Renal Anemia: The Basics

Peter Yorgin, M.D.
University of California San Diego

Fundamentals of Dialysis in Children
Saturday, March 11, 2017
2:10-2:50 PM

Lecture Objectives

• Brief Review of Erythrocyte Function and Production in health and chronic kidney disease (CKD)
• Management of Erythropoiesis Stimulating Agents in children with CKD
  – Discuss the indications, dosing recommendations, beneficial and adverse effects of recombinant human ESAs.
  – Understand the causes of recombinant human erythropoietin resistance.
• Iron regulation and therapy in children with CKD

What do erythrocytes do?

• Hemoglobin-mediated delivery of oxygen to cells
• Regulate red blood cell delivery through hemodynamic regulation
  – Sheer stress induces release of ATP and nitric oxide which cause blood vessel walls to dilate.
  – Deoxygenation of hemoglobin molecules induces the release of S-nitrosothiols, which dilate blood vessels.
• Assist in the immune response
  – Release of free radicals when erythrocytes are lysed by bacteria.

Welcome to the erythocyte production floor!

• In blood: 3.9 - 5.7 x 10^{12} cells per liter = 4,000,000,000,000 (that’s trillions!).
• Blood volume: 70-80 mL/kg
• 25 kg child blood volume = 1750-2000 mL
• RBC life span
  – Infant 80-90 days
  – Adult 100-120 days
• Erythrocytes made per minute for 2L blood volume: 48,611,112
What is essential for an adequate environment for erythrocytosis?

• Healthy bone marrow

• Iron, copper, cobalt

• Vitamins C, B2, B5, B12 and folic acid

• Androgens, glucocorticoids and thyroid hormones
  • Hematopoietic growth factors

Bone marrow production “floor” for erythrocytes

Colony forming unit – stem cell
Blast forming unit – erythroid
Colony forming unit erythroid
Reticulocyte
Erythrocyte

Colony forming unit- stem cell (CFU-S)

CFU-S can be quiescent
CFU-S can self-replicate
CFU-S can differentiate creating erythrocytes, granulocytes, monocytes or platelets.

• Transcription factors, SCL and LM2, GATA-2, CBA alpha/beta, C-myb, HoxB4 are essential for expansion and differentiation to erythrocytes
A transcription factor, GATA-1, is essential for commitment to erythroid differentiation.  
- GATA-1 up-regulates a number of genes that are essential to development and function of erythrocytes.  
- GATA-1 down-regulates genes essential for erythroblasts.  
- GATA-1 knock-out mice die due to an inability to form erythrocytes.  
- Upregulates aminoleuvulinic acid synthase, the first enzyme required to start heme synthesis.

Erythropoietin suppresses erythroid apoptosis. Apoptosis begins when erythroid cells are deprived of erythropoietin for as little as 2 hours.  
- Other proteins critical to erythropoiesis:  
  - Erythropoietin receptor  
  - W  
  - SF (Steel factor) and c-kit  
  - IL-6, IL-11, IL-3  
  - Granulocyte macrophage colony stimulating factor receptor

Erythropoietin is produced by interstitial cells in the kidneys

Bone marrow production “floor” for erythrocytes

Bone marrow production “floor” for erythrocytes: Insertion of hemoglobin

- Colony forming unit – stem cell
- Blast forming unit – erythroid
- Colony forming unit erythroid
- Reticulocyte
- Erythrocyte
- Pro-erythroblast
- Basophilic erythroblast
- Polychromic erythroblast
- Orthochromic erythroblast

Heme biosynthesis

- Each erythrocyte has 280 million hemoglobin molecules and 1.08 billion oxygen molecules!

Iron homeostasis

What happens to hepcidin levels in children with CKD?


Erythroferrone to the rescue?

• Erythroferrone
  – Produced in erythroblasts after stimulation by erythropoietin.
  – released and inhibits expression of hepcidin.

  Kautz L. Nat Genet 2014, 46(7): 678–684

Which factors slow erythropoiesis?

