Anemia Management in Peritoneal Dialysis Patients

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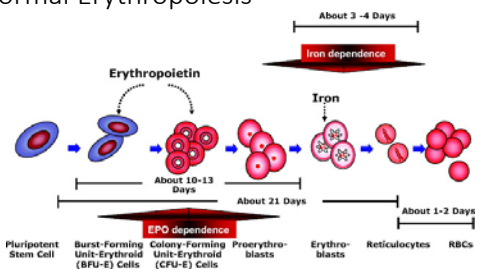
Definition of Anemia

Males:
- Hb < 13.0 g/dL

Females:
- Hb < 12.0 g/dL

WHO 2008

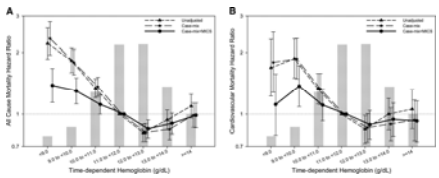
Normal Erythropoiesis



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



Hazard ratios of mortality for the entire range of hemoglobin in 9269 peritoneal dialysis patients using a time-dependent analysis for all-cause (A) and cardiovascular (B) mortality.

Miklos Z. Molnar et al. CJASN 2011;6:1973-1981

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 Neprol 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

Hemoglobin Level	Iron Saturations	Ferritin	Iron Therapy
≤ 10 g/dl	≤30%	≤500 ng/ml	Yes
≤ 10 g/dl	≤30%	>500 ng/ml	Maybe
10-12 g/dl	≤30%	≤500 ng/ml	If on ESA therapy
> 12 g/dl	≤20%	≤100 ng/ml	Yes

Adapted from KDIGO 2012

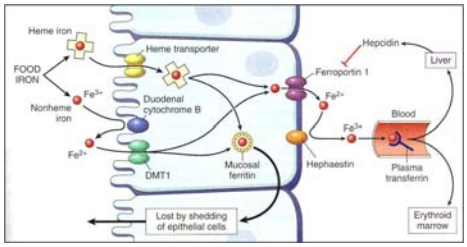
Iron Replacement Strategies

- 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

End Point	Ferric Citrate (n=292)	Active Control (n=149)	Adjusted Mean Difference (95% CI)	p
Ferritin (ng/ml)	593 vs 899	609 vs 628	282 (197 to 366)	< 0.001
TSAT (%)	31.2 vs 39.3	30.9 vs 29.7	9.5 (6.4 to 12.6)	< 0.001
IV iron use (mg/wk)	12.9	26.8	-12.5 (-17.2 to -7.9)	<0.001
ESA dose (IU/wk)	5303	6954	-1191 (-2632 to 0)	0.04
Hgb (g/dl)	11.61 vs 11.42	11.71 vs 11.14	0.33 (0.06 to 0.60)	0.02

J Am Soc Nephrol 26: 493–503, 2015

Limitations of Oral Iron Therapies[1,2]

Impaired intestinal iron absorption	• Concomitant food or medication (e.g. phosphate binders, H_2 blockers, proton pump inhibitors) – by raising the pH non-heme foods cannot be absorbed • Exacerbated by elevated hepcidin and other inflammatory cytokine levels in conditions where there is an inflammatory component
May be inadequate during ESA therapy	• Accelerated erythropoiesis can increase demand for iron beyond the amount supplied orally
Gastrointestinal adverse events	• Can affect over 50% of patients • Can adversely affect nutritional intake • Improved if iron tablets are taken with food, but this decreases absorption
Compliance	• Pill burden: usually 2 or 3 tablets per day • Affected by gastrointestinal intolerance
Oxidative stress	• High oral iron doses can saturate the iron transport system if the iron is rapidly released, resulting in oxidative stress

1. Macdougall IC. *Curr Med Res Opin* 2010;26:473–83;
2. Crichton RR *et al. Iron Therapy With a Special Emphasis on Intravenous Administration* (4th edition). UNI-MED Verlag AG, Bremen, Germany, 2008

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 3
Response Rates[a]

Group[b,c]	Patients (n)	Full response (%)	Partial response (%)	Minimal response (%)	Ineffective (%)	Response rate (%)
IV	26	20 (83.3)	3 (11.5)	3 (11.5)	0	94.8[d]
Oral	20	6 (30.0)	5 (25.0)	9 (45.0)	0	55.0

IV = Intravenous.
[a] Full response: Hb ≥30 g/L or Hct ≥10% after or during therapy, or Hb concentration reaching 110 g/L, Hct reaching 33%; Partial response: Hb increase ≥15 g/L but <30 g/L after therapy, or Hct ≥5% but <10%; Minimal response: Hb or Hct increased after therapy, but the increase of Hb <15 g/L or the increase in Hct <5%.
[b] The IV group received 200 mg iron sucrose IV once every week for the first 4 weeks, then once every other week for 8 weeks.
[c] The oral group received ferrous succinate 200 mg, three times daily, taken without food when possible, for 8 weeks.
[d] Significant difference between groups ($p < 0.05$).

