Renal Anemia: The Basics

Meredith Atkinson, M.D., M.H.S.
Associate Professor of Pediatrics
Johns Hopkins School of Medicine
3 March 2023

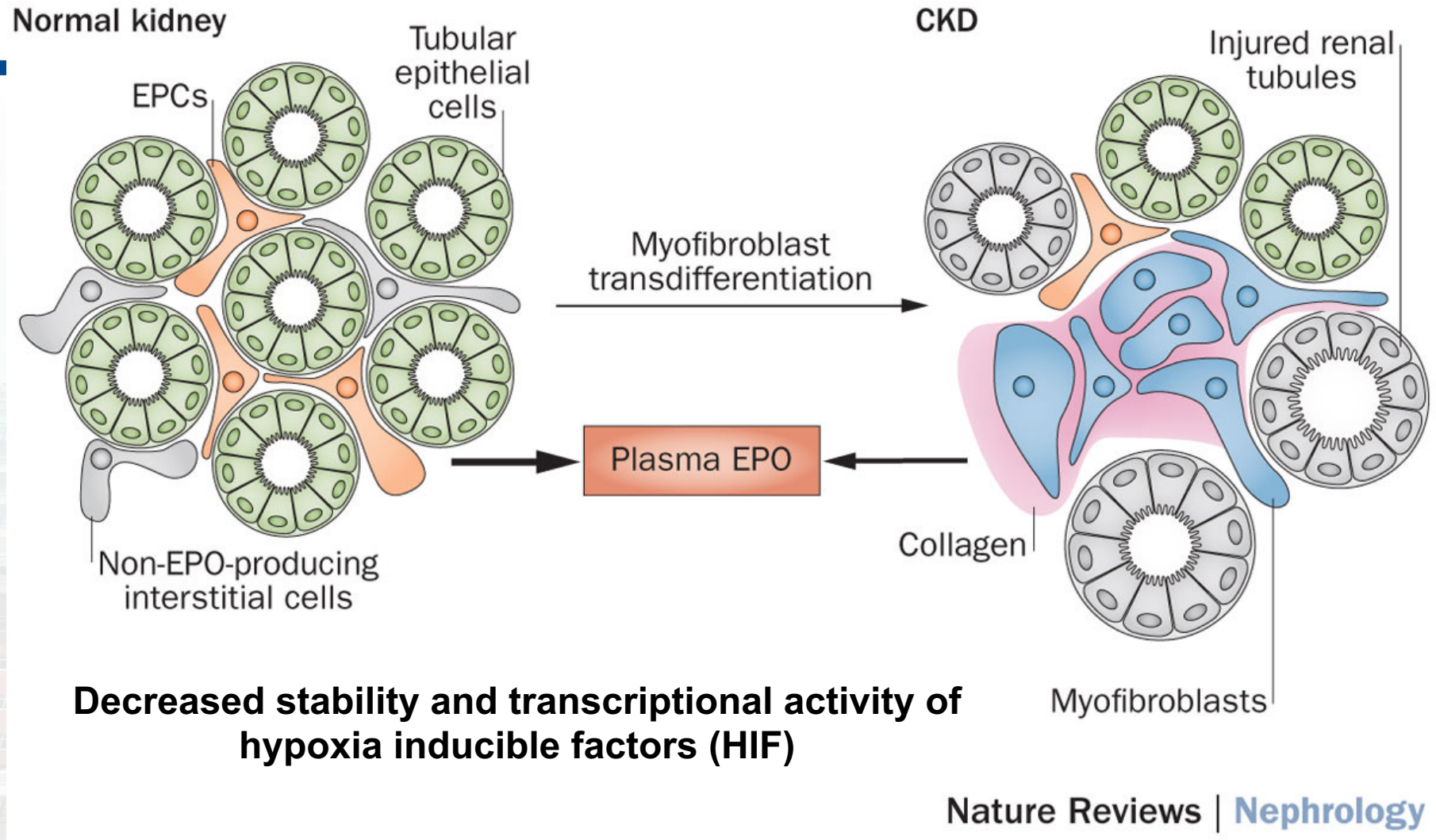
JOHNS HOPKINS
CHILDREN'S CENTER

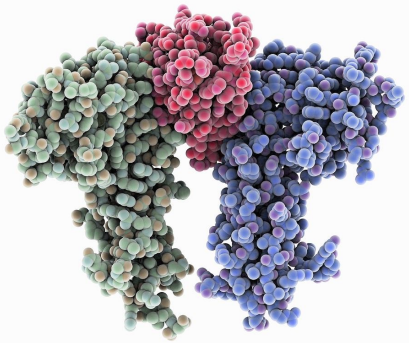
Disclosure: Consultancy with GlaxoSmithKline

Objectives

- Describe the etiology of the anemia of CKD in children
- Understand the formulations of erythropoiesis stimulating agents (ESA) and dosing schemes
- Describe indications for and approach to iron supplementation
- Recognize emerging anemia therapies
  - Next generation ESAs, novel iron supplementation, HIF stabilizers

Figure 5 Cellular basis of erythropoietin deficiency in renal failure

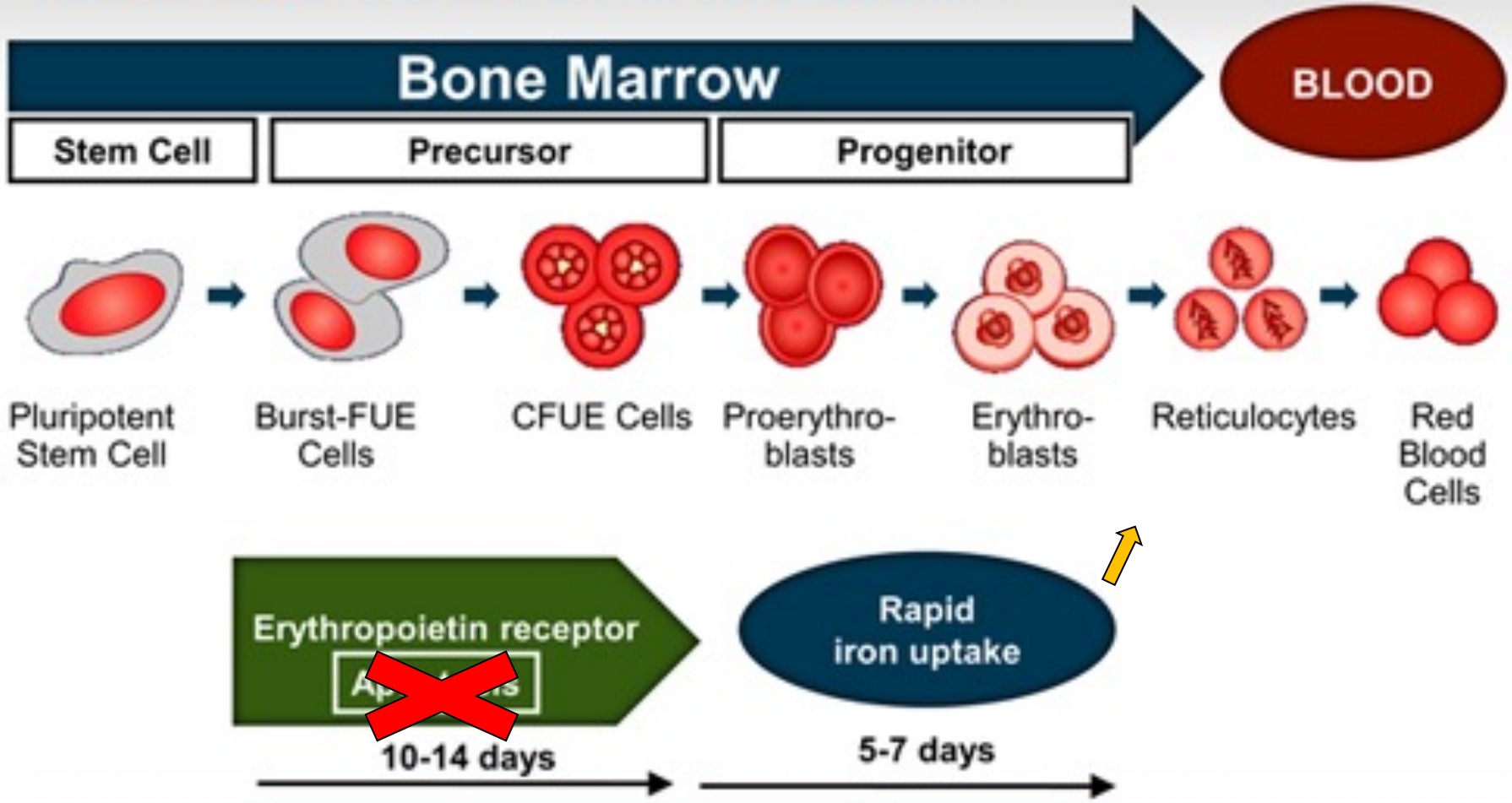




Human erythropoietin
Glycoprotein hormone

Koury, M. J. & Haase, V. H. (2015) Anaemia in kidney disease: harnessing hypoxia responses for therapy
Nat. Rev. Nephrol. doi:10.1038/nrneph.2015.82

