Renal Anemia: The Basics

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No Disclosures
Learning Objectives

• At the end of this session the listener will be able to:
  – Describe the etiology of the anemia of CKD in children
  – Define anemia and initiate a work-up
  – Understand formulations and dosing of erythropoiesis stimulating agents (ESA)
  – Describe indications for and approach to iron supplementation
  – Recognize emerging anemia therapies
    • Newer ESAs, novel iron supplementation, HIF stabilizers
Anemia of Kidney Disease

• 1839 - “..by far the most remarkable character of the blood in the advanced stage of Bright’s disease is a gradual and rapid reduction of its colouring...no other natural disease comes as close to hemorrhage for impoverishing the red particles of the blood.”

Figure 5 Cellular basis of erythropoietin deficiency in renal failure

**Decreased stability and transcriptional activity of hypoxia inducible factors (HIF)**

3-4 grams of iron in the typical adult human body:

- 2-3 grams incorporated into hemoglobin (Hgb)
- EPO dysregulation and deficiency
- Iron deficiency
- Inflammation-associated iron restriction mediated by hepcidin
Hepcidin and Ferroportin

(Donovan et al, 2005; Nemeth et al, 2004)
Hepcidin and Ferroportin

Decreased Fe recycling

Decreased dietary uptake

(Donovan et al, 2005; Nemeth et al, 2004)
Etiology of Anemia of CKD

- Erythropoietin dysregulation and deficiency
- Iron deficiency
- Inflammation-associated iron restriction

ESA-Resistant Anemia
Epidemiology of Anemia in CKD/ESRD

Etiology of Anemia of CKD

• *Erythropoietin deficiency*
• *Iron deficiency*
• *Inflammation-associated iron restriction*
• Hyperparathyroidism
• “Uremic toxins”/Oxidative stress
• Other nutritional deficiencies
Adverse Associations of Anemia

- Anemia in CKD has been associated with a wide variety of adverse effects/outcomes including:
  - Hospitalization and mortality
  - Decreased quality of life
  - Increased risk for cardiovascular disease and CKD progression
  - Transfusions and allo-sensitization
Definition and Evaluation of Anemia

- CBC including red blood cell indices, WBC differential, and platelets
- Absolute reticulocyte count
- Serum ferritin
- Serum transferrin saturation, iron
  - % hypochromic red blood cells
  - Reticulocyte hemoglobin content
- Serum B$_{12}$ and folate
Definition and Evaluation of Anemia

• CBC including red blood cell indices, WBC differential, and platelets
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  • % hypochromic red blood cells
  • Reticulocyte hemoglobin content
• Serum $B_{12}$ and folate
• Hemoglobin electrophoresis
• Screen for hemolysis
• Screen for blood loss
ESA for Anemia of CKD

1985

Human EPO gene isolated
rHuEPO

Eschbach et al. (1987) NEJM 316(2):73-78
ESA for Anemia of CKD

Prior to availability of rHuEPO, cobalt salts and androgens were used for treatment of anemia of CKD.

Long-term cobalt ingestion caused cardiomyopathy, neuropathy, thyroid dysfunction.

1 Epo unit = dose producing the same erythropoiesis-stimulating response as 5 µmol cobaltous chloride in experimental animals.

Packed red blood cell transfusions:
- Infection
- Iron overload
- Allosensitization

1985

Human EPO gene isolated

rHuEPO

HIF stabilizer?
1985

Human EPO gene isolated

→
rHuEPO

1987

Seminal NEJM paper reported that rHuEPO effectively raised Hgb and eliminated transfusions in 25 adults on HD

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Epoetin alfa approved by U.S. FDA
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\[ \text{rHuEPO} \]

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Eschbach et al. (1987)

*NEJM* 316(2):73-78

Epoetin alfa approved by U.S. FDA

Darbepoetin alfa approved by U.S. FDA
• Darbepoietin alfa – two additional sialic-acid-containing carbohydrates result in extended in vivo biologic activity
ESA for Anemia of CKD

