Anemia Management in Peritoneal Dialysis Patients

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Definition of Anemia

Males:
• Hb < 13.0 g/dL
Females:
• Hb < 12.0 g/dL

WHO 2008

Normal Erythropoiesis
Consequences of Anemia in Stage 5 Chronic Kidney Disease Patients

- Cardiovascular consequences
  - Coronary artery disease
  - Left ventricular hypertrophy (LVH)
- Congestive heart failure
- Increased hospitalizations
- Increased mortality
- Decreased quality of life

Association of Hemoglobin and Survival in Peritoneal Dialysis Patients


Pathophysiology of Anemia in CKD

- Deficiency of erythropoietin
- Shortened RBC life span due to uremia
- Blood loss
- Gastrointestinal bleeding
- Severe hyperparathyroidism
- Protein malnutrition
- Aluminum accumulation
- Infection
- Inflammation
Differences in Anemia in PD and HD Patients

- Higher blood loss-access, circuit, GI in HD
- More inflammation and oxidative stress in HD
- Erythrocyte rigidity index is higher in HD
- Hgb fluctuations due to ultrafiltration in HD
- Higher residual kidney function in PD-Higher endogenous production of EPO
- Hemodilution in PD

Differences in Anemia Management in PD and HD Patients

- Observational study of 14958 PD and 221866 HD patients
  - 80.1% of PD patients received ESAs compared with 92% of HD patients in 2011
  - 36.6% of PD patients received IV iron compared with 74.5% of HD patients in 2011
- rHuEPO dose is 1/3rd – 1/4th lower in PD

Am J Nephrol 2015; 41: 354-361

Assessment of Anemia

- Complete blood count (CBC), which should include Hgb concentration, red cell indices, white blood cell count and differential, and platelet count
- Absolute reticulocyte count
- Serum ferritin level
- Serum transferrin saturation (TSAT)
- Serum vitamin B12 and folate levels
Case

- 70-year old AAF with ESRD from diabetic nephropathy on automated peritoneal dialysis since Jan 3, 2016
- Hgb 8.6 g/dl on 1/3/16 and 9.2 g/dl on 2/17/16
- Kt(peritoneal+ renal)/V urea=2.3
- Iron saturations 14%; Ferritin 88 ng/ml
- How would you like to manage her anemia?

Absolute Iron Deficiency in Dialysis

- Iron saturations < 20%
- Ferritin < 100 ng/ml
- Reticulocyte hemoglobin concentration < 29 pg
- Percentage of hypochromic cells > 6%
- Bone marrow iron diminished to absent

Indications for Iron Therapy

<table>
<thead>
<tr>
<th>Hemoglobin Level</th>
<th>Iron Saturations</th>
<th>Ferritin</th>
<th>Iron Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 10 g/dl</td>
<td>≤20%</td>
<td>≤500 ng/ml</td>
<td>Yes</td>
</tr>
<tr>
<td>≤ 10 g/dl</td>
<td>≤20%</td>
<td>&gt;500 ng/ml</td>
<td>Maybe</td>
</tr>
<tr>
<td>10-12 g/dl</td>
<td>≤20%</td>
<td>≤500 ng/ml</td>
<td>If on ESA therapy</td>
</tr>
<tr>
<td>&gt; 12 g/dl</td>
<td>≤20%</td>
<td>≤500 ng/ml</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Adapted from KDIGO 2012
Iron Replacement Strategies

- Dietary iron
- Oral iron
- Parenteral iron
- Blood transfusion

Oral Iron Preparations

- Ferrous gluconate, ferrous sulfate, ferrous fumarate
- Heme iron polypeptides
- Ferric maltol
- Liposomal iron
- Ferric citrate

Iron Absorption
Ferric Citrate has Benefit on ESA/Iron Usage

<table>
<thead>
<tr>
<th>End Point</th>
<th>Ferric Citrate (n=292)</th>
<th>Active Control (n=149)</th>
<th>Adjusted Mean Difference (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferritin (ng/ml)</td>
<td>593 vs 899</td>
<td>609 vs 628</td>
<td>282 (197 to 366)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>TSAT (%)</td>
<td>34.2 vs 39.3</td>
<td>30.9 vs 29.7</td>
<td>9.5 (6.4 to 12.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>IV iron use (mg/wk)</td>
<td>12.9</td>
<td>26.8</td>
<td>-12.5 (-17.2 to -7.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ESA dose (IU/wk)</td>
<td>5305</td>
<td>6954</td>
<td>-1191 (-2632 to 0)</td>
<td>0.04</td>
</tr>
<tr>
<td>Hgb (g/dl)</td>
<td>11.1 vs 11.46</td>
<td>11.7 vs 11.14</td>
<td>0.59 (0.20 to 0.60)</td>
<td>0.02</td>
</tr>
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</table>


Limitations of Oral Iron Therapies1,2


- Impaired intestinal iron absorption
- May be inadequate during ESA therapy
- Gastrointestinal adverse events
- Compliance
- Oxidative stress