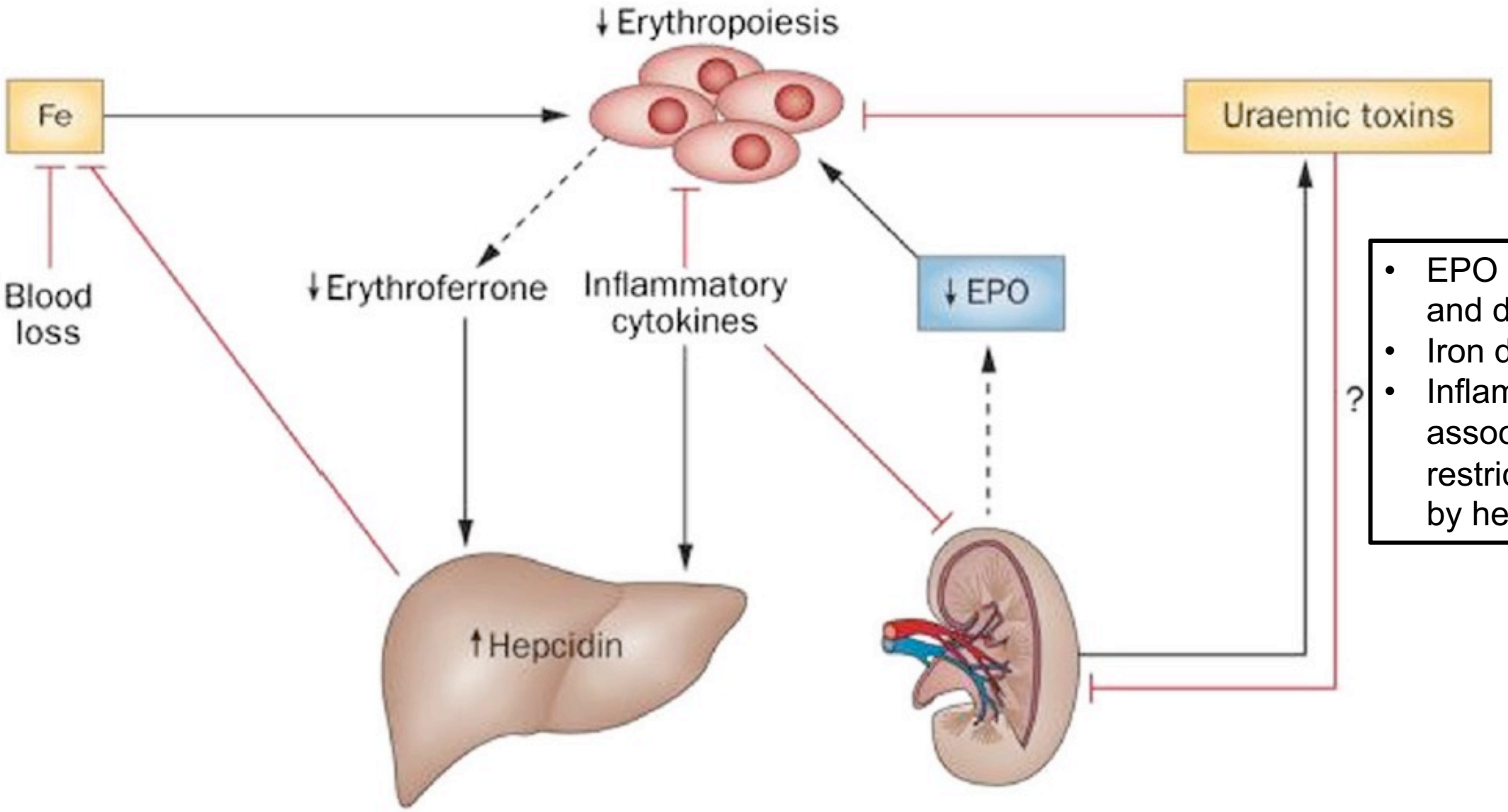
Red Blood Cell Maturation



Requires on average a 3-week cycle for red blood cell maturation

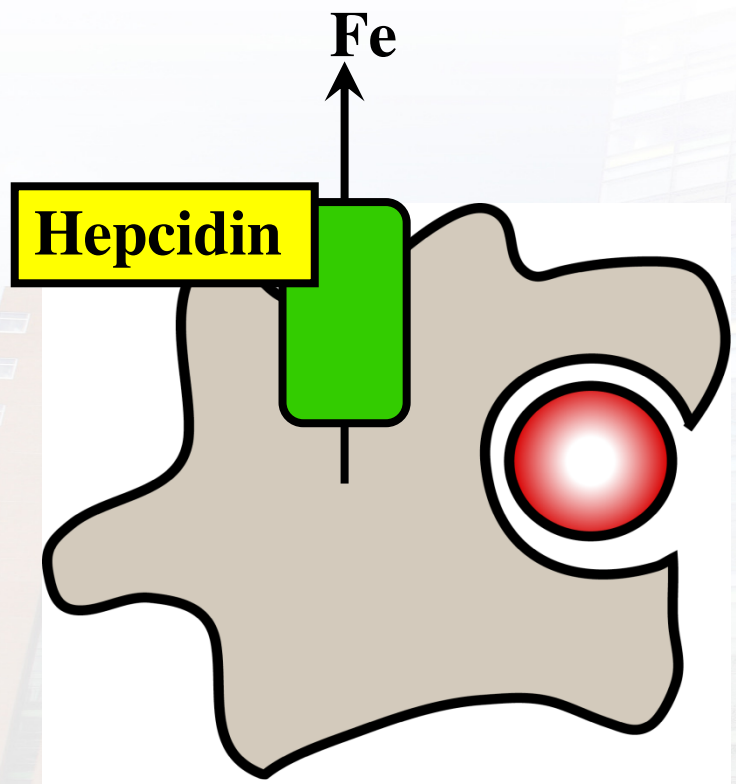
Reprinted from Lankhorst CE, Wish JB. Anemia in renal disease: diagnosis and management. *Blood Rev*. 2010;24:39-47, with permission from Elsevier.