1985
Human EPO gene isolated
downward arrow
rHuEPO

1987
Seminal NEJM paper reported that rHuEPO effectively raised Hgb and eliminated transfusions in 25 adults on HD
Eschbach et al. (1987)
NEJM 316(2):73-78

1989
Epoetin alfa approved by U.S. FDA

2001
Darbepoetin alfa approved by U.S. FDA

2007
CERA approved by U.S. FDA
Methoxy polyethylene glycol-epoetin beta (Mircera®)
Hoffman-La Roche
SC or IV administration
• Integration of a large methoxy polyethylene glycol polymer chain
• Extended half-life of up to 130 hours when given SC, 90 hours IV
• Allows for a monthly dosing regimen
Mean in vivo half-lives of available erythropoiesis stimulating agents

- SC: Subcutaneous
- IV: Intravenous

CERA
- SC: 140 hours
- IV: 130 hours

Darbepoetin alfa
- SC: 80 hours
- IV: 70 hours

Epoetin beta
- SC: 40 hours
- IV: 30 hours

Epoetin alfa
- SC: 20 hours
- IV: 10 hours

3.4.5: For all pediatric CKD patients, we suggest that the selection of Hb 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)

- ESA initiation for hemoglobin 9-10 g/dl (90-100 g/l)
- *Children: maintain hemoglobin 11-12 g/dl (110-120 g/l)
• Physicians and their patients with chronic kidney disease should weigh the possible benefits of using ESAs to decrease the need for red blood cell transfusions against the increased risks for serious adverse cardiovascular events. For each patient, individualize dosing and use the lowest dose of ESA sufficient to reduce the need for transfusion.

• For patients with the anemia of chronic kidney disease NOT on dialysis
  • Consider starting ESA treatment only when the hemoglobin level is less than 10 g/dL and when certain other considerations apply
  • If the hemoglobin level exceeds 10 g/dL, reduce or interrupt the dose of ESA.

• For patients with the anemia of chronic kidney disease on dialysis
  • Initiate ESA treatment when the hemoglobin level is less than 10 g/dL.
  • If the hemoglobin level approaches or exceeds 11 g/dL, reduce or interrupt the dose of ESA.

“WARNING: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE”

See full prescribing information for complete boxed warning.
ESA Dosing

• Goal rate of hemoglobin increase: 1-2 g/dL/month
• Epoetin alfa or beta
  – 20-50 IU/kg/dose three times weekly IV or SC
• Darbepoetin alfa
  – 0.45 µg/kg SC or IV weekly
  – 0.75 µg/kg SC or IV every 2 weeks

- Darbepoetin alfa can be safely administered either weekly or q 2 weeks in ESA-naïve pediatric pts to achieve Hgb targets of 10-12.
• 275-350 units/kg/week in infants

• 200-250 units/kg/week in older children

• Children and adolescents on HD may require higher absolute doses than adults despite lower body weight

• Increased drug clearance with growth?
ESA Dosing

• Make dose adjustments after 4 weeks of therapy
• No more often than q 2 weeks
• When a decrease in hemoglobin is necessary, decrease dose rather than hold therapy
• Long-acting ESAs – lower starting dose and less frequent adjustments
Phase II, open label, multicenter, multiple-dose study conducted at 28 sites in 10 countries

64 children aged 6-17 years on chronic HD received CERA (Mircera®) monthly

Objective: identify a conversion factor for switching from previous ESAs (epoetin or darbepoetin) to CERA

- Safety and efficacy
Efficacy and Long-Term Safety of C.E.R.A. Maintenance in Pediatric Hemodialysis Patients with Anemia of CKD

Michel Fischbach,1 Elke Wühl,2 Sylvie C. Meyer Reigner,3 Zoe Morgan,4 and Franz Schaefer2


Figure 2. | Hemoglobin (Hb) was maintained within the target range in the higher conversion factor group during the core trial period. Mean Hb values with 95% confidence intervals are shown. Dashed lines indicate target range.
Efficacy and Long-Term Safety of C.E.R.A. Maintenance in Pediatric Hemodialysis Patients with Anemia of CKD