<table>
<thead>
<tr>
<th>Microcytic Low MCV</th>
<th>Normocytic Normal MCV</th>
<th>Macrocytic High MCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>High RDW</td>
<td>Thalassemia</td>
<td>Hereditary hemoglobinopathy (β0, 0)</td>
</tr>
<tr>
<td>Low RDW</td>
<td>Chronic disease</td>
<td>Chronic liver disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(α0, 0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal MCV</td>
<td></td>
<td>Aplastic anemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pre-leukemia</td>
</tr>
</tbody>
</table>

Colony forming unit – stem cell
Blast forming unit – erythroid
Colony forming unit erythroid
Reticulocyte
Erythrocyte

What causes the anemia in CKD?

<table>
<thead>
<tr>
<th>CKD stage</th>
<th>Anemia with a Hgb &lt;12 g/dL or ESA treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td>30%</td>
</tr>
<tr>
<td>3</td>
<td>66%</td>
</tr>
<tr>
<td>4-5</td>
<td>95%</td>
</tr>
</tbody>
</table>


Low erythropoietin levels cause anemia in CKD and ESRD

Colony forming unit – stem cell
Blast forming unit – erythroid
Colony forming unit erythroid
Reticulocyte
Erythrocyte

Erslev AJ. Seminars in Hematology 28 (3, suppl 3):2-8, 1991
Can we control the production floor to keep erythrocyte numbers in target?

- Keep the bones in good health with the active form of vitamin D and cholecalciferol/ergocalciferol?
- Provide vitamins that are removed during dialysis?
- Infuse ESA to keep erythrocyte production high enough to replacing all the cells that are being lost? Without making too many cells?
- Give enough iron so that heme molecules are being made?
- Keep the production floor "clean" with dialysis?
- Take steps to keep the patient infection free?

What is the recommended frequency of screening for anemia?

<table>
<thead>
<tr>
<th>Patients without anemia</th>
<th>No dialysis</th>
<th>Dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD 3</td>
<td>CKD 4-5</td>
<td>CKD 5PD</td>
</tr>
<tr>
<td>At least annually</td>
<td>At least twice per year</td>
<td>At least every three months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients with anemia</th>
<th>No dialysis</th>
<th>Dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least every three months</td>
<td>At least every three months</td>
<td>At least every three months</td>
</tr>
</tbody>
</table>

Kidney International Supplements 2012, 2, 283–287 [KDIGO: 1.1.1 and 1.1.2]

What is the KDIGO definition of anemia in children?

<table>
<thead>
<tr>
<th>Age group in years</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 15 years of age</td>
<td>&lt;13.0</td>
<td>&lt;12.0</td>
</tr>
<tr>
<td>0.5-5 years of age</td>
<td>&lt;11.0</td>
<td>&lt;11.5</td>
</tr>
<tr>
<td>5-12 years of age</td>
<td>&lt;11.5</td>
<td>&lt;12.0</td>
</tr>
</tbody>
</table>

Kidney International Supplements 2012, 2, 283–287 [KDIGO: 1.1.1 and 1.1.2]

Erythropoiesis stimulating agent (ESA) therapy

<table>
<thead>
<tr>
<th></th>
<th>In the United States</th>
<th>In Europe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythropoietin</td>
<td>Darbepoetin</td>
<td>Epoetin zeta</td>
</tr>
<tr>
<td>alpha</td>
<td>Methoxy polyethylene glycol-epoetin beta</td>
<td>Epoetin alpha</td>
</tr>
<tr>
<td>Brand names</td>
<td>Epogen, Procrit</td>
<td>Binocrit, Retacrit</td>
</tr>
<tr>
<td>Half life</td>
<td>IV: 4-13 hours</td>
<td>IV: 4-5 hours</td>
</tr>
<tr>
<td></td>
<td>SQ: 13-37 hours</td>
<td>SQ: 12-18 hours</td>
</tr>
<tr>
<td>FDA Approval</td>
<td>Approved</td>
<td>Not approved</td>
</tr>
<tr>
<td></td>
<td>Approved in USA</td>
<td>Not approved in USA</td>
</tr>
<tr>
<td></td>
<td>Approved in Europe</td>
<td>Approved in Europe</td>
</tr>
<tr>
<td>Cell line source</td>
<td>Chinese hamster ovary cells</td>
<td>Chinese hamster ovary cells</td>
</tr>
<tr>
<td></td>
<td>Chinese hamster ovary cells</td>
<td>Chinese hamster ovary cells</td>
</tr>
<tr>
<td></td>
<td>Chinese hamster ovary cells</td>
<td>Chinese hamster ovary cells</td>
</tr>
</tbody>
</table>

Erythropoietin dosing data in children receiving dialysis


What is the most appropriate initial erythropoietin dosing in children?