JOHNS HOPKINS CHILDREN'S CENTER

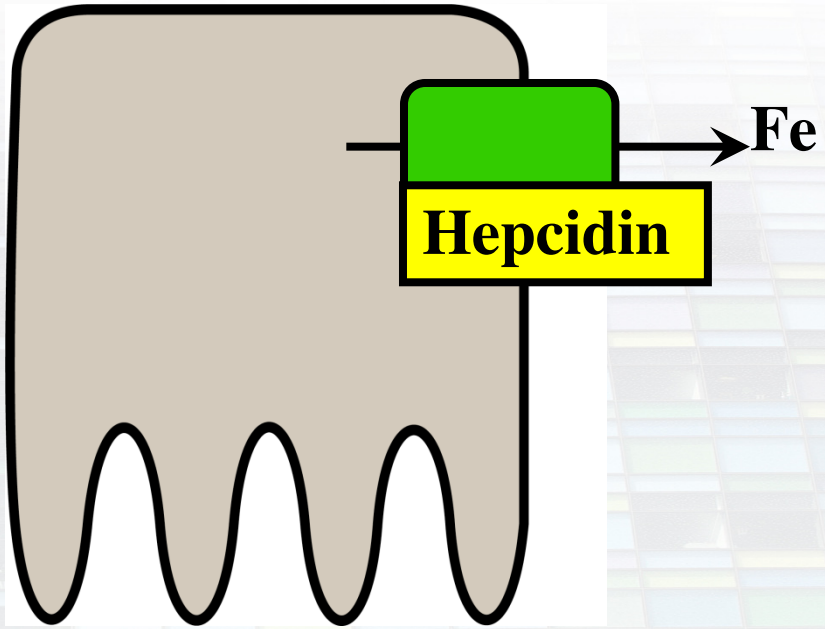


- EPO dysregulation and deficiency
- Iron deficiency
- Inflammation-associated iron restriction mediated by hepcidin

Hepcidin and Ferroportin



macrophage

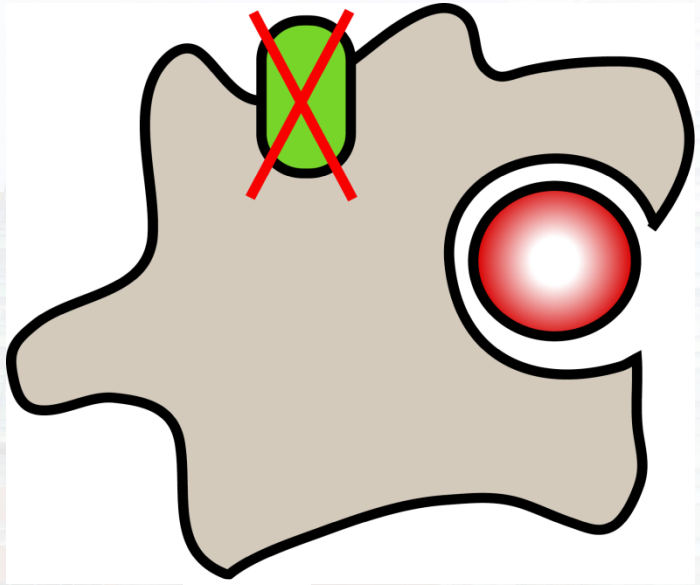


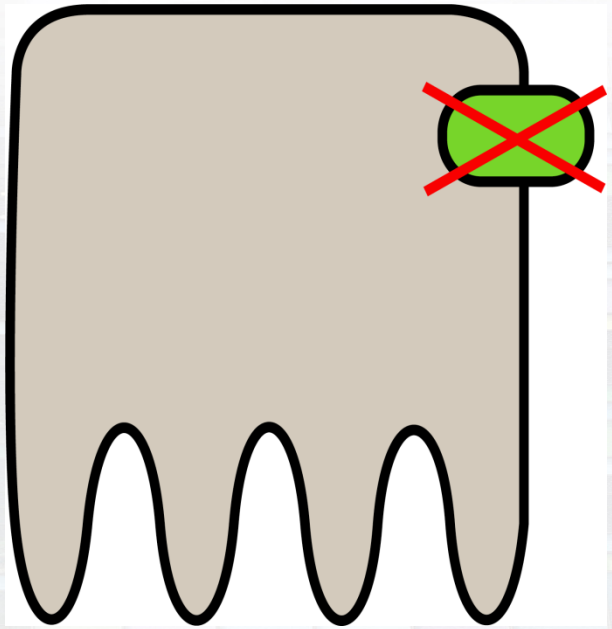
enterocyte

(*Donovan et al, 2005; Nemeth et al, 2004*)

JOHNS HOPKINS CHILDREN'S CENTER

Hepcidin and Ferroportin





Decreased Fe recycling

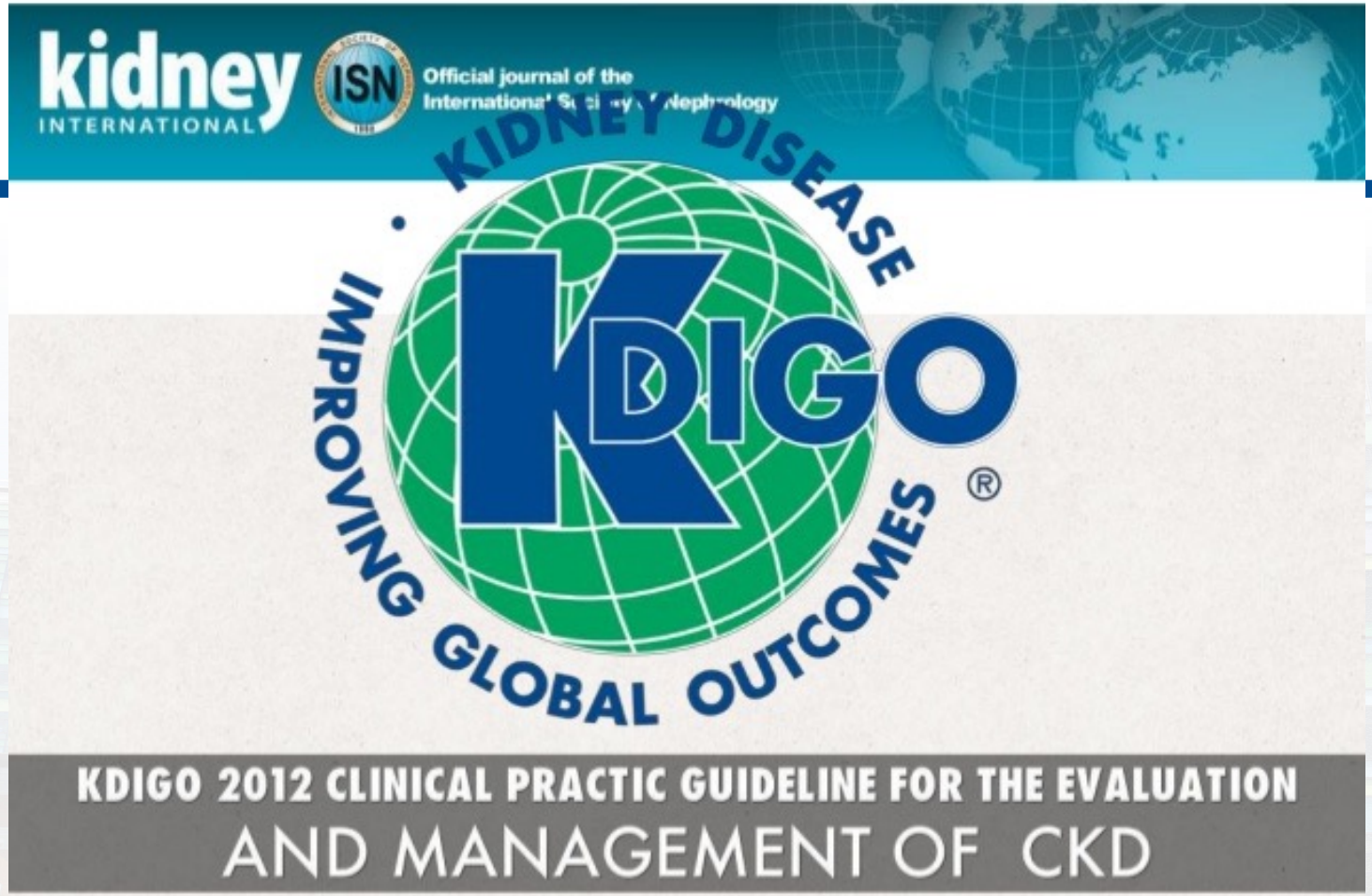
Decreased dietary uptake

(*Donovan et al, 2005; Nemeth et al, 2004*)