Michel Fischbach,1 Elke Wühl,2 Sylvie C. Meyer Reigner,3 Zoe Morgan,4 and Franz Schaefer2


Figure 5. | Hemoglobin (Hb) concentrations were maintained in both groups in patients who entered the extension phase. Mean Hb values with 95% confidence intervals are shown. Dashed lines indicate the target range.
On the basis of our results, patients aged 6–17 years with stable hemoglobin receiving darbepoetin alfa or epoetin alfa/beta can be switched to C.E.R.A. at a dose corresponding to 4 \( \mu g \) every 4 weeks for each 125 IU epoetin alfa/beta or 0.55 \( \mu g \) darbepoetin.
Iron Deficiency and Supplementation
Iron Deficiency (ID)

- Correction of ID reduces severity of anemia of CKD
- Untreated ID is a frequent cause of ESA hypo-responsiveness
- Risk factors include:
  - Blood loss
  - Inflammation
  - Poor absorption of enteral iron
Biomarkers of Iron Availability

• Ferritin (serum)
  – Intracellular iron-storage protein
  – by inflammation, iron overload
• Transferrin saturation (TSAT)
  – Transferrin binds to iron in plasma
  – Transports to bone marrow
KDIGO Iron Targets

- In ESA-treated patients, iron supplementation to maintain:
  - Ferritin $\geq$ 100 ng/mL
  - TSAT $\geq$ 20%
- Ferritin has limitations as a marker of accessible stored iron:
  - Hepcidin-mediated iron blockade
  - Low ferritin = iron deficiency
  - High ferritin does not rule out iron blockade
KDIGO Iron Targets

- No routine iron supplementation for
  - Ferritin > 500
  - TSAT > 30%
Hb grouped by concomitant serum ferritin levels.

P < 0.005

Dagmara Borzych-Duzalka et al. JASN 2013;24:665-676

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Iron Supplementation: Route

• Oral/Enteral
  – Pros: inexpensive, available, few adverse effects
  – Cons: poorly absorbed, adherence
  – Dosing: 2-6 mg/kg/day elemental iron

• Intravenous
## Iron Supplementation: Route

<table>
<thead>
<tr>
<th>POTENTIAL BENEFITS OF IV IRON</th>
<th>POTENTIAL RISKS/ADVERSE EFFECTS OF IV IRON</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Decrease PRBC transfusion rates</td>
<td></td>
</tr>
<tr>
<td>• Improved hemoglobin (and associated improved QOL?)</td>
<td></td>
</tr>
<tr>
<td>• Decrease in required ESA dose</td>
<td></td>
</tr>
<tr>
<td>• Adherence assured</td>
<td>• Anaphylaxis</td>
</tr>
<tr>
<td></td>
<td>• Oxidative stress, endothelial dysfunction</td>
</tr>
<tr>
<td></td>
<td>• Cellular iron deposition</td>
</tr>
<tr>
<td></td>
<td>• Pro-oxidant cell-signaling</td>
</tr>
<tr>
<td></td>
<td>• Infection</td>
</tr>
<tr>
<td></td>
<td>• Cost, burden of visits, monitored administration</td>
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Goals of Iron Supplementation

• Avoid depletion of iron stores
• Prevent iron-restricted erythropoiesis
Goals of Iron Supplementation

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- Avoid depletion of iron stores
- Prevent iron-restricted erythropoiesis

IV IRON
- Oxidative stress
- Increased inflammation
- Endothelial dysfunction
- Potentiating infection
- Tissue injury

