Anemia Management in Dialysis Patients

Shahram Taheri MD.

Associate Prof.

Isfahan Kidney Diseases Research Center

IUMS

Introduction

- Anemia is a common complication of chronic kidney disease (CKD), first identified in 1836 by Sir Richard Bright who noted a fading of the “healthy colors of the countenance” among patients with kidney disease.
- In late kidney disease, anemia is a pervasive problem that can cause a variety of uncomfortable symptoms, making it one of the most important problems treated in CKD.

Defining anaemia in CKD

Age or gender group	Hb below (g/dl)
Children	
6 months to 5 years	11.0
5 to 11 years	11.5
12 to 14 years	12.0
Women > 15 years (non-pregnant)	12.0
Men > 15 years	13.0

Hb cut-off levels – World Health Organization
KDIGO 2011

WHAT CAUSES ANEMIA IN CHRONIC KIDNEY DISEASE?

- Relative Erythropoietin (EPO) deficiency
- Iron deficiency
- Blood loss
- Shortened red cell life span
- Vitamin deficiencies
- The “uremic milieu” /Bone marrow suppression
- Inflammation
- Hyperparathyroidism

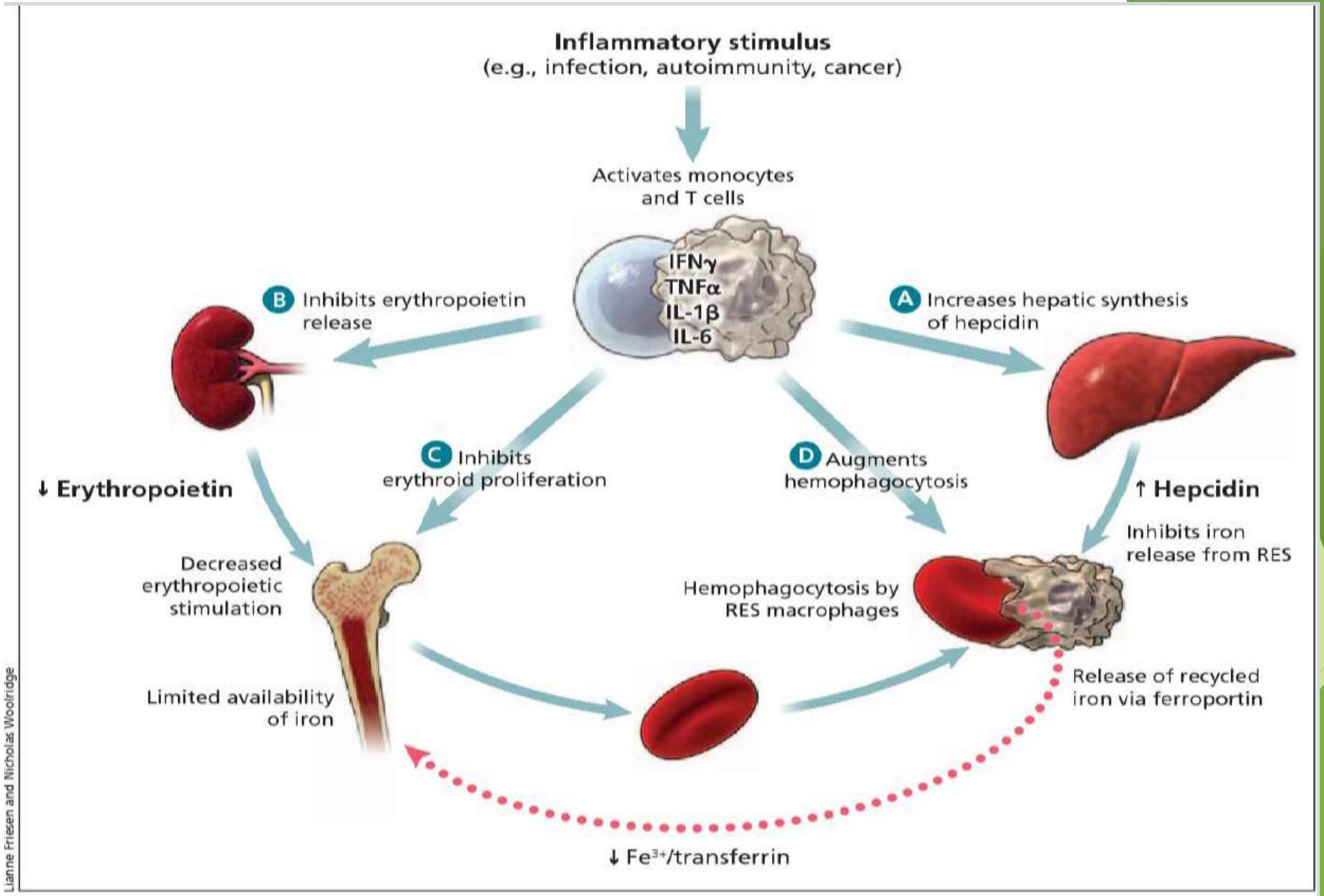
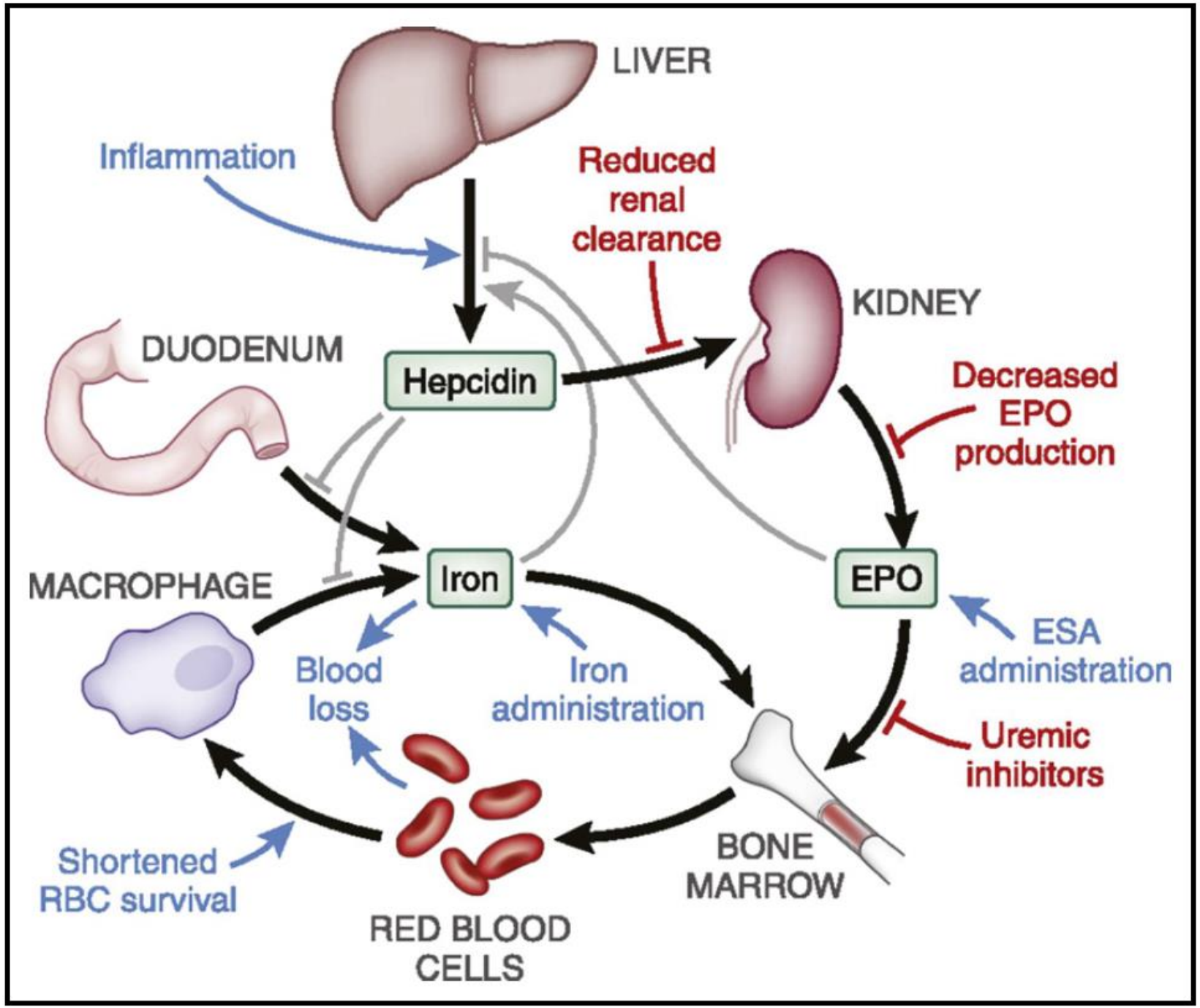


Figure 1: In inflammatory diseases, cytokines released by activated leukocytes and other cells exert multiple effects that contribute to the reduction in hemoglobin levels: (A) Induction of hepcidin synthesis in the liver (especially by interleukin-6 [IL-6], along with endotoxin). Hep-

Figure 2. Hepcidin plays a central role in iron metabolism and availability for erythropoiesis. When levels are elevated, intestinal iron absorption is diminished and release of stored reticuloendothelial system iron is blocked. The net effect is reduced iron availability for erythropoiesis. RBC, red blood cell. Republished with permission of the American Society of Nephrology from Babitt et al[2]; permission conveyed through Copyright Clearance Center, Inc.