JOHNS HOPKINS CHILDREN'S CENTER

Etiology of Anemia of CKD

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



http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO-Anemia%20GL.pdf

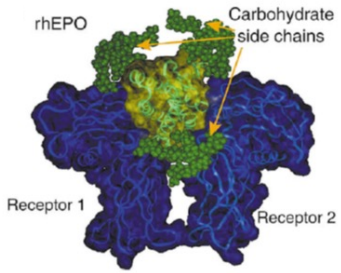
ESA for Anemia of CKD

1985

Human *EPO* gene isolated

↓

rHuEPO



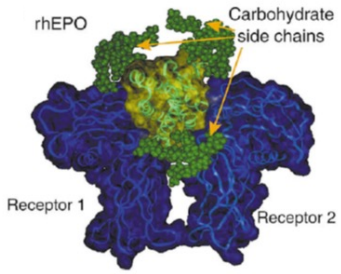
ESA for Anemia of CKD

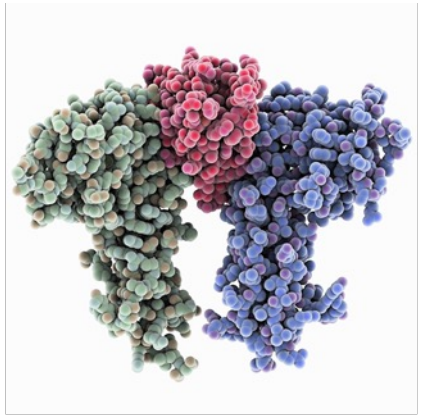
1985

Human *EPO* gene isolated

↓

rHuEPO





Human erythropoietin
Glycoprotein hormone

ESA for Anemia of CKD

1985

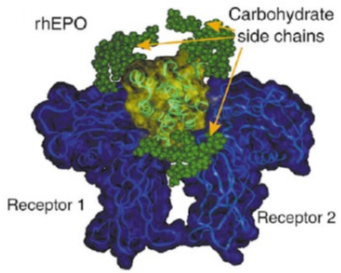
Prior to availability of rHuEPO, cobalt salts and androgens were used for treatment of anemia of CKD