Li H. Intravenous iron sucrose in peritoneal dialysis patients with renal anemia. Peritoneal Dialysis International 2008;28:149–54.

Drugs for Intravenous Iron Replacement

Iron Product	FDA Approval	Carbohydrate Shell	Max Approved Single Dose	Max Dose (Off Label)
LMW Iron Dextran	1991	Dextran	100 mg over > 30 sec	>1000 mg IV over 4 hrs
HMW iron Dextran	1996	Dextran	100 mg over > 30 sec	>1000 mg IV over 4 hrs
Sodium Ferric Gluconate Complex	1999	Gluconate	125 mg over 10 min	250 mg over 15 min
Iron Sucrose	2000	Sucrose	200 mg over 2-5 min	300 mg over 1 hr
Ferumoxytol	2009	Polyglucose sorbitol	510 mg over 15 min	-
Ferric carboxymaltose	2013	Carboxymaltose	750 mg over 15 min	-
Iron Isomaltoside	-	Isomaltoside	20 mg/kg over 30-60 min	-

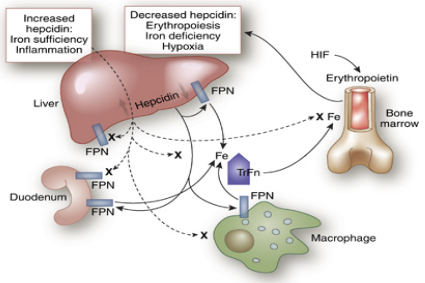
Case

- 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

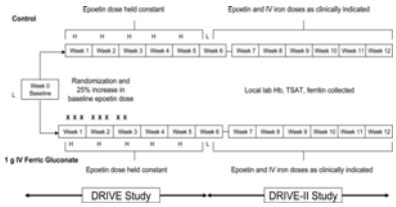
- Characterized by the presence of adequate iron stores as defined by conventional criteria, but an inability to sufficiently mobilize this iron from the liver and other storage sites to adequately support erythropoiesis with the administration of erythrocyte stimulating agents (ESA).
- Serum ferritin 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
Kapoian T. J Am Soc Nephrol. 2008;19(2):372-9

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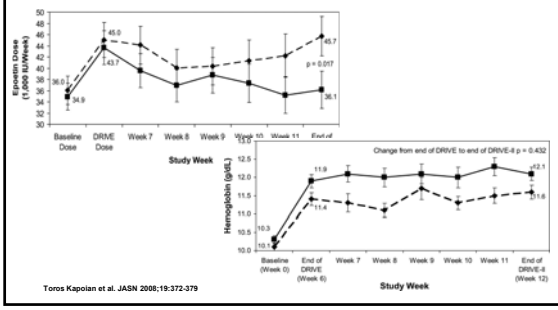

Toros Kapoian et al. JASN 2008;19:372-379

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
    - Initiating or increasing ESA therapy
    - Blood loss
    - After iv iron

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- Treated with 1000 mg of ferrous sucrose (iv) in Feb 2016 (Hgb 8.6 g/dl)
- 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
- H/H 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:
  - 1-2 g/4wk is ideal
  - >1 g/2wk or 2g/4wks: Reduce dose 25% or hold
  - < 1 g/2wk: Increase dose 25%
- 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

J Am Soc Nephrol 2007; 18: 3164 –3170
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 mantain 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).
- ERI= $\frac{\text{rHuEPO (IU)/wk/Body weight (kg)}}{\text{Hgb (g)}} > 10.11$

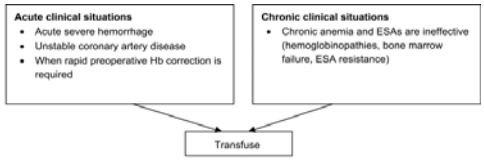
Kidney Dialysis Quality Initiative
European Best Practice Guidelines

Causes of ESA Hypo Responsivess and Resistance

Easily correctable	Potentially correctable	Impossible to correct
Absolute iron deficiency	Infection/ inflammation	Hemoglobinopathies
Vitamin B_{12}/folate deficiency	Underdialysis	Bone marrow disorders
Hypothyroidism	Hemolysis	
ACE-Inhibitors/ARB	Bleeding	
Non-adherence	Hyperparathyroidism	
	Pure red cell aplasia	
	Malignancy	
	Malnutrition	

KDIGO 2012

Indications for Transfusion



Kidney International Supplements 2012 2, 311-316DOI: (10.1038/kisup.2012.36)

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