## IV Iron: Safety

### Table 1. Physiochemical characteristics of iron formulations

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<thead>
<tr>
<th>Properties</th>
<th>Ferric Gluconate</th>
<th>Ferric Citrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular mass (D)</td>
<td>200,000</td>
<td></td>
</tr>
<tr>
<td>Carbohydrate shell</td>
<td>Gluconate, loosely associated sucrose</td>
<td></td>
</tr>
<tr>
<td>Median shell/particle diameter (nm)</td>
<td>8.6</td>
<td></td>
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<tr>
<td>Relative catalytic iron release</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Relative stability of elemental iron within the carbohydrate shell</td>
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<td></td>
</tr>
<tr>
<td>Relative osmolality</td>
<td>Isotonic</td>
<td></td>
</tr>
<tr>
<td>Administration (iv push) rates</td>
<td>30 mg/1</td>
<td></td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>Approximately 1</td>
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D, daltons; nm, nanometer; iv, intravenous

**IV Iron: Safety**

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<td>Administration (iv push) rates</td>
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<tr>
<td>$t_{1/2}$ (h)</td>
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Iron is essential for bacterial growth
• May impair host immune response by decreasing PMN and T-cell function
• Children not on an ESA and not on HD, treat with oral iron unless “intolerant” or target Hgb is not reached within 3 months
• On ESA and not on HD → trial of oral iron
• Offer IV iron to children on HD
Novel Routes of Iron Supplementation
Intradialysate Soluble Ferric Pyrophosphate Citrate (FPC) (Triferic®)

- Water soluble, no-carbohydrate shell, tightly complexed salt of Fe, electrostatically bonded to pyrophosphate
- Added to bicarbonate concentrate at each hemodialysis session
  - Dialysate with 110 µg/L iron
- Crosses the dialyzer membrane and donates iron directly to transferrin, bypassing hepcidin induced iron-sequestration
- Approved by U.S. FDA in 2015 for iron replacement and to maintain Hgb in adults on hemodialysis
- Also available in an IV formulation
Intradialysate Soluble Ferric Pyrophosphate Citrate (FPC) (Triferic®)

- FPC designed as a maintenance therapy, not repletion
  - Small doses of iron that are immediately bioavailable/bound to transferrin and rapidly delivered to iron-requiring tissue
- Different from parenteral iron products?
  - No carbohydrate shell
  - Iron more tightly bound to pyrophosphate compared to carbohydrate complexes
  - Rapidly bound to transferrin -> bone marrow, may avoid storage in reticuloendothelial system

Courtesy of Dr. Ajay Gupta via Dr. Brad Warady
• Study Objectives
  – Evaluate pharmacokinetics and preliminary safety of FPC
  – Evaluate the dose of FPC delivered via dialysate in children on chronic HD
  – Examine the feasibility of IV administration of FPC in pediatric patients
    • Providing a dosing option for patients in HD systems which do not use liquid bicarbonate concentrate
• Study Design
  – Multicenter, open-label, two-period, single dose study
  – 2 week screening period followed by two sequential FPC treatment sessions
    • Single 0.07 mg/kg dose in D5W as a continuous IV infusion throughout the HD session
    • FPC added to dialysate to deliver a final dose of 110 µg/L throughout the HD session
Pharmacokinetics of ferric pyrophosphate citrate administered via dialysate and intravenously to pediatric patients on chronic hemodialysis

Raymond D. Pratt¹ ⋆ · Sarah Grimberg¹ · Joshua J. Zaritsky² · Bradley A. Warady³

Pediatric Nephrology (2018) 33:2151–2159

Fig. 1 Mean concentration-time plots for serum total iron (sFe) after administration of ferric pyrophosphate citrate (FPC) via hemodialysis (HD) at a concentration of 2 μM (110 μg/L) iron (a) and after intravenous (IV) administration of 0.07 mg Fe/kg of FPC by age group (years) and overall (b).
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![Graphs showing the relationship between dialyzer SA (m²) and mg Fe/Hd, and BW (kg) and mg Fe/Hd.](image-url)
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Fig. 3  Amount of iron (Fe) administered during hemodialysis (HD) by dialysate flow rate (Qd) (a) and blood flow rate (Qb) (b). Regression lines are fitted by nonlinear regression in SigmaPlot V14.0.
Total iron exposure was greater after FPC administration via dialysate than after IV administration for all patients.

