based on the type of anemia

3. Evaluate the effectiveness of a medication therapy plan for anemia
ANEMIA

• Hemoglobin or RBC volume decreased from normal for age, sex, and race
• Compensation for anemia
  • Increased cardiac output
  • Augmented oxygen extraction
  • Shunting blood flow to more vital organs
  • Increase in erythropoietin
• Initial evaluation
  • Hemoglobin/Hematocrit
  • Red cell indices
  • Reticulocyte count
  • Peripheral smear
DIFFERENTIATING ANEMIA

Morphology: RBC size (MCV) RBC appearance
Decreased production OR Increased destruction
Underlying cause

Anemia
- Microcytic Low reticulocyte
  - Iron deficiency
  - Lead poisoning
- Normocytic Low reticulocyte
  - Anemia of Inflammation
- Macrocytic Low reticulocyte
  - Folate deficiency
  - Vit B12 deficiency

MICROCYTIC ANEMIA
IRON DEFICIENCY (ID)

• Most common single-nutrient deficiency
• Affected age groups:
  • Pre-term infants
  • Term infants
  • Adolescents
• ID due to chronic conditions
• Deficiency may be absolute or functional

## DIAGNOSIS

<table>
<thead>
<tr>
<th></th>
<th>Serum Iron</th>
<th>Transferrin Saturation</th>
<th>Serum Ferritin</th>
<th>Hemoglobin</th>
<th>Mean Corpuscular Volume</th>
<th>Mean Corpuscular Hemoglobin</th>
</tr>
</thead>
<tbody>
<tr>
<td>ID</td>
<td>↓</td>
<td>≥ 16</td>
<td>&lt; 60</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Functional ID</td>
<td>--/↓</td>
<td>--/↓</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>IDA*</td>
<td>↓</td>
<td>&lt; 16</td>
<td>&lt; 12</td>
<td>↓</td>
<td>&lt; 80</td>
<td>&lt; 27</td>
</tr>
<tr>
<td>IDA in Chronic Diseases</td>
<td>↓</td>
<td>--/↓</td>
<td>&lt; 100</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

*IDA, iron deficiency anemia

## PREVENTING IRON DEFICIENCY

<table>
<thead>
<tr>
<th></th>
<th>Preterm Infants</th>
<th>Term Infants</th>
<th>Ages 1-3 years</th>
</tr>
</thead>
</table>
| **Iron Requirement** | 2 – 4 mg/kg per day | < 6 months: 0.27 mg/day  
|                      |                  | ≥ 6 months: 11 mg/day     | 7 mg/day       |
| **Age for Supplementation** | 1 – 12 months | 4 – 12 months | -- |
| **Iron Supplementation Based on Feeds** |                      |                           |                |
| Human Milk           | 2 mg/kg per day | 1 mg/kg per day | -- |
| Formula              | 1 mg/kg per day | None                     | -- |
| Iron-fortified foods | Introduce as appropriate | Sufficient dietary intake |                |
| Cow’s Milk Restriction | Restrict to > 12 months of age | < 24 ounces per day |                |

MANAGEMENT OF IRON DEFICIENCY ANEMIA

- Oral iron replacement
- Intravenous iron replacement
- Management of underlying chronic disease
ORAL V. IV THERAPY

**Oral**
- **Pro**
  - Cheap
  - Readily available
  - Multiple dosage forms
  - Effective at replacing iron stores in most patients
- **Con**
  - Tolerability
  - Impaired absorption in chronic disease/inflammatory states

**IV**
- **Pro**
  - Rapid replacement of iron stores
  - Overcome absorption issues with oral therapy
  - Known adherence to therapy
- **Con**
  - Requires IV access
  - Risk of severe adverse effects
# Oral Iron Preparation Comparison