<table>
<thead>
<tr>
<th></th>
<th>Hemodialysis</th>
<th>Peritoneal dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 5 years of age</td>
<td>250-300 units/kg/week</td>
<td>100-150 units/kg/week</td>
</tr>
<tr>
<td>Age &gt; 5 years of age</td>
<td>150-200 units/kg/week</td>
<td>50-100 units/kg/week</td>
</tr>
</tbody>
</table>

Darbepoetin use in chronic kidney disease

- Prospective, phase IV, observational registry study with 391 patients observed for less than two years.
- Inclusion criteria: children ≤ 16 years of age with CKD anemia and receiving darbepoetin.
- Of 434 serious adverse events reported in 162 children, the most common were peritonitis (10.0%), gastroenteritis (6.0%), and hypertension (4.1%).
- Four patients (1.3%) experienced six serious adverse drug reactions.
- Darbepoetin dose range was 1.4-2.0 μg/kg/month.
- No new safety signals for darbepoetin were identified.
- Based on hemoglobin concentrations and transfusion requirements, darbepoetin was effective at managing anemia in these patients.


- When converting from subcutaneous to intravenous erythropoietin, a dose increase of 11 percent is needed to maintain the hemoglobin.
What influences darbopoetin dosing?


What is the conversion factor for changing erythropoietin to darbopoetin?

- Conversion factor for patients receiving erythropoietin:
  - 200 units erythropoietin = 1 microgram darbopoetin
  - Darbepoetin dose may be lower, 267-800 units erythropoietin = 1 microgram darbopoetin
    - Pediatr Nephrol 19:337-340, 2004
  - 100 units erythropoietin = 0.42 microgram darbopoetin
    - (Amgen Pediatric Study)

Is injection pain greater with darbopoetin?


Is there pediatric dosing information for Mircera?

- Prospective pediatric study in Chile.
  - 16 subjects, mean age 9.7 ± 3.9 years.
  - All peritoneal dialysis dependent
  - Receiving EPO therapy prior to study.
  - Initial dosing 0.86 μg/kg every two weeks.
  - Final dosing 1.67 mcg/kg
  - Two subjects switched to q month dosing.
  - No hypertension or other adverse events reported.

What is the best way to adjust ESA dosing?

• It is important to make small (10-25%) incremental changes in the ESA dose no more frequently than every two-four weeks.
• Frequent adjustments in ESA can hinder the maintenance of a steady-state hemoglobin level.
• If the hemoglobin is rising rapidly, >2 g/dL in 4 weeks, or if the hemoglobin level is >12 g/dL, then the ESA dose should be decreased by 25-50%.
• Initial unresponsiveness to ESA: Dose should not be increased to more than double of the starting ESA dose.
• Medicare expects a 25 percent reduction in the dosage of the drug for patients whose hematocrit exceeds 39.0 (hemoglobin of 13.0). In lieu of a GS modifier, and the dosage is not reduced, payment will be made for the drugs as if the reduction had occurred. Also a new maximum limitation for each drug per month is created.
  — CMS Pub 100-04

What is the adverse effect profile of ESAs in children?

• Early RCT trial: Iron deficiency, flu-like symptoms, hypertension (30-66%), hyperkalemia (33%).

<table>
<thead>
<tr>
<th>Table 3</th>
<th>ESAs administered intravenously for stable children (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESA</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Epogen</td>
<td>7.3 ± 2.2</td>
</tr>
<tr>
<td>Retacrit</td>
<td>6.8 ± 1.9</td>
</tr>
<tr>
<td>Aranesp</td>
<td>6.3 ± 1.7</td>
</tr>
</tbody>
</table>

Is it possible to monitor hemoglobin levels in children on HD using the Critline™?

Stavinoha A et al, Hemodialysis Int 2013; 17:S7–S10

What is hemoglobin target in children with CKD and ESRD?