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

Human *EPO* gene isolated

↓

rHuEPO



Packed red blood cell transfusions

- Infection
- Iron overload
- Allosensitization

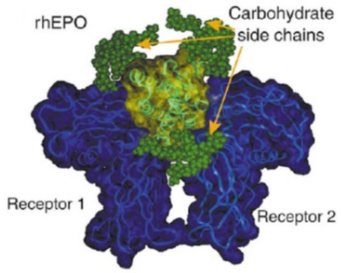
ESA for Anemia of CKD

1985

Human *EPO* gene isolated

↓

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

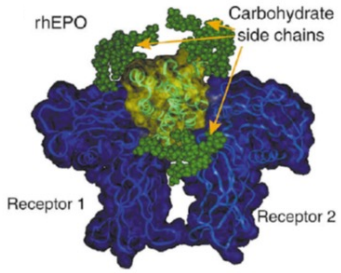
ESA for Anemia of CKD

1985

Human *EPO* gene isolated

↓

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

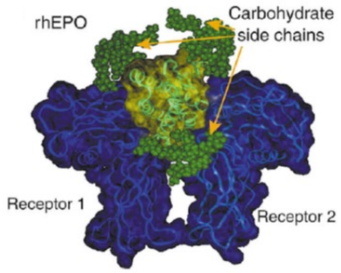
ESA for Anemia of CKD

1985

Human *EPO* gene isolated

↓

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

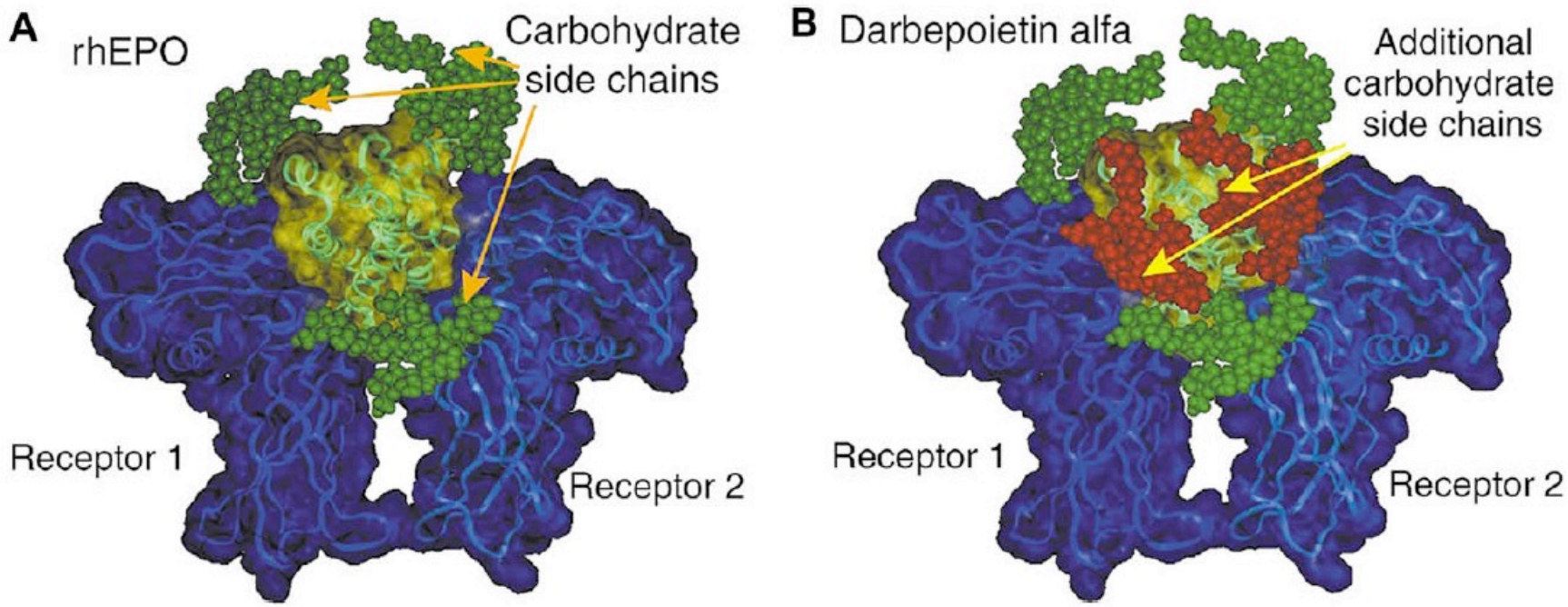


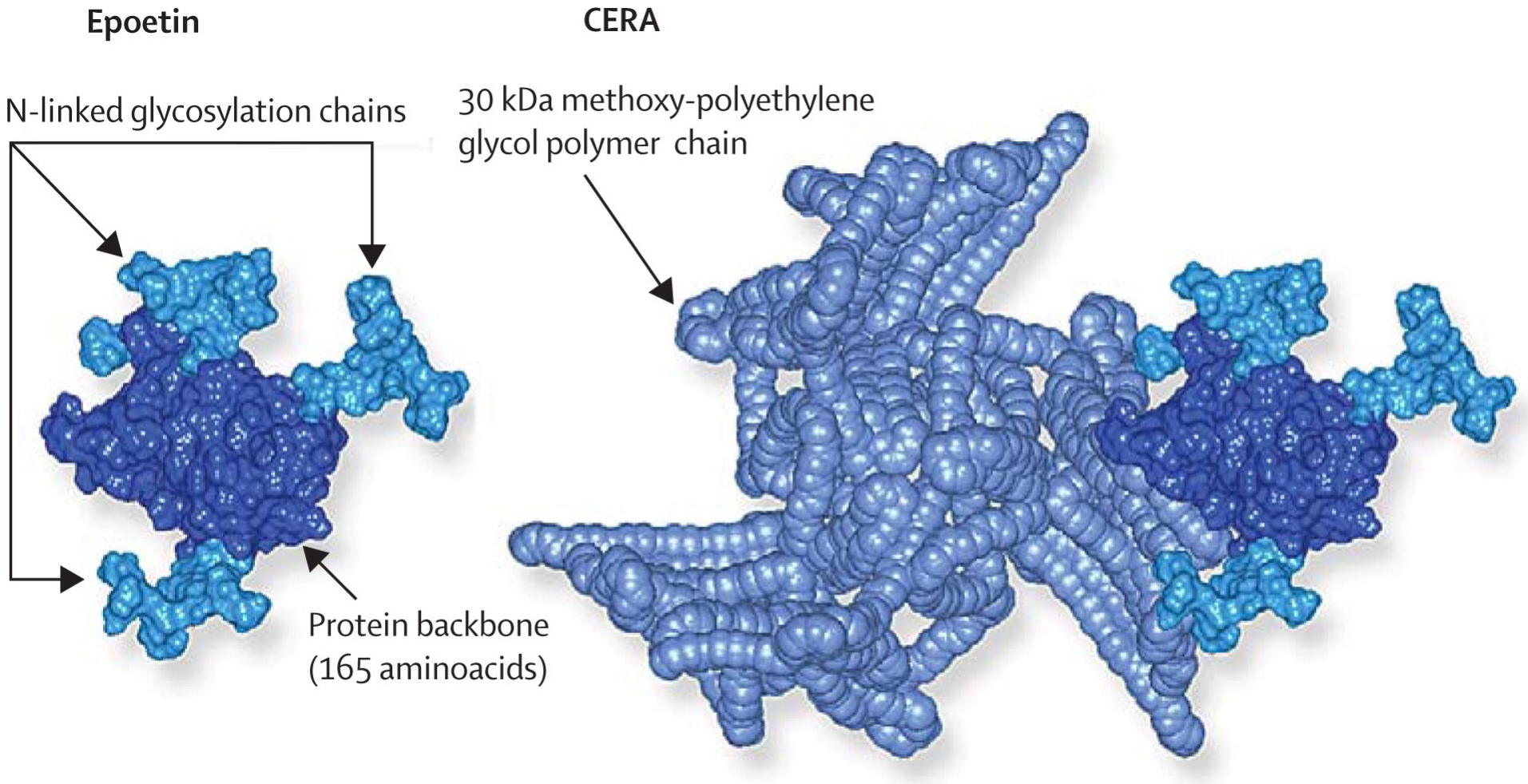
Figure 5. Molecular structures of rhEPO (**A**) and darbepoetin alfa (**B**). Reprinted by permission from Macmillan Publishers Ltd: Nature Biotechnology [7], 2003. rhEPO = recombinant human erythropoietin.

Experimental Hematology 2008;36:1573–1584

- Darbepoietin alfa – two additional sialic-acid-containing carbohydrates result in extended in vivo biologic activity

ESA for Anemia of CKD

Eschbach et al. (1987)
NEJM 316(2):73-78



- Integration of a large methoxy polyethylene glycol polymer chain
- Slower association with EPO receptor
- Extended half-life of up to 130 hours when given SC, 90 hours IV
- Allows for a monthly dosing regimen

ESA Initiation

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 >10 g/dl (90-100 g/l)
- *Children: maintain hemoglobin 11-12 g/dl (110-120 g/l)

JOHNS HOPKINS CHILDREN'S CENTER

KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney International* 2(4): August 2012

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

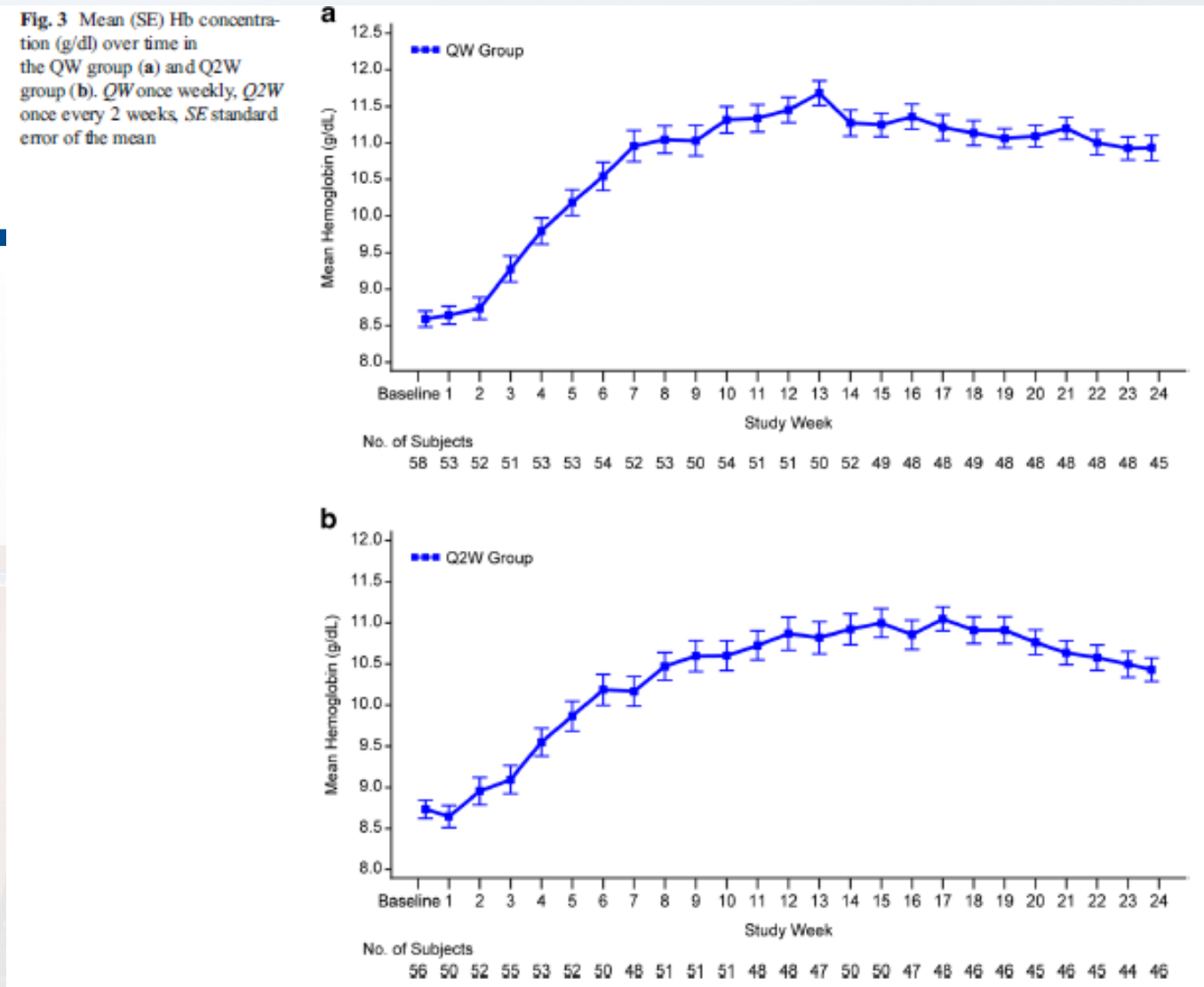


Fig. 3 Mean (SE) Hb concentration (g/dl) over time in the QW group (**a**) and Q2W group (**b**). *QW* once weekly, *Q2W* once every 2 weeks, *SE* standard error of the mean

- Darbepoetin alfa can be safely administered either weekly or q 2 weeks in ESA-naïve pediatric pts to achieve Hgb targets of 10-12
- 116 pediatric pts aged 1-18 years

Warady et al. De novo weekly and biweekly darbepoetin alfa dosing in pediatric patients with chronic kidney disease. *Pediatric Nephrology*. 2018;33:125-137.