Frequency of testing for anemia in ESRD

- For ESRD patients without anemia:
  - At least every 3 months in patients with CKD 5HD and CKD 5PD
- ESRD patients with anemia not being treated with an ESA, measure Hb concentration when clinically indicated and
  - At least every 3 months in patients with CKD 5PD
  - At least monthly in patients with CKD 5HD

Frequency of testing for anemia in ESRD

- During the initiation phase of ESA therapy, measure Hb concentration at least monthly.
- For CKD 5D patients, during the maintenance phase of ESA therapy measure Hb concentration at least monthly.

Investigation of anemia

- In patients with CKD and anemia (regardless of age and CKD stage), include the following tests in initial evaluation of the anemia:
  - Complete blood count (CBC), which should include Hb 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

Additional tests

- High sensitivity C-reactive protein (CRP) may be indicated if occult inflammation is a concern.
- In certain countries and/or in patients of specific nationalities or ethnicities, testing for hemoglobinopathies, parasites, and other conditions may be appropriate.

CAUSES ANEMIA
IN CKD

IDA in CKD

- Blood loss from GI tract

- In HD patients : Repeated Blood Loss ; retention of Blood in Dialyzer and blood lines.
- Frequent Blood Sampling for Ix
- Loss from Surgical Procedures (vascular access)
- Interference with absorption due to Meds (Gastric acid inhibitors ,Phosphate Binders)

- Reduced absorption due to inflammation

Part 1:

Iron Deficiency vs. Overload

Causes of Absolute Iron Deficiency

- Blood losses associated with:[1-3]
  - Laboratory tests and hospitalization
  - HD (from dialyzer and access)

	Healthy Patient	Non-dialysis CKD Patient	Hemodialysis Patient
Daily Blood Loss	0.83 ml/d	3.2 ml/d	5.0 ml/d
Annual Blood Loss	0.3 L/yr	1.2 L/yr	2–5 L/yr
Annual Iron Loss	0.1 g/yr	0.4 g/yr	1–2 g/yr to 4–5 g/yr

1. Sargent JA et al. Blood Purif 2004;22:112-113.
2. Rosenblatt SG et al. Am J Kidney Dis 1982;1:232-236.
3. Wizemann V et al. Kidney Int Suppl 1983;16:S218-S220.

Causes of Absolute Iron Deficiency

- GI losses due to anticoagulant or antiplatelet drugs.
- Reduced iron absorption due to medications (e.g., proton pump inhibitors and phosphate binders).
- Reduced iron absorption due to increased hepcidin levels.
- Reduced iron intake due to poor appetite, diet, and malnutrition.

Causes of Functional Iron Deficiency

- Inflammation results in:
  - Sequestration of iron within reticuloendothelial system (RES).
  - Reduced total iron binding capacity.
  - Lowered absolute amount iron available for erythropoiesis.

  ESAs can create increased demand for iron and worsen iron availability in chronically inflamed patients.

Measuring Iron Deficiency

- Both ferritin and TSAT have shortcomings when used to assess iron status.
- Ferritin 200 µg/l is frequently used as a cutoff value in dialysis patients.

1. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. Kidney Int Suppl. 2012;2:279–335.
2. NICE Guideline No. 8, 2015.

Measuring Iron Deficiency

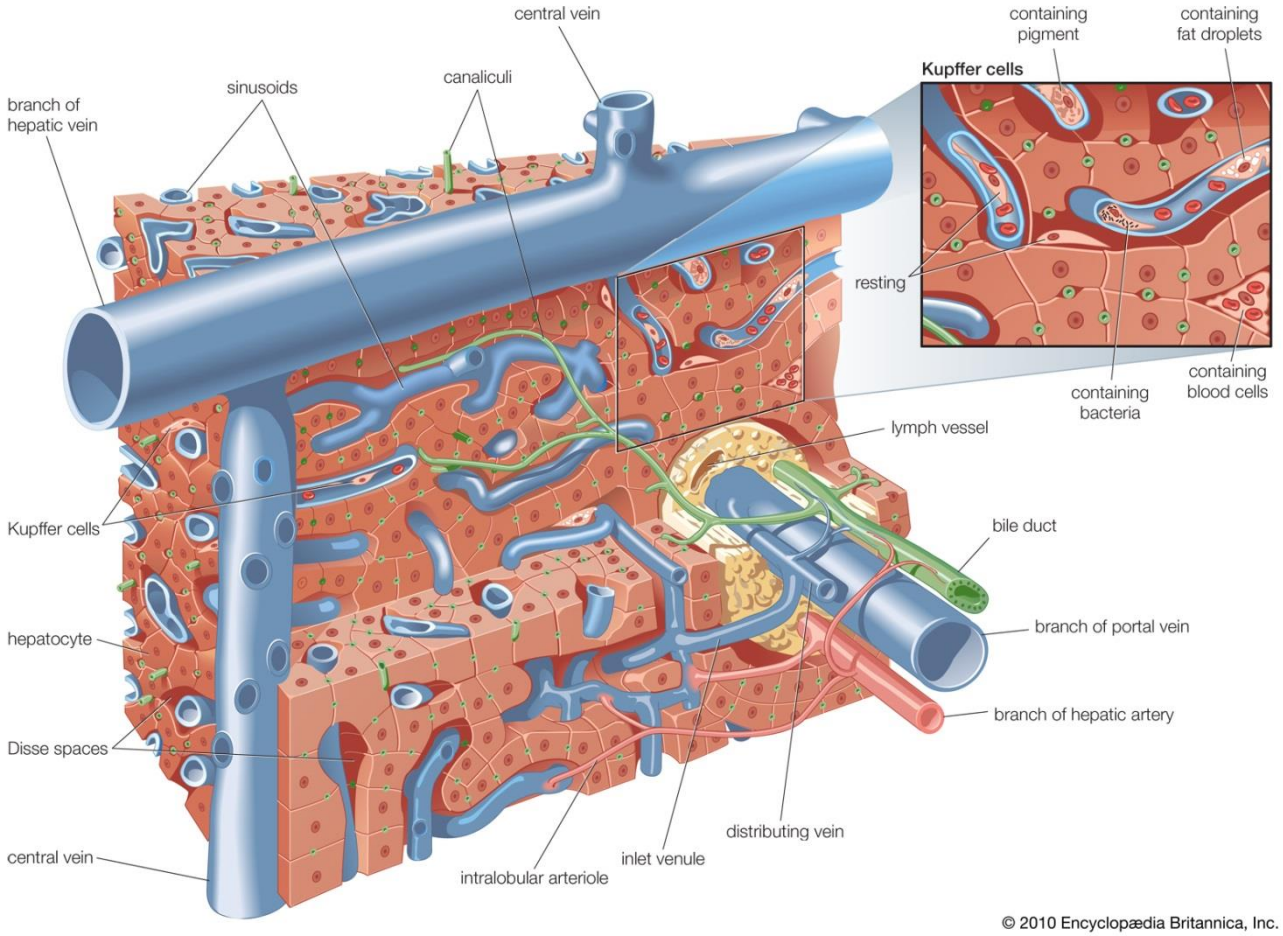
- Although evidence is limited, TSAT <20% generally indicates absolute iron defiency.[1] However, TSAT >20% does not exclude this condition.
- In CKD patients, ferritin and TSAT should be used together.[1,2]
- Percentage of hypochromic red cells and reticulocyte Hb content can indicate inadequate iron supply, but the method is not practical for wide adoption.

1. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. Kidney Int Suppl. 2012;2:279-335.
2. NICE Guideline No. 8, 2015.

Iron Dosing

- Precise dosing to correct iron deficiency is uncertain, since the true amount of iron loss is unknown.
- In general, IV iron doses >3 g/yr are likely to be associated with an increased risk of exceeding the ongoing iron loss and inducing positive iron balance.
- The consequences of applying IV iron in excess of ongoing losses remain unknown.
- Higher IV iron requirements should prompt investigation of increased losses (especially GI).

Iron Deposition in the Liver



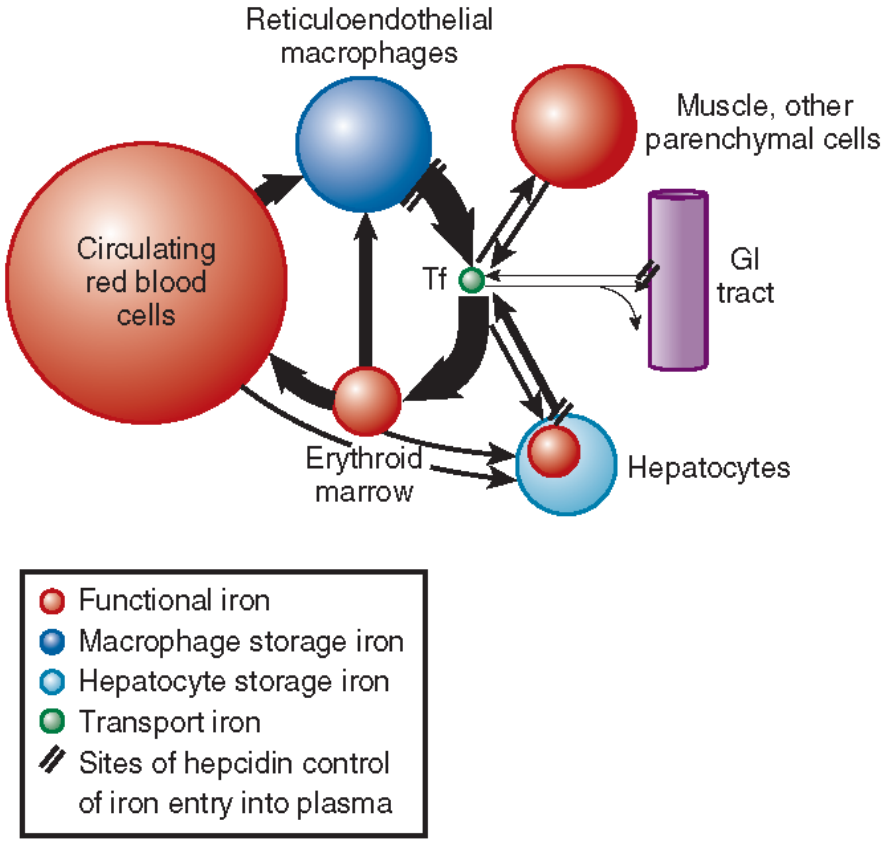
Intravenous iron is deposited and stored in Kupffer cells of the reticuloendothelial system (RES) which is the iron storage system of the liver

Iron can also be deposited in hepatocytes of the liver parenchyma

Liver: structure of human liver. Art. Encyclopædia Britannica Online. Web. 07 Dec. 2015. http://www.britannica.com/science/liver/images-videos/Microscopic-structure-of-the-liver-Liver-cells-or-hepatocytes-have/60419>

Iron Compartmentalization in the Body

It has been hypothesized that parenchymal iron excess and labile iron can be harmful while iron sequestered within cells of the reticuloendothelial system may be of less concern



Size of the circles denotes the relative proportion of iron in various compartments

Source: Hoffmann Hematology Basic Principles and Practice, 2012

Defining Iron Overload

- No feasible method exists to determine total body iron content.
- Iron overload is a condition of increased body iron content.
  - Possibly associated with risk of organ dysfunction
- Pathologic iron overload is a condition of increased total body iron content with signs of organ dysfunction.
  - Described for hematological diseases (e.g., hemochromatosis)

Assessing Iron Overload

- Elevated serum ferritin does not always correlate with elevated liver iron content.
- High ferritin + high TSAT can be of particular concern based on observations in hereditary hemochromatosis and transfusion-induced iron overload.
- Hyperferritinemia is not synonymous with iron overload.
- Serum ferritin does not differentiate iron stored in parenchymal cells or RES.

MRI: Assessing Iron Overload

- MRI has been shown to be reliable for detecting tissue iron content in the non-CKD population.
- However, there is limited experience in HD patients.
- The relevance of increased liver iron content in the absence of elevated liver enzymes is unclear.
- There is insufficient evidence to use MRI to guide IV iron therapy.

Iron Overload: Hematological Disorders

- Organ toxicity associated with iron overload depends upon the magnitude and speed of iron accumulation.
- The main target organs are liver, myocardium, endocrine glands, and joints.

Organ Toxicity Induced by Iron Overload

- The magnitude, distribution, and duration of iron overload in CKD may be insufficient to produce similar toxicity as observed for hematological disorders.
- Given that IV iron use has increased markedly in HD over the last few years, the exposure may not have been long enough to detect toxicity.
- End-organ damage has not been established unequivocally; therefore, the toxicity of repeated high-dose IV iron cannot be excluded.

Case Study: “Barry”

- 58-y.o.male on HD for 3 yrs
- End-stage kidney failure due to hypertensive nephropathy
- Known chronic liver disease due to hepatitis C
- On EPO alfa 4000 units x3 per week + IV iron 200 mg monthly
- Lab results
  - Hb 9.4 g/dL
  - Ferritin 1145 µg/L
  - TSAT 18%
  - CRP 2 mg/L

Case Study: “Barry”

What would you do next?

A. Continue present dose of EPO and IV iron
B. Increase his dose of EPO and continue IV iron
C. Increase his monthly prescription of IV iron and continue same dose of EPO
D. Increase both his dose of EPO and his monthly dose of IV iron
E. Continue EPO and reduce monthly iron dose

Part 2:

Oxidative Stress

Oxidative Stress in CKD

- Oxidative stress early in CKD and is thought to herald poor prognosis.
- It results from an overproduction of reactive oxygen/nitrogen species or impairment in the cellular antioxidant enzymatic activities, leading to oxidation of macromolecules.

Oxidative Stress in CKD

- Markers (NO_2, HOCl, and OH) are present in uremic plasma and are thought to be the fingerprints of increased oxidative stress.
- However, diagnostic tools and the relevance of these markers to guide therapy in CKD are not established.

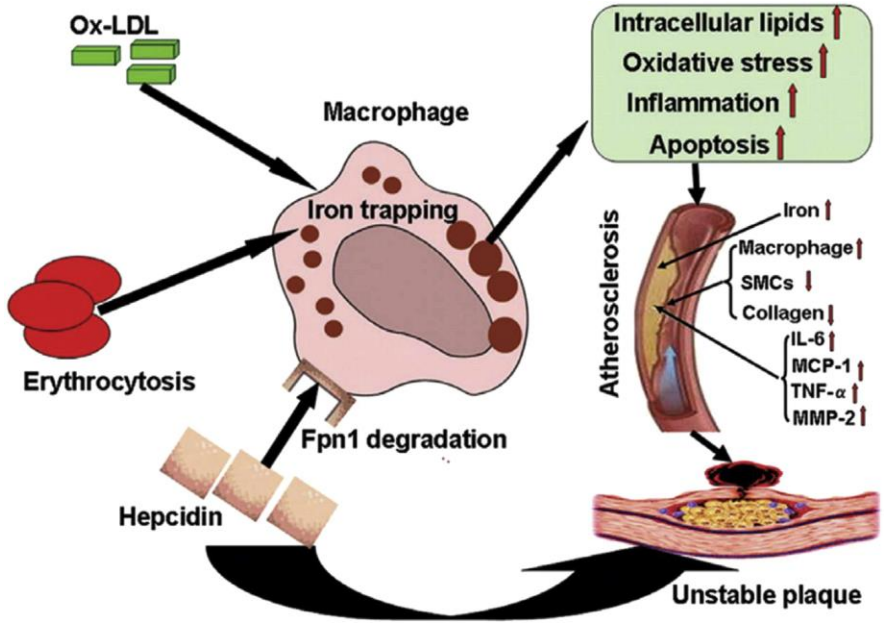
IV Iron, Oxidative Stress, and CV Risk

- IV iron promotes oxidative damage of peripheral lymphocyte DNA[1] and endothelial dysfunction.[2,3]
- However, the question of how IV iron accelerates atherosclerosis remains unresolved.
- Accumulation of iron in plaques has not been proven to promote CV disease.
- Limitations of observational studies do not allow any firm conclusions to be made on IV iron dose and CV risk.