<table>
<thead>
<tr>
<th>Iron Product</th>
<th>Dosage forms</th>
<th>Elemental Iron</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous sulfate</td>
<td>Elixir</td>
<td>20%</td>
<td>• Most readily available</td>
</tr>
<tr>
<td></td>
<td>Solution</td>
<td></td>
<td>• Many dosage forms</td>
</tr>
<tr>
<td></td>
<td>Syrup</td>
<td></td>
<td>• Use caution with liquid products – multiple concentrations</td>
</tr>
<tr>
<td></td>
<td>Tablets</td>
<td></td>
<td>• ER tablets reserve for maintenance of iron stores v replacement</td>
</tr>
<tr>
<td></td>
<td>ER tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferrous fumarate</td>
<td>Tablet</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>Tablet</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>Polysaccharide iron complex</td>
<td>Capsule</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liquid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferric citrate</td>
<td>Tablet</td>
<td>20%</td>
<td>• Also used as phosphate binder</td>
</tr>
</tbody>
</table>
ORAL IRON REPLACEMENT THERAPY

• Dose:
  • 3 – 6 mg/kg per DAY of elemental iron in 3 divided doses
  • Adult size patients: 100 – 200 mg per DAY of elemental iron in 3 divided doses
  • Maximum: 65 mg of elemental iron 3 times per day

• Therapeutic endpoint/duration:
  • Increase in Hgb by 1 mg/dL in 1 months
  • Full replacement: 3-6 months

DEPARTMENT OF PHARMACY

Camashella C. Blood 2019;133:30-9
OPTIMIZING ABSORPTION

• Administer on empty stomach
  • 1 hour prior to or 2 hours following meals

• Avoid:
  • Acid suppressing agents
  • Concomitant administration agents that chelate with iron
ADVERSE EFFECTS

• Gastrointestinal adverse effects are common
• Dyspepsia
• Nausea
• Vomiting
• Abdominal pain
• Constipation
• Diarrhea
ORAL IRON FAILURE

- Intolerance
- Non-adherence
- Diminished iron absorption
INTRAVENOUS IRON REPLACEMENT

- Severe deficiency
- Need for rapid hemoglobin response
- Intolerance to oral iron
- Unlikely to respond to oral iron
**IV IRON PREPARATIONS**

- Doses vary greatly based on indication
- Use caution when transition between products is needed

<table>
<thead>
<tr>
<th>Iron Product</th>
<th>Iron per mL</th>
<th>Maximum Single Dose</th>
<th>Infusion Time</th>
<th>Test Dose Recommended</th>
<th>Number of Doses for Replacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron dextran (LMW)</td>
<td>50 mg</td>
<td>Total replacement</td>
<td>Up to 6 hours</td>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>Iron sucrose</td>
<td>20 mg</td>
<td>400 mg</td>
<td>2.5 hours</td>
<td>No</td>
<td>At least 3</td>
</tr>
<tr>
<td>Ferric gluconate</td>
<td>12.5 mg</td>
<td>125 mg</td>
<td>1 hour</td>
<td>No</td>
<td>5</td>
</tr>
<tr>
<td>Ferric carboxymaltose</td>
<td>50 mg</td>
<td>750 mg</td>
<td>15 minutes</td>
<td>No</td>
<td>2</td>
</tr>
</tbody>
</table>

RISK OF SERIOUS ADVERSE EVENTS

- High risk of serious adverse reactions extrapolated from high-molecular weight iron dextrans
  - No longer used or available in the US
- Risk cannot be extrapolated to currently available IV iron products
- Recent data supports a small risk of serious adverse effects
- Test doses may give false security that reactions will not occur
- Awareness of risk minimization strategies

European Medicines Agency. New recommendations to manage risk of allergic reactions with IV iron-containing medicines. 2013
### FACTORS ASSOCIATED WITH SERIOUS ADVERSE EFFECTS

<table>
<thead>
<tr>
<th>Risk and Poor Outcome</th>
<th>Poor Outcome</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Previous adverse reaction to IV iron</td>
<td>• Severe respiratory disease</td>
<td>• Healthcare provider anxiety</td>
</tr>
<tr>
<td>• History of other drug allergies</td>
<td>• Severe cardiac disease</td>
<td>• Patient anxiety</td>
</tr>
<tr>
<td>• Fast infusion rate</td>
<td>• Use of b-blockers or ACE inhibitors</td>
<td></td>
</tr>
<tr>
<td>• History of severe atopy or mastocytosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MINIMIZING RISK OF SERIOUS ADVERSE REACTIONS