ESA Dosing

- 275-350 units/kg/week in infants
  - Koshy et al. Anemia in children with CKD. *Ped Neph* 23: 2008
- 200-250 units/kg/week in older children
  - Koshy et al. Anemia in children with CKD. *Ped Neph* 23: 2008
- Children and adolescents on HD may require higher absolute doses than adults despite lower body weight
  - Bamgbola et al. Analyses of age, gender, and other risk factors for Epo resistance. Ped Neph 24:2009
- 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

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 Schaefer[2]

Clin J Am Soc Nephrol 13: 81–90, January, 2018

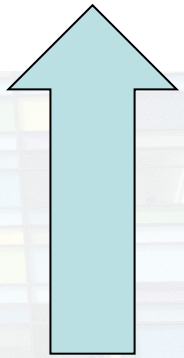
- Phase II, open label, multicenter, multiple-dose study conducted at 28 sites in 10 countries
- 64 children aged 6-17 years on **chronic HD** received CERA (Mircera®) monthly
- Objective: identify a conversion factor for switching from previous ESAs (epoetin or darbepoetin) to **intravenous** CERA
  - 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 Schaefer[2]

Clin J Am Soc Nephrol 13: 81–90, January, 2018

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 μg every 4 weeks for each 125 IU epoetin alfa/beta or 0.55 μg darbepoetin.



Weekly dose

Subcutaneous C.E.R.A. for the Maintenance Treatment of Anemia in Pediatric Patients With CKD: A Phase 2, Open-Label, Single-Arm, Multicenter Study

Bradley A. Warady, Sylvie Meyer Reigner, Chitra Tirodkar, and Dorota Drozdz

AJKD Vol XX | Iss XX | Month 2023

Rationale & Objective: The optimum starting dose of intravenous continuous erythropoietin receptor activator (C.E.R.A.) has been previously determined; this study ascertains the optimum starting dose of subcutaneous C.E.R.A. administration in pediatric patients.

Study Design: Phase 2, open-label, single-arm, multicenter study.

Setting & Participants: Patients aged 3 months to 17 years with renal anemia and chronic kidney disease (CKD; including those treated with maintenance dialysis and those not treated with dialysis) who were receiving maintenance treatment with erythropoiesis-stimulating agents (ESAs).

Table 1. Starting Doses of Subcutaneous C.E.R.A. Based on Previously Defined Dose Conversion Factors

Previous Epoetin Alfa/Beta Dose, IU/wk	Previous Darbepoetin Alfa Dose, μg/wk	C.E.R.A. Dose, μg, 1×/4 wk
<1,300	<6	30
1,300-<2,000	6-<9	50
2,000-<2,700	9-<12	75
2,700-<3,500	12-<15	100
3,500-<4,200	15-<19	120
4,200-<5,500	19-<24	150
5,500-<7,000	24-<31	200
7,000-<9,500	31-<42	250
≥9,500	≥42	360

Conversion factors based on the DOLPHIN Study.[18] Abbreviation: C.E.R.A., continuous erythropoietin receptor activator.

JOHNS HOPKINS CHILDREN'S CENTER

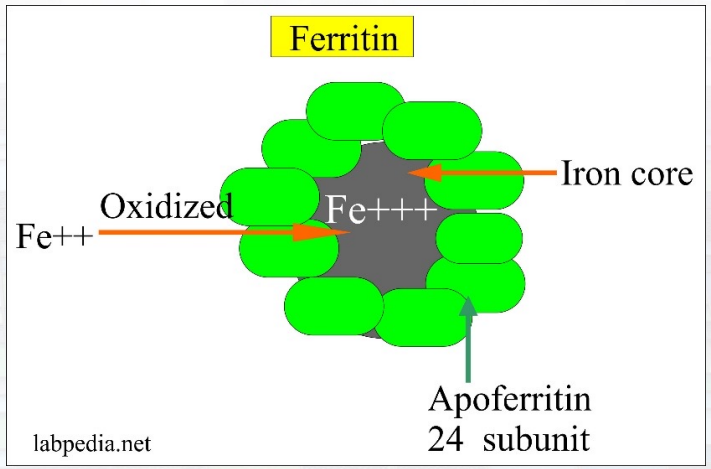
Iron Deficiency and Supplementation

Iron Deficiency (ID)

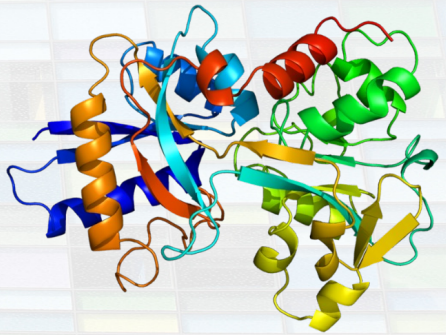
- Correction of ID reduces severity of anemia of CKD
- Untreated ID is a frequent cause of ESA hypo-responsiveness
- Risk factors in dialysis patients include:
  - Blood loss
  - Inflammation
  - Poor absorption of enteral iron

Biomarkers of Iron Availability

- Ferritin (serum)
  - Intracellular iron-storage protein
  - ↑ by inflammation, iron overload



- Transferrin saturation (TSAT)
  - Transferrin binds to iron in plasma
  - Carrier protein, transports iron from storage site to bone marrow



JOHNS HOPKINS CHILDREN'S CENTER

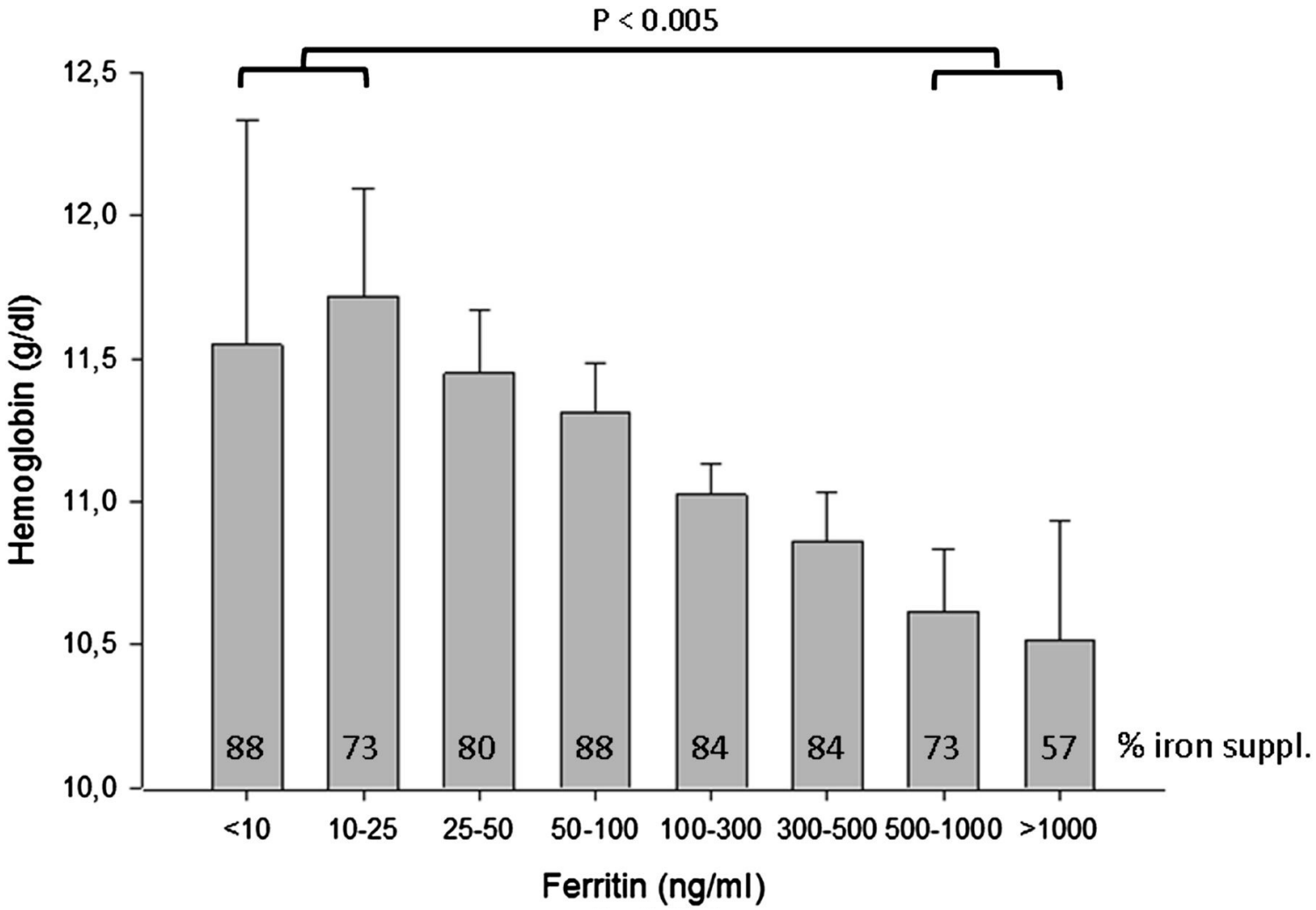
KDIGO Iron Targets

- Iron supplementation to maintain
  - Ferritin ≥ 100 ng/mL
  - TSAT ≥ 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.