1. Kuo KL et al. J Am Soc Nephrol. 2008;19:1817-1826.
2. Kamanna VS et al. Am J Nephrol. 2012;35:114-119.
3. Rooyakkers TM et al. Eur J Clin Invest. 2002;32 (Suppl 1): 9-16.

Hepcidin and CV Risk

- Some studies suggest that hepcidin upregulation may increase CV risk in the general population. However, there is limited evidence in CKD patients.



Potential mechanism of hepcidin-mediated plaque instability

Source: Li JJ, et al. Arterioscler Thromb Vasc Biol. 2012;32:1158-1166.

Ferritin as a Risk Factor

- Like hepcidin, ferritin is just as likely to reflect an inflammatory response as an iron-replete state.
- In the general population, elevated serum ferritin is associated with increased risk for MI and carotid plaques.
- In CKD patients, the association between ferritin levels and outcomes is not clear.
- Prospective controlled studies are needed to assess whether elevated ferritin merely represents a risk marker or is an actual risk factor.

Antioxidants and Iron Supplementation

- Some studies have shown benefits of limited antioxidant treatments on lipid peroxidation.
- However, a recent RCT in HD patients did not show beneficial effects of antioxidative therapy.[1]
- No definitive conclusion can be drawn as to whether iron-related oxidative stress responds to antioxidant therapy.

1. Himmelfarb J, et al. J Am Soc Nephrol. 2014;25:623–633.

Case Study: “John”

- 68-y.o. male on HD for 6 yrs
- On EPO and IV iron to maintain ferritin levels above KDIGO minimum
- Wants to stop IV iron because of his concerns about “oxidative stress”

Case Study: “John”

What would you do next?

A. Agree to John’s request and stop IV iron without further discussion
B. Tell John you will run some tests to assess oxidative stress level
C. Continue with IV iron after explaining the reasons for confusion in the medical literature
D. Do options B and C

Part 3:
Risk of Infections

IV Iron: Infection Risk in HD Patients

- Critical review[1] of studies (largely observational) evaluating infection risk association with a) ferritin, and b) iron usage:
  - Ferritin: showed association (1.5- to to 3.1-fold higher incidence of infection or infection-related mortality).
  - Iron usage: showed association (14%–45% higher risk of infection-related mortality).

1. Ishida JH, Johansen KL. Semin Dial. 2014;27:26–36.
2. Brookhart MA, et al. J Am Soc Nephrol. 2013;24:1151–1158.

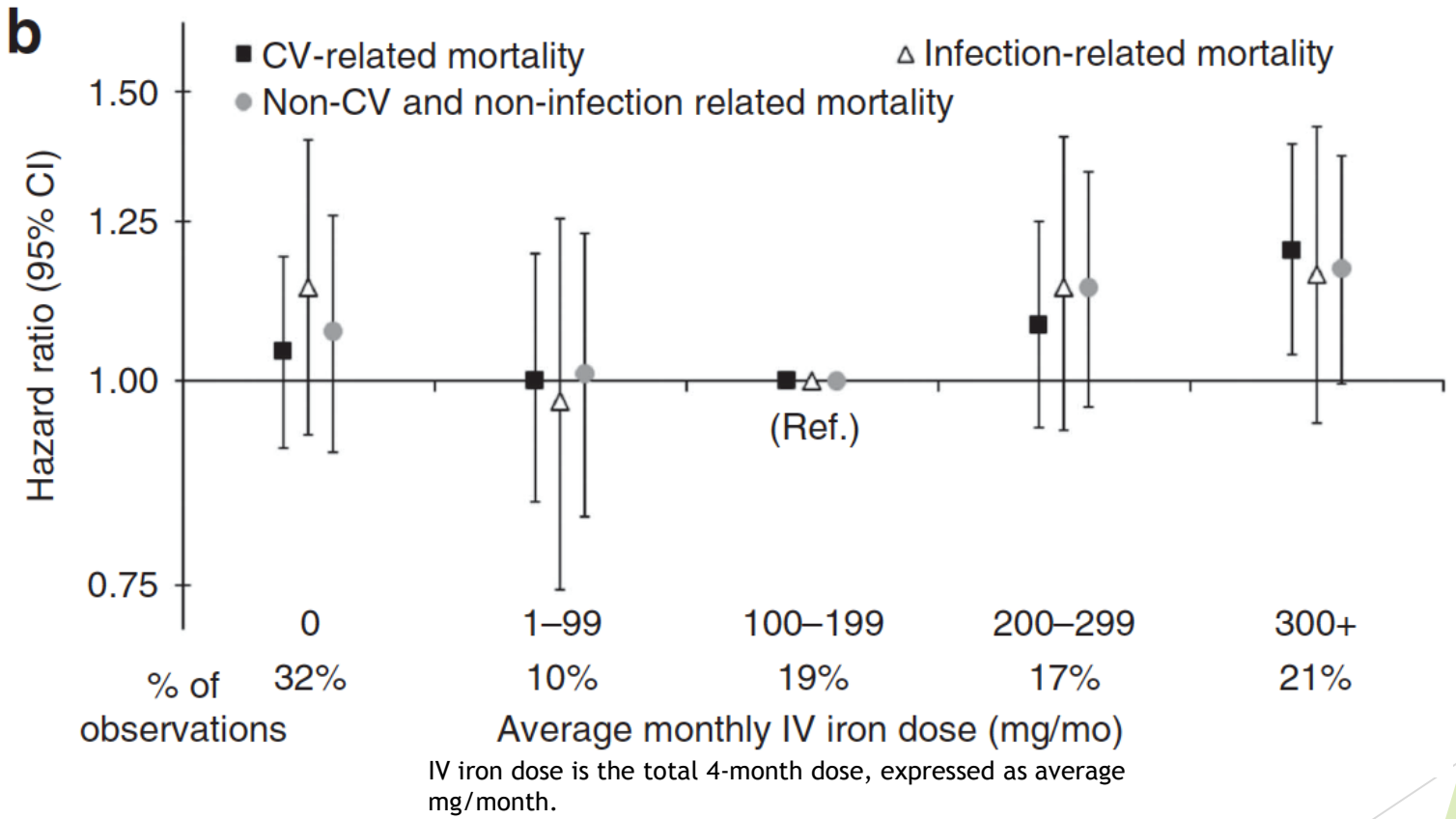
IV Iron: Infection Risk in HD Patients

- Bolus dosing was reported to show higher risk than maintenance dosing for patients with a catheter and history of infection.[2]
  - In contrast, maintenance dosing or low dosing was not associated with increased risk.

1. Ishida JH, Johansen KL. Semin Dial. 2014;27:26–36.
2. Brookhart MA, et al. J Am Soc Nephrol. 2013;24:1151–1158.

IV Iron in HD: Infection-Related Outcomes

Association of IV iron dose and cause-specific mortality in HD.[1]



IV iron dose is the total 4-month dose, expressed as average mg/month.