- Appropriate facility
- Trained personnel
- Educate patients
- Assessment of risk prior to administration
- Thorough documentation of reactions

MANAGEMENT OF SERIOUS ADVERSE EVENTS

Hypersensitivity Reaction

Mild:
1. Pause infusion ≥ 15 minutes
2. If symptoms improve/resolve → restart infusion at 50% of rate and observe after infusion
3. If symptoms do not resolve or worsen → manage as moderate or severe based on symptoms

Moderate:
1. Stop infusion
2. Consider fluid bolus and IV hydrocortisone
3. Observe for at least 1 hour
4. If symptoms worsen → manage as severe reaction

Severe or Life-threatening:
1. Stop infusion
2. Consider fluid bolus and IV hydrocortisone
3. Call emergency response team → manage via anaphylaxis or ACLS algorithm as appropriate
4. If symptoms do not improve or worse → transfer to ICU
PREVENTION OF ID

• Oral prevention therapy
  • 0-5 years: 2 mg/kg per DAY of elemental iron
  • 5-12 years: 30 mg per DAY of elemental iron
  • > 12 years: 60 mg per DAY of elemental iron

• IV maintenance therapy

LEAD TOXICITY

• Anemia results from:
  • RBC destruction
  • Interference with heme synthesis
  • Impaired iron absorption
• Remove lead source
• Chelation therapy for severe
• Manage ID
NORMOCYTIC ANEMIA
ANEMIA OF INFLAMMATION

• Second most common after iron deficiency anemia

• Pathophysiology
  • Iron restriction
  • Suppression of erythropoietic activity
  • Decreased erythrocyte survival

Associated Chronic Conditions

• Chronic kidney disease
• Malignancy
• Autoimmune diseases
• Congestive heart failure
• Chronic pulmonary diseases
• Chronic infections

Mild to moderate anemia
Normochromic, normocytic
Ferritin may be normal or elevated
May occur in conjunction with ID or IDA
  - Children are more susceptible to concomitant anemias
Additional coexisting evaluation:
  - Renal function
  - Liver function
  - Thyroid function
  - Markers of hemolysis
  - Vitamin/mineral status: folate, vitamin $B_{12}$, vitamin D

MANAGEMENT OF ANEMIA OF INFLAMMATION

- Treatment of underlying condition
- Correct all other vitamin and mineral deficits
- Erythropoiesis-stimulating agents
  - Individualize hemoglobin target
  - Lowest dose to minimize need for transfusion and manage symptoms

# ERYTHROPOIESIS-STIMULATING AGENTS (ESA)

<table>
<thead>
<tr>
<th>ESA Type</th>
<th>Characteristics</th>
</tr>
</thead>
</table>
| **Epoetin Alfa**         | • Recombinant human erythropoietin  
                          • Short half-life  
                          • Subcutaneous ($t_{1/2} = 19-24$ h) and IV ($t_{1/2} = 6-8$ h)  
                          • Multiple time per week dosing  
                          • Initial dose 150 units/kg per week divided 3 times per week |
| **Darbepoetin Alfa**     | • Analog of recombinant human erythropoietin  
                          • Half-life ~ 2-3x longer than epoetin alfa  
                          • Subcutaneous ($t_{1/2} = 48$ h) and IV ($t_{1/2} = 19$ h)  
                          • Allows for less frequent dosing  
                          • 0.45 mcg/kg weekly or 0.75 mcg/kg bi-weekly (subcutaneous only) |
| **Methoxy Polyethylene Glycol-Epoetin Beta** | • Continuous erythropoietin receptor activator (CERA)  
                          • Long duration of action → complex with large polymer chain results  
                          • Lower receptor affinity and longer half-life ($t_{1/2} \approx 139$ h)  
                          • Subcutaneous and IV  
                          • 0.6 mcg/kg every 2 weeks |