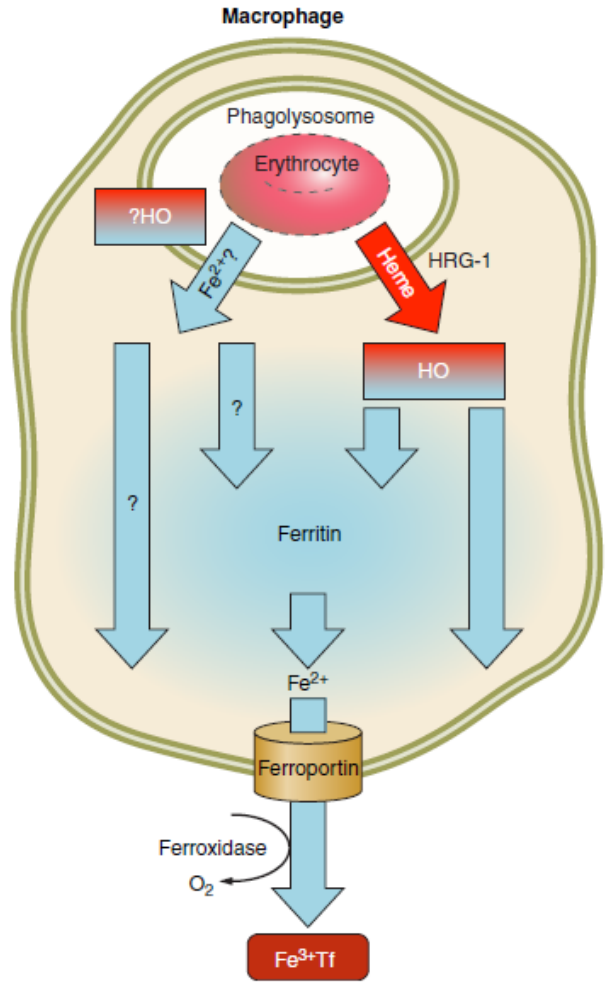
Dagmara Borzych-Duzalka et al. JASN 2013;24:665-676

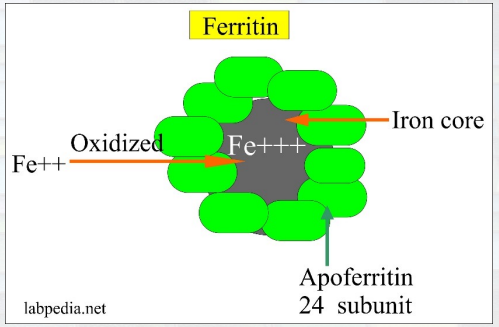
Goals of Iron Supplementation

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

Goals of Iron Supplementation

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

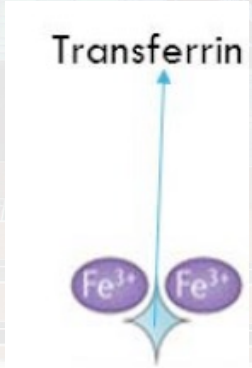


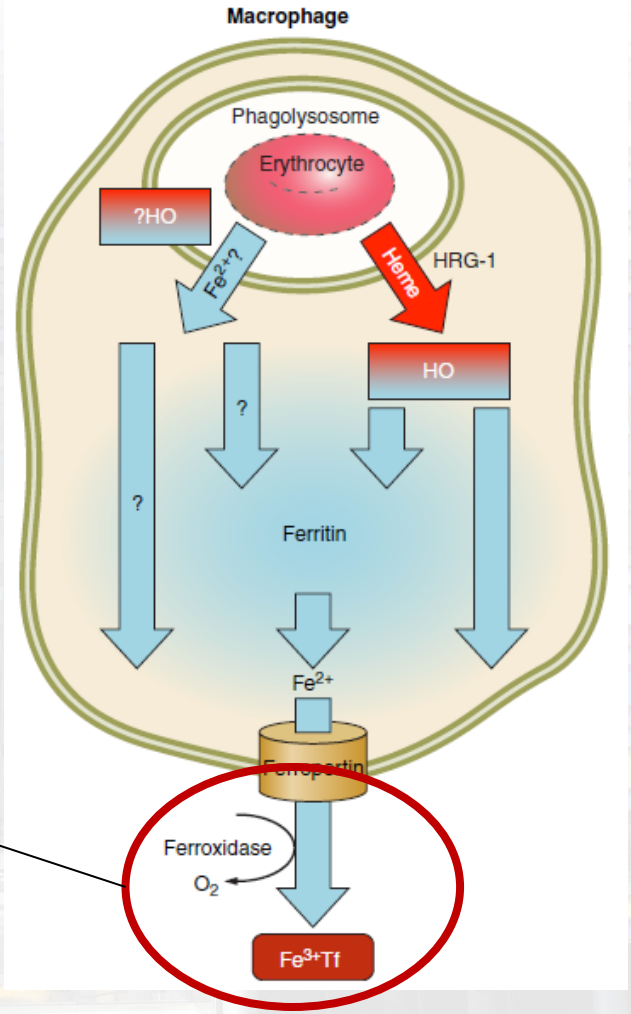


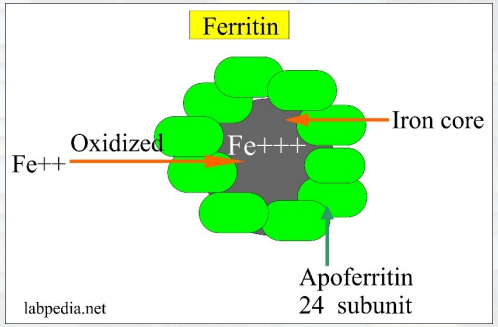
Ganz. Systemic Iron Homeostasis (2013) Physiol Rev 93:1721-1741.