1. Bailie G, et al. Kidney Int. 2015;87:162–168.

IV Iron in HD: Infection-Related Outcomes

Relationship between IV iron dose and infection-related hospitalization.[1]

Duration of Iron Exposure	Doses (mg)	N (Hosp.)	Infectious Hosp: HR (95% CI)
1 month	None	2187	0.92 (0.76, 1.11)
	>0 to 150	1200	1 (ref)
	>150 to 350	1648	0.94 (0.77, 1.15)
	>350	1825	0.91 (0.77, 1.09)
3 months	None	1047	1.03 (0.81, 1.33)
	>0 to 450	1381	1 (ref)
	>450 to 1050	2151	1.01 (0.81, 1.25)
	>1050	1513	1.08 (0.86, 1.36)
6 months	None	399	1.15 (0.79, 1.68)
	>0 to 900	1383	1 (ref)
	>900 to 2100	2589	0.94 (0.75, 1.19)
	>2100	845	1.26 (0.94, 1.69)

IV Iron in HD: Infection-Related Outcomes

Association between IV iron and CV or sepsis-related mortality.[1]

	All-cause mortality			CV or sepsis mortality**		
	HR	(95% CI)	P-value	HR	(95% CI)	P-value
Age (years)	1.05	(1.03–1.08)	<0.001	1.04	(1.02–1.07)	<0.001
Sex						
Female	Ref.			Ref.		
Male	1.14	(0.68–1.90)	0.6	1.38	(0.73–2.60)	0.3
Type of renal replacement therapy						
Hemodialysis	Ref.			Ref.		
Peritoneal dialysis	0.28	(0.07–1.03)	0.06	0.55	(0.14–2.12)	0.4
Transplantation	0.47	(0.14–1.54)	0.2	0.38	(0.08–1.72)	0.2
Diabetes mellitus						
No	Ref.			Ref.		
Yes	1.31	(0.81–2.12)	0.3	1.54	(0.87–2.73)	0.1
Iron supplementation						
No	Ref.			Ref.		
Yes	0.22	(0.08–0.58)	0.002	0.31	(0.09–1.04)	0.06
C-reactive protein (mg/dL)	1.13	(1.10–1.17)	<0.001	1.11	(1.07–1.15)	<0.001
Albumin (g/dL)	0.33	(0.21–0.50)	<0.001	0.31	(0.18–0.53)	<0.001
Hemoglobin (g/dL)	0.95	(0.81–1.12)	0.5	0.90	(0.75–1.08)	0.3

* Adjusted for age, sex, diabetes mellitus and the time-dependent variables type of renal replacement therapy, C-reactive protein, albumin and hemoglobin.
** **Cardiovascular or sepsis mortality**: myocardial infarction (MI), heart failure, sudden death, ischemic stroke, hemorrhagic stroke, sepsis.

1. Zitt E, et al. PLoS ONE. 2014;9:e114144.

Studies in PD and Nondialysis Patients

- One study showed more peritonitis episodes in PD patients after IV iron infusion.[1]
- A recent single-center RCT (REVOKE) also showed IV iron was associated with higher rate of adverse events; however, the findings are controversial.[2]
- The FIND-CKD global multicenter study (non-dialysis CKD patients) found that the incidence of infections and CV events was identical for high-ferritin, low-ferritin, and oral iron groups.[3]

1. Prakash S, et al. Perit Dial Int. 2001;21:290–295.
2. Agarwal R, et al. Kidney Int. 2015;88:905–914.
3. Macdougall IC, et al. Nephrol Dial Transplant. 2014;29:2075–2084.

REVOKE Study

	REVOKE[1]	
	Oral ferrous sulfate	IV iron sucrose
Patients	69	67
Study Period	104 weeks	
SAE (%)	40 (58)	37 (55)
SAE infections (%)	11 (16)	19 (28)

1. Agarwal R, et al. Kidney Int. 2015;88:905–914.

FIND-CKD Study

	FIND-CKD[1]	
	Oral ferrous sulfate	IV ferric carboxymaltose
Patients	312	304
Study Period	56 weeks	
SAE (%)	59 (19)	75 (25)
SAE infections (%)	12 (3.8)	11 (3.6)

1. Macdougall IC, et al. Nephrol Dial Transplant. 2014;29:2075–2084.

Existing Evidence: Inconclusive

- Studies in HD, PD, and non-dialysis CKD patients provide conflicting evidence for the association between IV iron and infection risk.
  - Most data are derived from observational studies in HD (subject to confounding) and the few RCTs conducted to date were of short duration or underpowered to assess the risk of infection
- Current KDIGO recommendations are still prudent which calls for:
  - balancing potential benefits vs. risks of IV iron
  - avoiding IV iron use in patients with active systemic infections

Case Study: “Tammy”

- 67-y.o. female on HD
- Admitted with ruptured diverticular abscess and cutaneous fistula
- On weekly protocol: iron sucrose 100 mg/wk (KDOQI Guidelines) and epoetin alfa 6000 units/wk, target Hb 10.0–11.5 g/dL
- Lab results
  - Hb 9.2 g/dL
  - Ferritin 335 µg/L
  - TSAT 10%

Case Study: “Tammy”

What would you do next?

A. Increase the EPO dose
B. Continue to administer IV iron due to low TSAT
C. Withhold IV iron and increase EPO dose
D. Withhold IV iron and maintain EPO dose
E. Continue with the same dose of EPO and frequency of IV iron

CAUSES ANEMIA
IN CKD

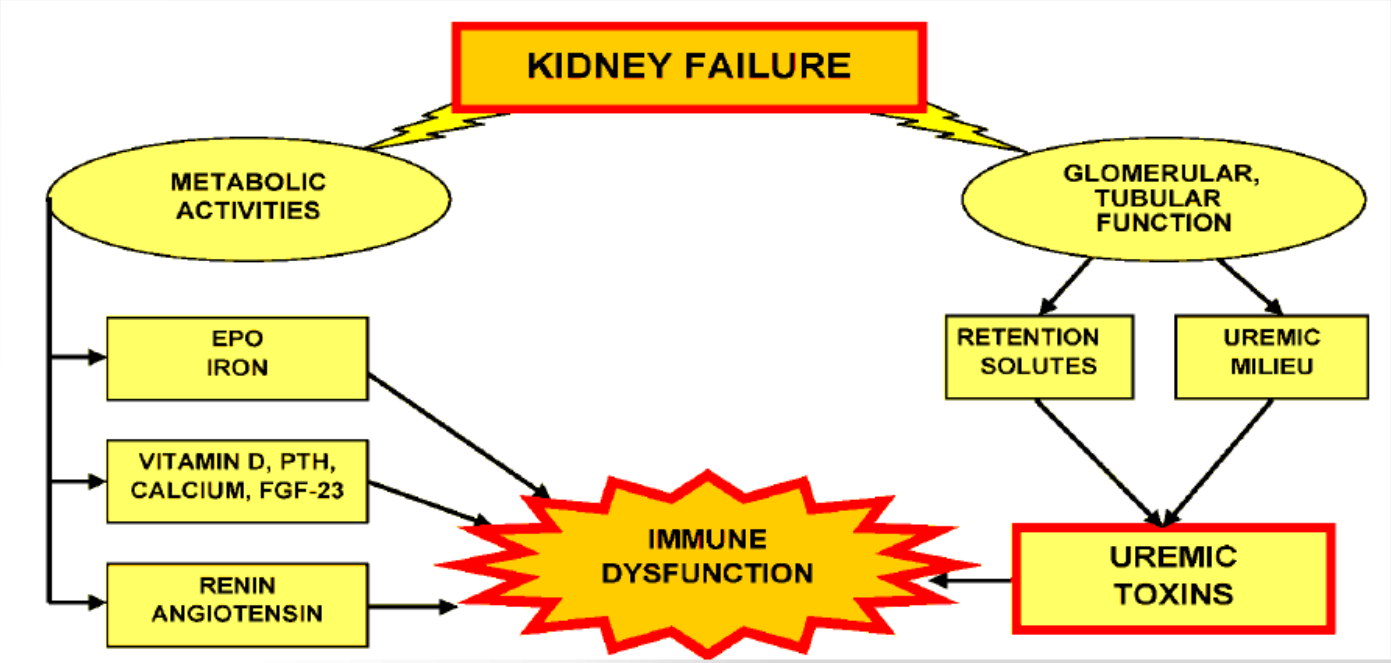
Shortened red blood cell life span

- The life span of red cells is reduced by approximately one third in hemodialysis patients

CAUSES ANEMIA
IN CKD

"uremic milieu"

The "uremic milieu" is a term that is overused in attempts to explain the multiple organ dysfunction of chronic kidney disease.



- For example, "uremic" serum has been shown to inhibit primary bone marrow cultures of early erythroid cell lines.

Use of ESAs and other agents to treat anemia in CKD

- We recommend using ESA therapy with great caution, if at all, in CKD patients with active malignancy—in particular when cure is the anticipated outcome— (1B), a history of stroke (1B), or a history of malignancy (2C).