---

*Warady BA, Pediatr Nephrol 2014;29:1493-1505*  
ESA HYPO-RESPONSIVENESS

• Iron deficiency
• Vitamin D insufficiency or deficiency
• Inflammation
• Hyperparathyroidism
• Malnutrition
• Chronic infection
• ESA neutralizing antibodies → pure red cell aplasia
ESA RISK

- Mortality risk
  - Increase risk in cardiovascular endpoints
- Increased Hb or increase ESA dose?
- Possible mechanism:
  - Effect on coagulation or angiogenesis
  - Direct proliferative effects on malignant cells
  - Immunomodulatory effects
- REMS program ended April 2017

https://www.fda.gov/Drugs/DrugSafety/ucm109375.htm
MACROCYTIC ANEMIA
FOLATE DEFICIENCY

- Dependent on dietary source
  - 4 – 7 months of age
  - Nutritional deficit most common cause
  - Occurs rapidly with malnutrition
- Other potential etiologies:
  - Decreased absorption
  - Inborn errors in folate metabolism or transport
  - Drug-induced

MANAGEMENT OF FOLATE DEFICIENCY

- Folic acid
- Dosage form considerations
  - Only available as tablets
  - Oral liquid maybe compounded
- Duration
  - 3-4 weeks
  - Definitive hematologic response

<table>
<thead>
<tr>
<th></th>
<th>Infants</th>
<th>Children &lt; 4 years</th>
<th>Children ≥ 4 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replacement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.4 – 1 mg/day</td>
<td></td>
<td>Higher doses may be needed in resistant cases</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>In adults doses of 1 – 5 mg/day and up to 15 mg/day have been recommended</td>
<td></td>
</tr>
<tr>
<td>Maintenance</td>
<td>0.1 mg/day</td>
<td>0.3 mg/day</td>
<td>0.4 mg/day</td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
<td></td>
<td>0.4 – 0.8 mg/day</td>
</tr>
</tbody>
</table>
VITAMIN B12 DEFICIENCY

- Vitamin $B_{12}$ refers to all biologically active cobalamins
- Dependent on dietary sources
  - 6 – 18 months of age
  - In older children and adults requires prolonged malnutrition
- Other etiologies:
  - Impaired absorption
  - Vitamin $B_{12}$ transport protein deficiency
  - Inborn errors of cobalamin metabolism
**MANAGEMENT OF VITAMIN B12 DEFICIENCY**

- Replacement dosing and duration dependent on cause
- Concurrent folic acid supplementation may be required
- Dosage form considerations
  - Parenteral
  - Nasal spray
  - Tablets

<table>
<thead>
<tr>
<th></th>
<th>IM or Subcutaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pernicious anemia</strong></td>
<td>• Option 1:</td>
</tr>
<tr>
<td></td>
<td>• 100 mcg daily x 7 days</td>
</tr>
<tr>
<td></td>
<td>• 100 mcg every other day x 7 doses</td>
</tr>
<tr>
<td></td>
<td>• 100 mcg every 3-4 days x 2-3 weeks</td>
</tr>
<tr>
<td></td>
<td>• 100 mcg monthly</td>
</tr>
<tr>
<td></td>
<td>• Option 2</td>
</tr>
<tr>
<td></td>
<td>• 1000 mcg daily x 7 days</td>
</tr>
<tr>
<td></td>
<td>• 100 mcg weekly x 4 weeks</td>
</tr>
<tr>
<td></td>
<td>• 100 mcg monthly</td>
</tr>
<tr>
<td><strong>Dietary deficiency</strong></td>
<td>• 250 – 1000 mcg daily x 7-14 days</td>
</tr>
<tr>
<td></td>
<td>• 250 – 1000 mcg weekly until recovery</td>
</tr>
<tr>
<td><strong>Malabsorption</strong></td>
<td>• 250 – 1000 mcg daily to every other day x 7 days</td>
</tr>
<tr>
<td></td>
<td>• 250 – 1000 mcg weekly x 4-8 weeks</td>
</tr>
<tr>
<td></td>
<td>• 250 – 1000 mcg monthly</td>
</tr>
</tbody>
</table>
COMMENTS/QUESTIONS?