Intravenous Iron is Preferably in PD Patients

- IV iron: Iron sucrose 200 mg q wk x 4 wks and then 200 mg q other wk x 4 wks
- Oral iron: Ferrous succinate, 200 mg three times per day, for 8 weeks

**TABLE I**

<table>
<thead>
<tr>
<th>Response (%)</th>
<th>Group</th>
<th>Patients (n)</th>
<th>Initial response (%)</th>
<th>Partial response (%)</th>
<th>Minimal response (%)</th>
<th>no response (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>20</td>
<td>1 (5.0)</td>
<td>4 (20.0)</td>
<td>14 (70.0)</td>
<td>1 (5.0)</td>
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<tr>
<td></td>
<td>Yes</td>
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<td>2 (10.0)</td>
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*IV iron therapy: 200 mg iron sucrose (200 mg iron) 3 times weekly for 6 months, followed by tinidazole (5 mg/kg) daily.*

**TABLE II**

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Drugs for Intravenous Iron Replacement

<table>
<thead>
<tr>
<th>Iron Product</th>
<th>FDA Approval</th>
<th>Carbohydrate Shell</th>
<th>Max Approved Single Dose (Off Label)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMW Iron Dextran</td>
<td>1991</td>
<td>Dextran</td>
<td>&gt;1000 mg over 4 hrs</td>
</tr>
<tr>
<td>HMW Iron Dextran</td>
<td>1996</td>
<td>Dextran</td>
<td>&gt;1000 mg IV over 4 hrs</td>
</tr>
<tr>
<td>Sodium Ferric Gluconate Complex</td>
<td>1999</td>
<td>Glucuronate</td>
<td>125 mg over 10 min</td>
</tr>
<tr>
<td>Iron Sucrose</td>
<td>2000</td>
<td>Sucrose</td>
<td>100 mg over 2-5 min</td>
</tr>
<tr>
<td>Ferumoxytol</td>
<td>2009</td>
<td>Polylactic acid</td>
<td>50 mg over 15 min</td>
</tr>
<tr>
<td>Ferric Oxymaltose</td>
<td>2011</td>
<td>Carboxymaltose</td>
<td>750 mg over 15 min</td>
</tr>
<tr>
<td>Iron Isomaltoside</td>
<td>-</td>
<td>Isomaltoside</td>
<td>20 mg/kg over 15-60 min</td>
</tr>
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Case

- 70-year old AAF with ESRD from diabetic nephropathy on automated peritoneal dialysis since Jan 3, 2016
- Treated with 1000 mg of ferrous sucrose (iv) in Feb 2016 in 3 doses
- April 14, 2016: Hgb 10.8 g/dl (no ESA)
- June 2, 2016: Peritonitis; resolved with ip antibiotics
- Aug 8, 2016: Hgb 7.6 g/dl; transferrin saturations 18%; Ferritin 1028 ng/ml
- How will you like to treat her anemia?

Functional Iron Deficiency

- Characterized by the presence of adequate iron stores as defined by conventional criteria, but an inability to sufficiently mobilize this iron from the liver and other storage sites to adequately support erythropoiesis with the administration of erythrocyte stimulating agents (ESA).
- Serum ferritin level > 100 ng/ml, and TSAT < 20%.
- The hallmark of functional iron deficiency is that it responds to iron supplements with an increase in hemoglobin and/or decrease in ESA requirements.
Role of Inflammation & Hepcidin in anemia in CKD

Dialysis Patient’s Response to IV Iron with elevated Ferritin (DRIVE)

- Inclusion criteria:
  - S. ferritin 500-1200 ng/ml
  - Hb ≤ 11.0 g/dl
  - TSAT ≤25%
  - Receiving EPO ≥ 225 IU/Kg/wk or ≥22,500 IU/wk
  - IV Iron ≤ 125 mg per week in any of the 4 weeks prior to screening

Coyne D. J Am Soc Nephrol. 2007;18(3):975-84
Toros Kapoian et al. JASN 2008;19:372-379
Iron Therapy

- Usual total initial dose is 1000 mg in a single or multiple doses
- Do not administer when patient has an active infection
- Side-effects:
  - Anaphylaxis
  - Hypotension
  - Nausea/vomiting
  - Arthralgias
  - Risk of infections
- Follow up:
  - Iron studies every month to 3 months
  - Iron studies q month
  - Initiate or increasing ESA therapy
  - Acute loss
  - After a virus

Case

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- April 14, 2016: Hgb 10.8 (no ESA)
- June 2, 2016: Peritonitis; resolved with ip antibiotics
- Aug 8, 2016: Hgb 7.6; transferrin saturations 18%; Ferritin 1028 ng/ml
- Treated with iv ferrous sucrose, Hgb improved to 10 g/dl
- Sept 18, 2016: Hgb 8.9, transferrin saturations 32%; Ferritin 760 ng/ml
- Now what?