Patient presentation

- A 38-year-old nulliparous white woman on chronic hemodialysis (HD) for 4 years has recently been diagnosed with ***breast cancer***.
- She has been receiving 2200 U of epoetin thrice weekly in HD and 50 mg of IV iron sucrose weekly; her Hb range was 10.5 to 11.2 g/dL

How I treat renal anemia

Steven Fishbane[1,*] and Daniel W. Coyne[2,*]

[1]Department of Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Great Neck, NY; and [2]Division of Nephrology, School of Medicine, Washington University, St. Louis, MO

Anemia is a frequent complication of kidney disease. When severe, it causes symptoms that can be debilitating. The course of anemia tends to track the decline in kidney function, with prevalence increasing in more advanced disease. Although the most common cause is relative erythropoietin deficiency, other factors such as reduced iron availability contribute to the pathobiology. In this review, we use cases to explore the surprising complexity of decision-making in management of renal anemia. (*Blood*. 2020;136(7):783-789)

Patient presentation

- In addition to addressing whether she should continue on an ESA, consideration was given to the patient's desire for a kidney transplant although she had heard that transfusions could reduce her chances of receiving one.
- Which one is your dicision about ESA therapy
  A. Continue ESA
  B. Reduce ESA
  C. Discontinue ESA

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Case Discussion

- Our general approach is to discuss the relevant issues with the patient and oncologist.
- We ask oncologists about the likelihood of cure and goals of therapy, their perception of ESA adversely affecting the cancer outcome, and expected cancer treatment and its likelihood of inducing severe anemia or requiring transfusions.

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Case Discussion

- We review the ESA product information with patients, listen to the their concerns, and ascertain whether they are willing to continue on an ESA.
- In addition to ESA treatment, other tools that can improve Hb concentration in these patients include: avoiding use of dialysis catheters as they increase inflammation, blood loss, and risk of infection; controlling hyperparathyroidism; and modifying the dialysis prescription.

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Case Discussion

- In many cases, we initially withhold the ESA, continue maintenance IV iron, and monitor Hb twice monthly with a goal of maintaining Hgb 9 g/dL.

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Case Discussion

- If Hgb falls below this threshold, we reassess the patient's fatigue, and reweigh the risks of benefits of ESA use.
- If Hb is persistently 8 g/dL, we usually will favor use of low doses of epoetin (10 000 IU/weekly) to maintain Hgb 9 g/dL, provided the patient and oncologist are agreeable.

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Use of ESAs treat anemia in ESRD

- For adult CKD 5D patients, we suggest that ESA therapy be used to avoid having the Hb concentration fall below 9.0 g/dl (90 g/l) by starting ESA therapy when the hemoglobin is between 9.0–10.0 g/ dl (90–100 g/l). (2B)
- Individualization of therapy is reasonable as some patients may have improvements in quality of life at higher Hb concentration and ESA therapy may be started above 10.0 g/dl (100 g/l). (Not Graded)

ESA MAINTENANCE THERAPY

- In general, we suggest that ESAs not be used to maintain Hb concentration above 11.5 g/dl in adult patients with CKD. (2C)
- Individualization of therapy will be necessary as some patients may have improvements in quality of life at Hb concentration above 11.5 g/dl and will be prepared to accept the risks. (Not Graded)

ESA MAINTENANCE THERAPY

- An increase of Hb above 11.5 g/dl towards 13 g/dl may also be justified in individual patients with a high bleeding tendency since this results in lower transfusion needs, as shown by 8 RCTs.
- In all adult patients, we recommend that ESAs not be used to intentionally increase the Hb concentration above 13 g/dl. (1A)

ESA DOSING

- We recommend determining the initial ESA dose using the patient's Hb concentration, body weight, and clinical circumstances. (1D)
- The objective of initial ESA therapy is a rate of increase in Hb concentrations of 1.0 to 2.0 g/dl per month.

ESA DOSING

- The rate of increase varies greatly as a function of individual ESA responsiveness.
- Poor responders are more likely to be female, to have a history of cardiovascular disease, to have signs of iron deficiency and inflammation, and to be overweight.

ESA DOSING

- Epoetin-alfa or epoetin-beta dosing usually starts at ***20 to 50 IU/kg*** body weight three times a week.
- Darbepoetin-alfa dosing usually starts at ***0.45 mg/kg*** body weight once weekly by subcutaneous (SC) or IV administration,
- or ***0.75 mg/kg*** body weight once every 2 weeks by SC administration.

ESA DOSING

- CERA dosing starts at ***0.6 mg/kg*** body weight once every 2 weeks by SC or IV administration for CKD ND and CKD 5D patients, respectively,
- or 1.2 mg/kg body weight once every 4 weeks by SC administration for CKD ND patients.

ESA DOSING

- Higher baseline Hb concentrations require lower initial ESA doses, except for CERA for which there is no initial dose change.
- In patients with a history of CVD, thrombo-embolism or seizures, or in those with high blood pressure, the initial doses should be in the lower range.

ESA DOSING

- Epoetin-alfa or epoetin-beta dosage may subsequently be increased every 4 weeks by a weekly dose of 3x20 IU/kg if the increase of Hb is not adequate.
- Increases in dose should not be made more frequently than once a month.
- If the Hb is increasing and approaching 11.5 g/dl, the dose should be reduced by approximately 25%.

ESA DOSING

- If the Hb continues to increase, doses should be temporarily withheld until the Hb begins to decrease, at which point therapy should be reinitiated at a dose approximately 25% below the previous dose.
- If the Hb increases by more than 1.0 g/dl in any 2-week period, the dose should be decreased by approximately 25%.

Frequency of administration

- We suggest determining the frequency of ESA administration based on CKD stage, treatment setting, efficacy considerations, patient tolerance and preference, and type of ESA. (2C)
- Epoetin-alfa efficacy decreases when the dosing is extended from 3 times weekly to once-weekly administration, and even more so when the dosing intervals are extended to every other week administration.

Frequency of administration

- Among long-acting ESAs, darbepoetinalfa appears to have maximum efficacy when administered every 2 weeks,
- Methoxy polyethylene glycol-epoetin-beta (CERA) every 4 weeks

Frequency of monitoring

- During the initiation phase of ESA therapy, measure Hb concentration at least monthly. (Not Graded)
- For CKD 5D patients, during the maintenance phase of ESA therapy measure Hb concentration at least monthly. (Not Graded)

Resistance to ESA therapy

- Inadequate response (‘resistance’) to ESA therapy is defined as failure to reach the target Hb level despite SC epoetin dose >300 IU/kg/week (450 IU/kg/week IV epoetin), or darbepoetin dose >1.5 microgram/kg/week.
- Hyporesponsive patients who are iron replete should be screened clinically and by investigations for other common causes of anaemia. (1A)

THE RENAL ASSOCIATION
founded 1950

Clinical Practice Guideline
Anaemia of Chronic Kidney Disease

Final Version: June 2017
Review Date: June 2022

Initial ESA hyporesponsiveness

- 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 dosing. (Not Graded)
- In patients with ESA hyporesponsiveness, we suggest avoiding repeated escalations in ESA dose beyond double the initial weight-based dose. (2D)

Subsequent ESA hyporesponsiveness

- 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)
- 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)

ESA hyporesponsiveness

- Relative resistance to the effect of ESAs is a common problem in managing the anemia of patients with CKD and remains the subject of intense interest.
- ESA hyporesponsiveness has been found to be among the most powerful predictors of the risk of cardiovascular events and mortality.

Table 3 | Potentially correctable versus non correctable factors involved in the anemia of CKD, in addition to ESA deficiency

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

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; PRCA, pure red cell aplasia.