• In adults, the hemoglobin target range is 10.0 to 11.5 g/dL
  — Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR)
  — Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE)
  — Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT)
• In children
  — Current KDIGO recommendations for children with CKD receiving ESA therapy, the target hemoglobin should be 11.0–12.0 g/dL.
  — Hemoglobin level at which ESA therapy is initiated should be determined by a number of factors, including quality of life and school performance.
  — In dialysis patients with CKD, start ESA when the hemoglobin is <9-10 g/dL.
  — The target should not be greater than 13.0 g/dL
  — For all pediatric CKD patients, we suggest that the selection of hemoglobin concentration at which ESA therapy is initiated in the individual patient includes consideration of potential benefits (e.g., improvement in quality of life, school attendance/performance, and avoidance of transfusion) and potential harms. (2D)

What is the best way to adjust ESA dosing?

• It is important to make small (10-25%) incremental changes in the ESA dose no more frequently than every two-four weeks.
• Frequent adjustments in ESA can hinder the maintenance of a steady-state hemoglobin level.
• If the hemoglobin is rising rapidly, >2 g/dL in 4 weeks, or if the hemoglobin level is >12 g/dL, then the ESA dose should be decreased by 25-50%.
• Initial unresponsiveness to ESA: Dose should not be increased to more than double of the starting ESA dose.
• Medicare expects a 25 percent reduction in the dosage of the drug for patients whose hematocrit exceeds 39.0 (hemoglobin of 13.0). In lieu of a GS modifier, and the dosage is not reduced, payment will be made for the drugs as if the reduction had occurred. Also a new maximum limitation for each drug per month is created.
  — CMS Pub 100-04

Is it possible to monitor hemoglobin levels in children on HD using the Critline™?

Stavinoha A et al, Hemodialysis Int 2013; 17:S7–S10

What is the adverse effect profile of ESAs in children?

• Early RCT trial: Iron deficiency, flu-like symptoms, hypertension (30-66%), hyperkalemia (33%).

<table>
<thead>
<tr>
<th>Table 3</th>
<th>ESAs administered intravenously for stable children (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESA</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Epogen</td>
<td>7.3 ± 2.2</td>
</tr>
<tr>
<td>Retacrit</td>
<td>6.8 ± 1.9</td>
</tr>
<tr>
<td>Aranesp</td>
<td>6.3 ± 1.7</td>
</tr>
</tbody>
</table>

Is it possible to monitor hemoglobin levels in children on HD using the Critline™?

Stavinoha A et al, Hemodialysis Int 2013; 17:S7–S10

What is the adverse effect profile of ESAs in children?

• Early RCT trial: Iron deficiency, flu-like symptoms, hypertension (30-66%), hyperkalemia (33%).

<table>
<thead>
<tr>
<th>Table 3</th>
<th>ESAs administered intravenously for stable children (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESA</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Epogen</td>
<td>7.3 ± 2.2</td>
</tr>
<tr>
<td>Retacrit</td>
<td>6.8 ± 1.9</td>
</tr>
<tr>
<td>Aranesp</td>
<td>6.3 ± 1.7</td>
</tr>
</tbody>
</table>

Is it possible to monitor hemoglobin levels in children on HD using the Critline™?

Stavinoha A et al, Hemodialysis Int 2013; 17:S7–S10

What is the best way to adjust ESA dosing?

• It is important to make small (10-25%) incremental changes in the ESA dose no more frequently than every two-four weeks.
• Frequent adjustments in ESA can hinder the maintenance of a steady-state hemoglobin level.
• If the hemoglobin is rising rapidly, >2 g/dL in 4 weeks, or if the hemoglobin level is >12 g/dL, then the ESA dose should be decreased by 25-50%.
• Initial unresponsiveness to ESA: Dose should not be increased to more than double of the starting ESA dose.
• Medicare expects a 25 percent reduction in the dosage of the drug for patients whose hematocrit exceeds 39.0 (hemoglobin of 13.0). In lieu of a GS modifier, and the dosage is not reduced, payment will be made for the drugs as if the reduction had occurred. Also a new maximum limitation for each drug per month is created.
  — CMS Pub 100-04

What is the adverse effect profile of ESAs in children?

• Early RCT trial: Iron deficiency, flu-like symptoms, hypertension (30-66%), hyperkalemia (33%).