Indications for Erythropoiesis Stimulating Agents

- Objective:
  - Prevent transfusions
  - Minimize anemia related symptoms
- Start ESA’s only after addressing all correctable causes of anemia
- Start ESA therapy when Hgb < 10g/dl; maintain Hgb < 11.5 g/dl
- In certain subsets, ESA’s may be started for Hgb >10 g/dl but maintain < 13 g/dl.
- Caution:
  - Malignancy
  - CVA
Initial Dosing of Erythropoiesis Stimulating Agents

- Recombinant human erythropoietin
  - Initial Dose: 50-100 IU/kg/wk
- Darbepoetin alfa
  - Initial Dose: 0.45 mcg/kg/wk or 0.75 mcg/kg/2 wks
- CERA (Continuous erythropoietin receptor activator)
  - Initial dose: 0.6 mcg/kg/2 wks

Subsequent Dosing of ESA’s

- Target Hgb level: 10-11.5 g/dl
- Wait 4 weeks to adjust initial doses and at least 2 weeks for subsequent dose adjustments
- Hgb must be checked at least monthly on ESA’s
- Dose adjustments: based on Hgb, rate of change, current ESA dose, and clinical circumstances
- Rate of hemoglobin increase/decrease:
  - +1 g/dl/4wk or 2 g/dl/8wks: Reduce dose 25% or hold
  - + 0.5 g/dl/2wk: Increase dose 15%
- Hemoglobin:
  - Hgb < 10 g/dl: Increase by 25%
  - Hgb > 11.5 g/dl: Decrease by 25% or hold

Adverse Effects with ESA’s

- Cardiovascular events
- Hypertension
- Thromboembolism; access thrombosis
- Cancer progression
- Pure red cell aplasia
Hemoglobin Variability with ESA Therapy

- Hemoglobin variability is associated with mortality in HD patients
  - Repeated ischemic episodes may cause left ventricular hypertrophy by repeated activation and resetting the cardiac growth signals.
  - Increased autonomic dysfunction
- Lower hemoglobin variability in PD than HD
- CERA associated with lower hemoglobin variability in PD
  - 88% of patients on epoetin beta experienced Hgb excursions compared to 68% CERA

Ren Fail 2013;35(3):314-9

Definition of ESA Hypo Responsiveness

- Initial ESA hyporesponsiveness:
  No increase in Hgb from baseline after 1 month of ESA treatment on appropriate weight based dosing

- Subsequent ESA hyporesponsiveness:
  After treatment with stable doses of ESA's, patients requiring 2 increases in ESA dosage up to 50% beyond the dose at which they were stable

KDIGO 2012

Definition of ESA Hypo Responsiveness

- Failure to achieve or maintain target Hgb while receiving EPO > 300 IU/kg/week sq or darbepoetin-alfa >1.5 mcg/kg
- ERI (erythropoietin resistance index): weekly weight-adjusted ESA dose (U/kg/week) divided by hemoglobin level (g/dl).
  \[ \text{ERI} = \frac{\text{weekly weight-adjusted ESA dose (U/kg/week)}}{\text{hemoglobin level (g/dl)}} \]

Kidney Dialysis Quality Initiative
European Best Practice Guidelines
### Causes of ESA Hypo Responsiveness and Resistance

<table>
<thead>
<tr>
<th>Easily correctable</th>
<th>Potentially correctable</th>
<th>Impossible to correct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute iron deficiency</td>
<td>Infections/ inflammation</td>
<td>Hemoglobinopathies</td>
</tr>
<tr>
<td>Vitamin B12/folate deficiency</td>
<td>Underdialysis</td>
<td>Bone marrow disorders</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Hemolysis</td>
<td></td>
</tr>
<tr>
<td>ACE-Inhibitors/ARB</td>
<td>Bleeding</td>
<td></td>
</tr>
<tr>
<td>Non-adherence</td>
<td>Hyperparathyroidism</td>
<td></td>
</tr>
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<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Malignancy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Malnutrition</td>
<td></td>
</tr>
</tbody>
</table>

### Indications for Transfusion

#### Acute clinical situations
- Acute severe hemorrhage
- Uncontrollable acute bleeding
- When rapid correction is required

#### Chronic clinical situations
- Chronic anemia and ESA are ineffective
- Hemoglobinopathies
- Bone marrow failure
- ESA-resistance

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### Indications for Transfusion

- Consultations with a hematologist
- Red blood cell transfusions
- Iron replacement
- Epoetin administration
- Erythropoietin

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### Indications for Transfusion

- 

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### Indications for Transfusion

- 

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Summary

• Target Hgb is 10 - 11.5 g/dl
• Assess cause of anemia
• Hgb and iron studies checked at least every 3 months if not on ESA's and every month if on ESA therapy
• Replace iron before starting ESA's
• Objective of ESA therapy is to minimize transfusions and anemia related symptoms
• Do not allow Hgb to exceed 13 g/dl with ESA therapy

Therapies in the Horizon

• Not directly targeting the EPO receptor
  • HIF Stabilizers
  • Activin traps

• Targeting the EPO Receptor
  • EPO mimetic peptides
  • EPO fusion molecules
  • Antibody agonists to EPO receptor
  • EPO gene therapy
  • Dimerization of EPO receptor intracellular domain with a CID