Evaluation for ESA Induced Pure Red Cell Aplasia (PRCA)

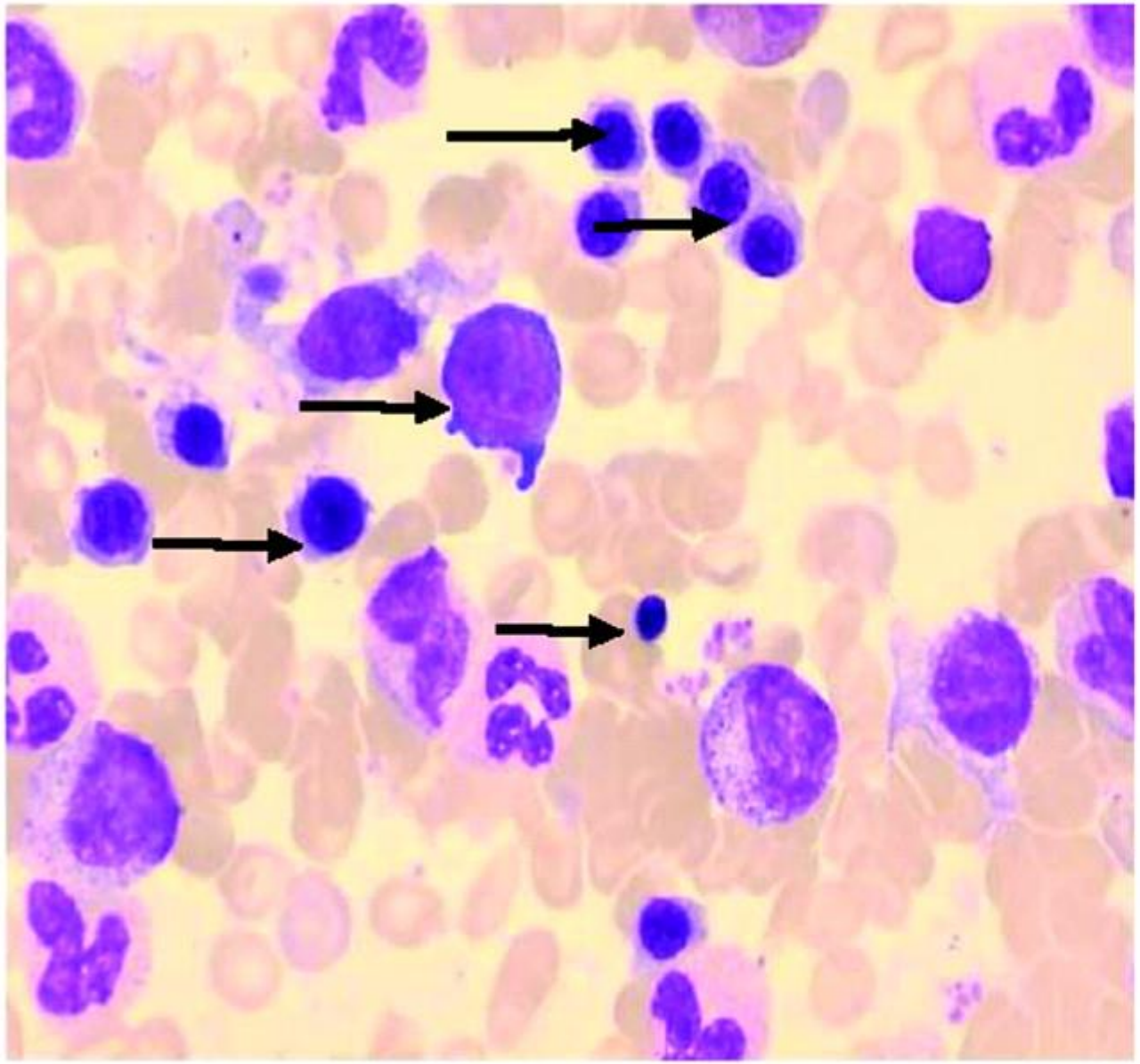
- PRCA due to anti-erythropoietin (EPO) antibodies should be suspected in an individual who has previously responded to EPO if the Hb level declines by >2 g/dl per month or the reticulocyte count is <20,000/uL.

Evaluation for ESA Induced Pure Red Cell Aplasia (PRCA)

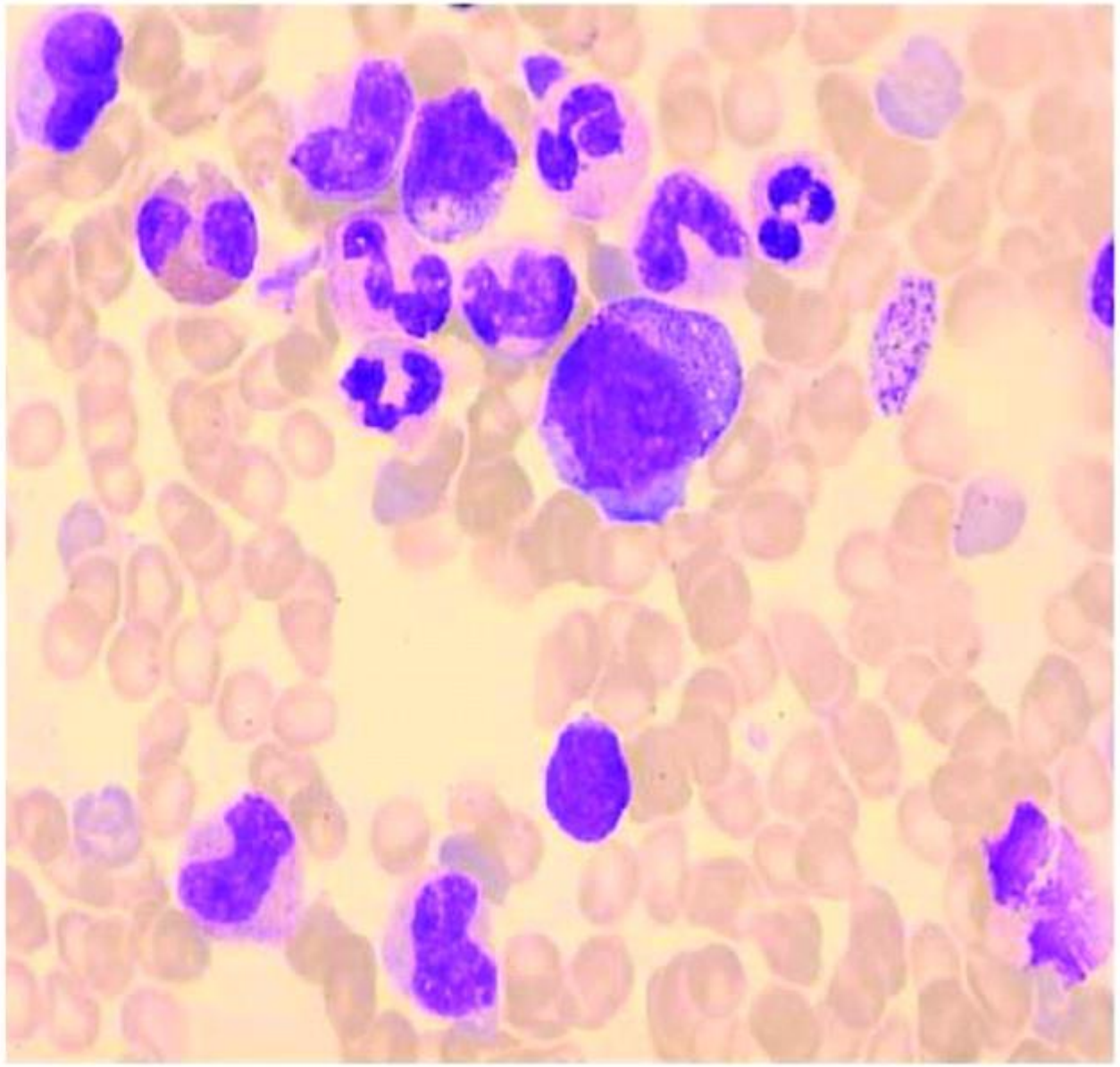
- PRCA is specifically characterized by the following clinical features:
  - A drop in Hb level of >7 to 10 g/L per week without transfusions or transfusion requirement of at least one unit per week to maintain adequate Hb, despite continued use of ESA at high doses.
  - Markedly reduced reticulocyte count (<10,000/uL).
  - Normal platelet and white blood cell count.
  - Elevated serum transferrin saturation and serum ferritin.

PRCA

- The diagnosis of PRCA is established by:
- Bone marrow examination: which confirms severe hypoplasia of erythroid precursors (<5%).
- The presence of anti-erythropoietin antibodies:
  - There are several available tests to detect antibodies to erythropoietin, with varying sensitivities and specificities.
  - Patients with suspected ESA induced PRCA who test positive using binding antibodies should have the diagnosis confirmed with the definitive testing for neutralizing antibodies



Normal BM containing polychromatophilic erythroblasts (arrows)



BM of a patient with Ab-mediated PRCA

Treatment of PRCA

- ESA induced PRCA is an immune mediated process.
- While spontaneous remissions after cessation of EPO therapy have been reported, immunosuppressive therapy is usually needed in most cases.
- Verhelst et al compared various immunosuppressive agents in 37 patients with antibody mediated PRCA compared to 10 with no treatment and found benefit with cyclophosphamide, plasma exchange and ciclosporin and also transplantation.

Treatment of PRCA

- it is advisable that retreatment with ESA may be considered in patients with a history of PRCA only if anti-EPO antibody level is no longer detectable.
- In addition, if epoetin therapy is to be reconsidered for these patients, ***only the intravenous*** rather than the subcutaneous route should be considered for drug administration.