<table>
<thead>
<tr>
<th>Table 3</th>
<th>ESAs administered intravenously for stable children (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESA</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Epogen</td>
<td>7.3 ± 2.2</td>
</tr>
<tr>
<td>Retacrit</td>
<td>6.8 ± 1.9</td>
</tr>
<tr>
<td>Aranesp</td>
<td>6.3 ± 1.7</td>
</tr>
</tbody>
</table>
**What are the most common causes of ESA resistance in children on dialysis?**

- **Definition:** > 500 units/kg/week
- The most predictive model of erythropoietin response for the pediatric cohort had, as the major variables,
  - Low Kt/V and urea reduction ratio (URR)
  - High intact parathyroid hormone (iPTH) levels
  - High blood loss
  - Low normalized protein catabolic rates (nPCR)
  - Indices of inflammation and malnutrition.

**Table 1: Practical approach in presence of ESA hyperresponsiveness**

<table>
<thead>
<tr>
<th>Tests</th>
<th>Finding and action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Check adherence</td>
<td>If low, attempt to improve (if self-injection)</td>
</tr>
<tr>
<td>2. Retrospective cause</td>
<td>If &gt;1000mL/kg/week, look for blood loss or hemolysis; endoscopy, colonoscopy, hemolysis screen</td>
</tr>
<tr>
<td>Serum vitamin B12, folate</td>
<td>If low, replenish</td>
</tr>
<tr>
<td>Iron status</td>
<td>If elevated, measure hepcidin tendonitis</td>
</tr>
<tr>
<td>Serum PTH</td>
<td>If elevated, check for and treat infection or inflammation</td>
</tr>
<tr>
<td>Underdiagnosis</td>
<td>If underdiagnosed, improve dialysis efficiency</td>
</tr>
<tr>
<td>ACS/MIB use</td>
<td>If use, consider reducing dose or discontinuing drug</td>
</tr>
<tr>
<td>3. Bone marrow biopsy</td>
<td>Manage condition diagnosed e.g., thalassemia, iron deficiency, anemia</td>
</tr>
</tbody>
</table>

**Which other factors cause ESA resistance?**

**Category**

- **Infections**
  - CRP, WBC (differential), Parvovirus
- **Severe bone disease**
  - Intact PTH, 25 OH vitamin D
- **Iron depletion**
  - Iron, Ferritin, TIBC
- **Vitamin and mineral deficiency**
  - Folate, Vitamin B12, Copper
- **Dialysis factors**
  - Chronic blood loss with dialysis and blood draws
  - Shortened RBC survival
- **Aluminum toxicity**
  - Aluminum level
- **Malnutrition**
  - Serum albumin, marrow, transferrin, serum carnitine
- **Medications**
  - H2 blockers and proton pump inhibitors
  - Aspirin and anti-platelet agents
  - Sulfa drugs
  - Metformin
  - Phenobarbital
  - Bisphosphonates
  - Phenytoin
  - Captoprildes
  - MAAIN
  - Chemotherapy agents
  - Sevelamer
- **Anti-erythropoietin antibody**
  - Anti-erythropoietin antibody
- **Hemolysis**
  - LDH, haptoglobin, Coombs
- **Shortened RBC survival**
  - RBC survival study

**What are the currently accepted definitions of iron deficiency for CKD?**

- **Functional iron deficiency = TSAT less than 20%**
- **Absolute iron deficiency = Ferritin <100 ng/mL**

Are the iron deficiency markers we currently use the best?

- Tests that are less specific (serum ferritin and TSAT) lead to more patients receiving iron therapy, incurring additional costs and complications.
- Tests that are less sensitive (requirement for both low TSAT and low ferritin) lead to patients failing to receive needed iron therapy which can reduce erythropoietin doses.


Can we determine if dialysis-dependent children have iron deficiency?

- 45 pediatric subjects with 606 observations.
- Reticulocyte hemoglobin values of 28.9 and 27.7 pg produced the best sensitivity and specificity for the diagnosis of absolute iron deficiency anemia and functional iron deficiency anemia, respectively.