Weight-normalized amount of iron delivered via dialysate was ~ 0.06-0.10 mg/kg.
Safety

- No SAE’s, no interruptions or discontinuations for AE’s
- All AE’s reported at low incidence, most mild, and not attributed to FPC
- 1 drug-related event reported
  - Moderate axillary pain
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The recommended initial dose of FPC for future studies in pediatric patients with CKD-5HD is 2 µM (110 µg iron/L) in dialysate or 0.1 mg iron/kg IV during HD, using weight-based dosing for patients weighing < 50 kg and 6.75 mg IV for patients weighing > 50 kg.

• Efficacy trial planned
Ferric Citrate

• Iron-based oral phosphate binder
• Approved by the U.S. FDA in 2014 for use as a phosphate binder in adults on dialysis
• Ferric ion dissociates in the GI tract and combines with dietary phosphorus and is excreted as ferric phosphate
Ferric Citrate

• Some of the ferric ions dissociated from ferric citrate are reduced by the bowel mucosa to ferrous iron and absorbed through the duodenal brush border – ferroportin channels

• Data in adults that ferric citrate in dialysis patients is associated with increased transferrin saturation, decrease IV iron requirement, and decreased ESA dose
Retrospective analysis of 11 children 4-17 years of age on dialysis (HD and PD) who received ferric citrate as a phosphate binder 2015-2017 (off-label) for median treatment time 214 days.
ESA Hypoalgesia
Regional variation of anemia control.

Dagmara Borzych-Duzalka et al. JASN 2013;24:665-676
**Initial ESA hyporesponsiveness**

3.13.1: Classify patients as having ESA hyporesponsiveness if they have no increase in Hb concentration from baseline after the first month of ESA treatment on appropriate weight-based dose.

3.13.2: In patients with ESA hyporesponsiveness, we suggest avoiding repeated escalations in ESA dose beyond double the initial dose (2D).

**Subsequent ESA hyporesponsiveness**

3.14.1: Classify patients as having acquired ESA hyporesponsiveness if after treatment with stable doses of ESA, they require 2 increases in ESA doses up to 50% beyond the dose at which they had been stable in an effort to maintain a stable Hb concentration. *(Not Graded)*

3.14.2: In patients with acquired ESA hyporesponsiveness, we suggest avoiding repeated escalations in ESA dose beyond double the dose at which they had been stable. *(2D)*
Some dialysis patients may have low Hgb levels due to dilution in red cell mass in volume overload rather than to an impaired response to ESA.

Careful attention to volume status and “challenging” dry weight with increased ultrafiltration can clarify the contribution of volume overload to low Hgb concentration.
Pure Red Cell Aplasia

- Sudden onset of severe, transfusion-dependent anemia after at least 8 weeks of therapy
- Rare: 0.5 cases/10,000 pt years
- Neutralizing antibodies to ESA and endogenous EPO
- Rare with IV administration
- Treatment: stop ESA
Transfusion

- Balance risks and benefits to patient
- HLA sensitization

**Acute clinical situations**
- Acute severe hemorrhage
- Unstable coronary artery disease
- When rapid preoperative Hb correction is required

**Chronic clinical situations**
- Chronic anemia and ESAs are ineffective (hemoglobinopathies, bone marrow failure, ESA resistance)

Transfuse
rHuEPO- and Iron-Independent Anemia Therapy?

- Small-molecule hypoxia-inducible factor (HIF) stabilizers/prolyl hydroxylase inhibitors
Normoxia: HIF-α is rapidly (1/2-life 5 min) hydroxylated and degraded

Hypoxia: HIF-α translocates to nucleus, binds HIF-β, activates hypoxia response element, EPO transcribed
rHuEPO- and Iron-Independent Anemia Therapy?

- Small-molecule hypoxia-inducible factor (HIF) stabilizers/prolyl hydroxylase inhibitors
- Administered orally in highly bioavailable preparations
  - Stabilize HIF and modulate HIF-controlled gene products
  - Stimulate endogenous EPO synthesis even in the setting of decreased renal oxygen consumption
  - Decrease hepcidin in adult trials