AJKD

Update on Anemia in ESRD and Earlier Stages of CKD: Core Curriculum 2018

Steven Fishbane and Bruce Spinowitz

Anemia is a frequent complication during the later stages of chronic kidney disease. When present, it may cause symptoms such as fatigue and shortness of breath. The pathogenesis of anemia in chronic kidney disease is complex, but a central feature is a relative deficit of erythropoietin. New information has elucidated the critical role of the hypoxia-sensing system in mediating erythropoietin synthesis and release. Iron deficiency is a second important factor in the anemia of chronic kidney disease. New insights into the dynamics of iron metabolism have clarified the role of chronic inflammation and hepcidin as key mediators of impaired iron utilization. In this article, we review the epidemiology, pathobiology, clinical evaluation, and treatment of anemia in chronic kidney disease.

Complete author and article information provided before references.

Am J Kidney Dis. 71(3): 423-435. Published online January 11, 2018.

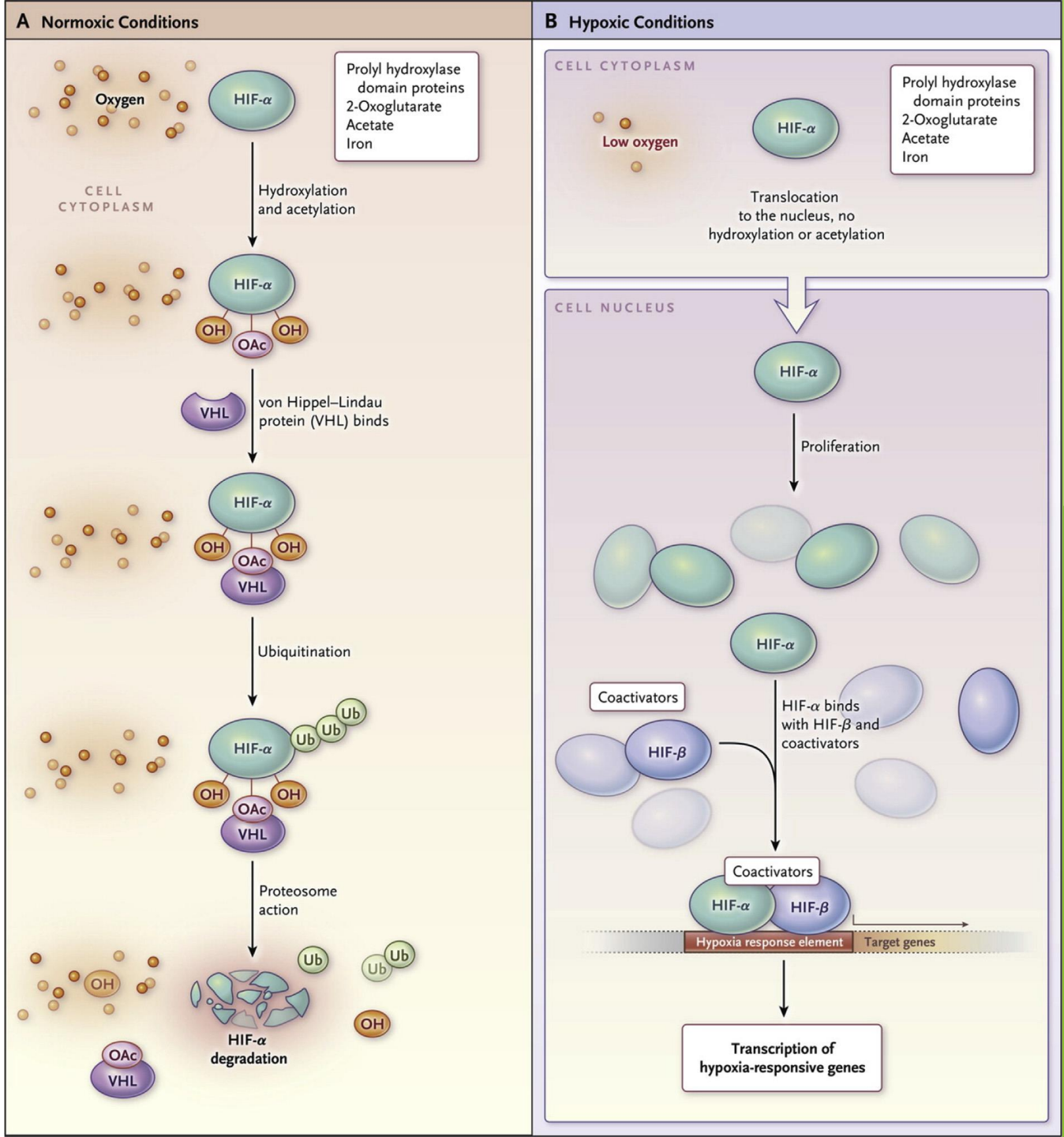
doi: 10.1053/j.ajkd.2017.09.026

Case: *A 54-year-old man with diabetes mellitus, hypertension, and coronary artery disease is*

Anemia remains an important complication experienced by patients with kidney disease,

FEATURE EDITOR: Asghar Rastegar

Figure 2. Under normoxic conditions, hypoxia inducible factor (HIF)-α is hydroxylated by prolyl hydroxylase domain proteins and then undergoes proteosomal degradation. Under hypoxic conditions, HIF-α does not undergo degradation, translocates to the nucleus, binds with HIF-β, and activates the hypoxia response element, initiating gene transcription of erythropoietin. Reproduced from West (NEJM. 2017;376:1965-1971) with permission of the copyright holder (Massachusetts Medical Society).



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Roxadustat (FG-4592) treatment for anemia in dialysis-dependent (DD) and not dialysis-dependent (NDD) chronic kidney disease patients: A systematic review and meta-analysis

Junduo Liu[a,*], Afang Zhang[b], John C. Hayden[c], Akshaya Srikanth Bhagavathula[d], Fatema Alshehhi[e], Giulia Rinaldi[f], Vasileios Kontogiannis[g], Jamal Rahmani[h]

ABSTRACT

- The effect of roxadustat (FG-4592) on individuals with chronic kidney diseases (CKD) patients receiving or not receiving the dialysis was unclear.
- The aim of this study was to evaluate the efficacy of roxadustat for the treatment of anemia in patients who are dialysis dependent (DD) or dialysis independent (NDD) CKD.

ABSTRACT

- We performed a systematic review of randomised controlled trials (RCTs) comparing treatment with roxadustat versus placebo or epoetin alfa up to November 2019.
- We investigated the efficacy of roxadustat in the levels of hemoglobin and other clinical parameters in renal anemia in patients with NDD and DD-CKD.

ABSTRACT

- We estimated weighted-mean difference (WMD) using random effect models.
- We included six RCTs comprising 1001 patients of whom 70.6 % were treated with roxadustat and 294 controls.
- The control group for studies of NDD-CKD patients was placebo whereas an active control of epoetin-alfa was used in studies of DD-CKD patients.

ABSTRACT

- Median follow-up time was 8 weeks.
- All trials were industry-sponsored.
- Overall, roxadustat increased hemoglobin levels by 1.20 g/dl (95 % CI:0.66, 1.75,P<0.0001)
- Hemoglobin levels increased by 1.99 g/dl in NDDCKD patients versus placebo and 0.52 g/dl in DD-CKD patients versus epoetin-alfa.

ABSTRACT

- Roxadustat was associated with a decrease the levels of hepcidin by -49.3 ng/dl (-38.5 ng/dl in NDD patients versus placebo and -27.7 ng/dl in DD patients versus epoetin alfa),
- Decrease in ferritin of -49.7 µmol/l (-52.2 µmol/l in NDD patients versus placebo and -7.3 µmol/l in DD patients versus epoetin alfa), and increase in total iron-binding capacity of 32.2 µmol/l (14.1 µmol/l in NDD patients versus placebo and 13.6 µmol/l in DD patients versus epoetin alfa).

ABSTRACT

- The percentage change in the transferrin saturation levels was −2.07 % (−6%, NDD patients versus placebo, and +3.7 % in DD patients versus epoetin alfa) in anemia associated CKD patients.
- This review found roxadustast increases the levels of hemoglobin, serum transferrin, intestinal iron absorption, and reduces hepcidin in both NDD and DD-CKD patients.
- Safety data is still emerging.