### Common forms of oral iron

<table>
<thead>
<tr>
<th>Form</th>
<th>Brand Name/mg/elemental iron dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous fumarate (elemental iron content = 11.6%)</td>
<td>Tablet: Ferretts: 325 mg (106 mg), 90 mg (29.5 mg), 324 mg (106 mg elemental iron),</td>
</tr>
<tr>
<td></td>
<td>Ferrimin 150: Elemental iron 150 mg, 106 mg elemental iron,</td>
</tr>
<tr>
<td></td>
<td>Hemocyte: 324 mg (106 mg elemental iron), 90 mg (29.5 mg elemental iron),</td>
</tr>
<tr>
<td></td>
<td>Ferrocite: 324 mg (106 mg elemental iron), 90 mg (29.5 mg elemental iron),</td>
</tr>
<tr>
<td></td>
<td>Tablet: 325 mg (106 mg elemental iron)</td>
</tr>
<tr>
<td>Ferrous gluconate (elemental iron content = 20-30%)</td>
<td>Tablet: Ferrogan: 240 mg [elemental iron 27 mg], 27 mg</td>
</tr>
<tr>
<td></td>
<td>Tablet: Fergon: 240 mg [elemental iron 27 mg], 27 mg</td>
</tr>
<tr>
<td></td>
<td>Tablet: Ferrous gluconate: 240 mg</td>
</tr>
<tr>
<td>Polysaccharide-iron complex</td>
<td>Capsule, Oral: EZFE 200: 200 mg, 150 mg</td>
</tr>
<tr>
<td></td>
<td>Ferrous: 150 mg, 100 mg, 50 mg, 25 mg, 15 mg, 5 mg</td>
</tr>
<tr>
<td></td>
<td>MyKrono: 150, 100 mg, 50 mg, 25 mg, 15 mg, 5 mg</td>
</tr>
<tr>
<td></td>
<td>Novoferrox: 50, 100 mg, 25 mg, 15 mg, 10 mg, 5 mg</td>
</tr>
<tr>
<td></td>
<td>Polyiron: 150, 100 mg, 50 mg, 25 mg, 15 mg, 10 mg, 5 mg</td>
</tr>
<tr>
<td></td>
<td>Novoferrox: 125 Polysaccharide-iron complex 125 mg and cholecalciferol 0.5 mg/5 mL</td>
</tr>
<tr>
<td></td>
<td>Novoferrox Pediatric Drops: 15 mg/mL (120 mL)</td>
</tr>
</tbody>
</table>

### Common forms of oral iron

<table>
<thead>
<tr>
<th>Form</th>
<th>Brand name/mg/elemental iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferric sulfate (elemental iron content = 20-30%)</td>
<td>Elixir, oral: Ferosulf: 220 (44 Fe) mg/mL (473 mL), 115 (28 Fe) mg/mL (473 mL), 57 (14 Fe) mg/mL (473 mL), 28 (7 Fe) mg/mL (473 mL)</td>
</tr>
<tr>
<td></td>
<td>Generic: 220 (44 Fe) mg/mL, 115 (28 Fe) mg/mL, 57 (14 Fe) mg/mL, 28 (7 Fe) mg/mL</td>
</tr>
<tr>
<td></td>
<td>Polyfer: 220 (44 Fe) mg/mL, 115 (28 Fe) mg/mL, 57 (14 Fe) mg/mL, 28 (7 Fe) mg/mL</td>
</tr>
<tr>
<td></td>
<td>Ferrous: 220 (44 Fe) mg/mL, 115 (28 Fe) mg/mL, 57 (14 Fe) mg/mL, 28 (7 Fe) mg/mL</td>
</tr>
<tr>
<td></td>
<td>Syrup, Oral: Ferr-Bol: 325 (65 Fe) mg</td>
</tr>
<tr>
<td></td>
<td>Ferrum: 325 (65 Fe) mg, 125 (30 Fe) mg, 62.5 (15 Fe) mg, 31.25 (7.5 Fe) mg, 15.625 (3.75 Fe) mg</td>
</tr>
<tr>
<td></td>
<td>Tablet, Oral: Fero-Bol: 325 (65 Fe) mg</td>
</tr>
<tr>
<td></td>
<td>Ferrum: 325 (65 Fe) mg, 125 (30 Fe) mg, 62.5 (15 Fe) mg, 31.25 (7.5 Fe) mg, 15.625 (3.75 Fe) mg</td>
</tr>
<tr>
<td></td>
<td>Liquid, Oral: Auryxia: Ferrous iron 210 mg (ferric citrate 1 g)</td>
</tr>
</tbody>
</table>
Is sucroferric oxyhydroxide an effective phosphate binder and iron supplement?

- Sucroferric oxyhydroxide is a non-calcium, iron-based phosphate binder indicated for the treatment of hyperphosphataemia in adult dialysis patients.
- Post-hoc analysis of a randomized, 24-week Phase 3 study and its 28-week extension was performed to evaluate the long-term effect of sucroferric oxyhydroxide on iron parameters.
- A total of 1059 patients were randomized to sucroferric oxyhydroxide 1.0-3.0 g/day (n = 710) or sevelamer carbonate ('sevelamer') 2.4-14.4 g/day (n = 349) for up to 52 weeks.
- There were small, but significantly greater increases in mean transferrin saturation (TSAT) and haemoglobin levels with sucroferric oxyhydroxide versus sevelamer during the first 24 weeks (change in TSAT: +4.6% versus +0.6%, P = 0.003; change in haemoglobin: +1.6 g/L versus -1.1 g/L, P = 0.037).
- Mean serum ferritin concentrations also increased from Weeks 0 to 24 with sucroferric oxyhydroxide and sevelamer (+119 ng/mL and +56.2 ng/mL respectively; no statistically significant difference between groups).
- In both treatment groups, ferritin concentrations increased to a greater extent in the overall study population (>70% of whom received concomitant intravenous (IV) iron), compared with the subset of patients who did not receive IV iron therapy during the study.


What are the common intravenous iron preparations?

<table>
<thead>
<tr>
<th>Iron Preparation</th>
<th>Dose</th>
<th>Frequency</th>
<th>Pediatric studies?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium ferric gluconate</td>
<td>1.5 mg/kg (maximum 125 mg)</td>
<td>3 mg/kg (maximum 100 mg)</td>
<td>Yes</td>
</tr>
<tr>
<td>Iron sucrose</td>
<td>3 mg/kg (maximum 100 mg)</td>
<td>510 mg</td>
<td>Yes</td>
</tr>
<tr>
<td>Ferumoxytol</td>
<td>510 mg</td>
<td>Two doses spaced over 3-5 days</td>
<td>No</td>
</tr>
</tbody>
</table>

What is ferric gluconate dosing in pediatric hemodialysis patients?

- Prospective, multicenter, open-label trial of maintenance therapy with sodium ferric gluconate complex (SFGC) in iron-replete pediatric HD patients receiving erythropoietin.
- Patients received SFGC weekly at an initial dose of 1.0 mg/kg/week, not to exceed 125 mg. Doses could be adjusted based on iron indices.
- Twenty-three patients (mean age: 13.2±2.3 years) were enrolled and received at least one dose of SFGC, but only twelve patients completed the study.
- After 12 weeks of treatment, the mean SFGC dose delivered was 1.0 mg/kg.
- No unexpected or unusual safety risks were associated with SFGC use.
- Maintenance SFGC starting dose should be 1.0 mg/kg, not to exceed 125 mg, with subsequent adjustments made according to TSAT and/or serum ferritin levels.


What is the maintenance dose of ferric gluconate in hemodialysis patients?

- Mean ferric gluconate dose 1.25 mg/kg/week, not to exceed 125 mg.
- Weekly dose adjustment based on TSAT, serum ferritin, and TSAT.
- No unexpected or unusual safety risks were associated with SFGC use.
- Maintenance SFGC starting dose should be 1.0 mg/kg, not to exceed 125 mg, with subsequent adjustments made according to TSAT and/or serum ferritin levels.

Iron sucrose dosing in pediatric HD, PD and CKD patients


Is there any preliminary data on ferumoxytol?


How are we doing running the erythrocyte production floor?

Trends in mean hemoglobin & weekly EPO dose

Figure 8.14 (continued, Volume 2)

Patient distribution by mean quarterly hemoglobin (g/dl)

Figure 8.14 (Volume 2)
How are we doing running the erythrocyte production floor?

Thanks!

• For copies of this presentation or questions:
  pyordin@ucsd.edu