Goals of Iron Supplementation

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





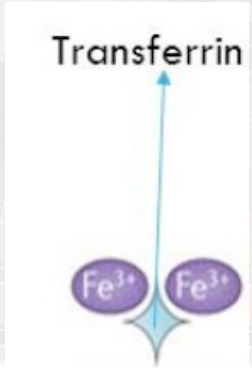


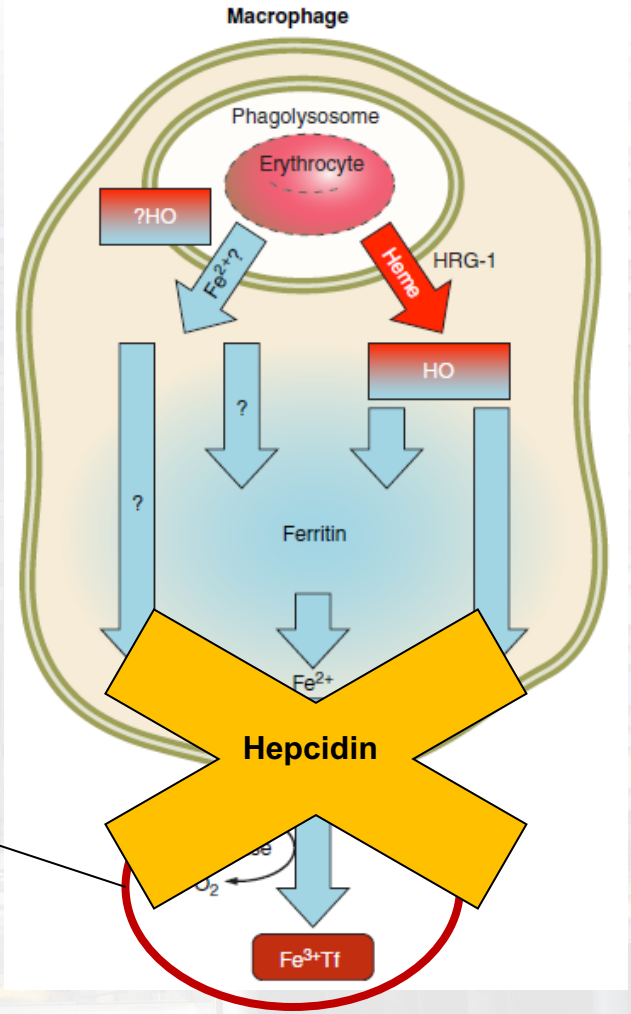
Ganz. Systemic Iron Homeostasis (2013) Physiol Rev 93:1721-1741.

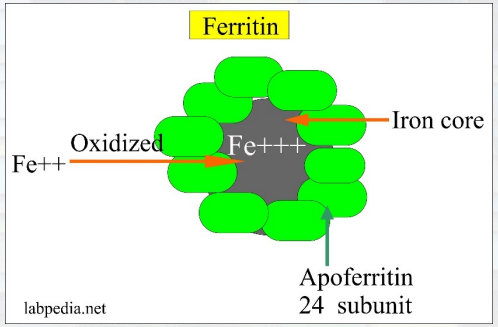
JOHNS HOPKINS CHILDREN'S CENTER

Goals of Iron Supplementation

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







Ganz. Systemic Iron Homeostasis (2013) Physiol Rev 93:1721-1741.

JOHNS HOPKINS CHILDREN'S CENTER

Iron Supplementation: Route

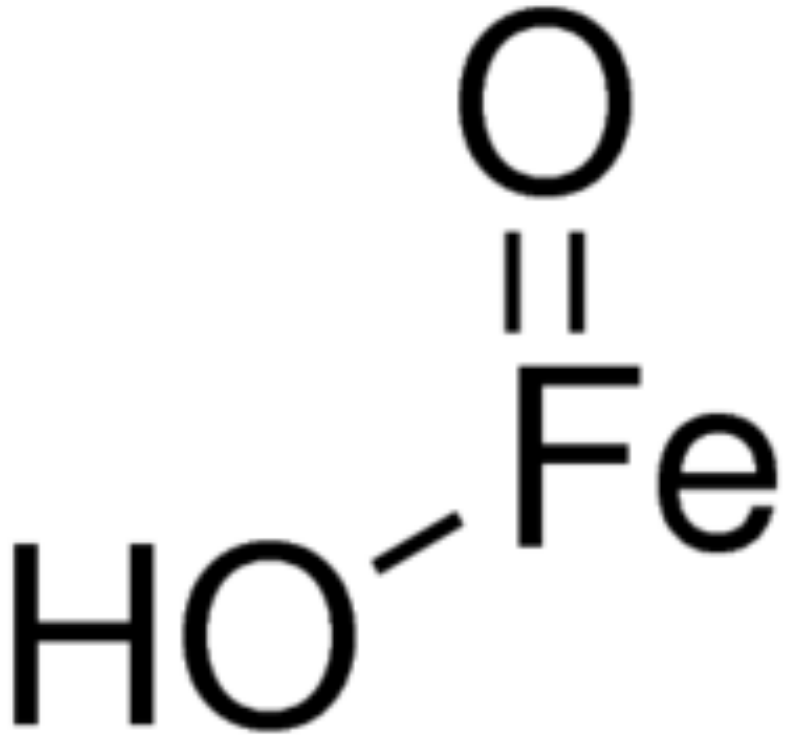
- Oral/Enteral
  - Pros: inexpensive, available, few adverse effects
  - Cons: poorly absorbed, adherence
- IV
  - Pros: Shown to decrease PRBC transfusion rates and ESA dose requirements, adherence assured
  - Cons: anaphylaxis, oxidative stress, cost

IV Iron: Safety

Table 1. Physiochemical char

Properties	Fer	n ose	Ferric Gluconate
Molecular mass (D)	7	000	200,000
Carbohydrate shell	Polyglu carbc		Gluconate, loosely associated sucrose
Median shell/particle diameter (nm)		3	8.6
Relative catalytic iron release		+	+++
Relative stability of elemental iron within the carbohydrate shell	High		Low
Relative osmolality	Isotonic		Hypertonic
Administration (iv push) rates	30 mg/	y 20 mg/min	12.5 mg/min
$t_{1/2}$ (h)	Approx		Approximately 1

D, daltons; nm, nanometer; iv, intraven



Charytan et al. Considerations and Challenges in Defining Optimal Iron Utilization in Hemodialysis. J Am Soc Nephrol 26:1238-1247:2015

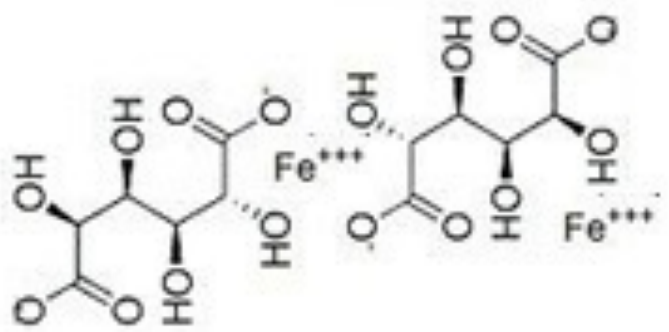
JOHNS HOPKINS CHILDREN'S CENTER

IV Iron: Safety

Table 1. Physiochemic

Properties	Ferric Gluconate
Molecular mass (D)	200,000
Carbohydrate shell	Gluconate, loosely associated sucrose
Median shell/particle diameter (nm)	8.6
Relative catalytic iron release	+++
Relative stability of elemental iron within the carbohydrate shell	Low
Relative osmolality	Hypertonic
Administration (iv push) rates	nin 12.5 mg/min
$t_{1/2}$ (h)	Approximately 1

D, daltons; nm, nanometer; iv, intravenous.



IRON SUCROSE COMPLEX
CAS #8047-67-4

Charytan et al. Considerations and Challenges in Defining Optimal Iron Utilization in Hemodialysis. J Am Soc Nephrol 26:1238-1247:2015

JOHNS HOPKINS CHILDREN'S CENTER

IV Iron: Safety

Table 1. Physiochemical characteristics and pharmacokinetics of IVI formulations

Properties	Ferumoxytol	Ferric Carboxy Maltose	Iron Dextran	Iron Sucrose	Ferric Gluconate
Molecular mass (D)	731,000	150,000	410,000	252,000	200,000
Carbohydrate shell	Polyglucose sorbitol carboxymethylether	Carboxymaltose	Dextran polysaccharide	Sucrose	Gluconate, loosely associated sucrose
Median shell/particle diameter (nm)	26.3	23.1	12.2	8.3	8.6
Relative catalytic iron release	+	+	++	+++	+++
Relative stability of elemental iron within the carbohydrate shell	High	High	High	Medium	Low
Relative osmolality	Isotonic	Isotonic	Isotonic		Hypertonic
Administration (iv push) rates	30 mg/s	Bolus push	50 mg (1	mg/min	12.5 mg/min
$t_{1/2}$ (h)	Approximately 15	7–12	5–2		Approximately 1

D, daltons; nm, nanometer; iv, intravenous.

Charytan et al. Considerations and Challenges in Defining Optimal Iron Utilization in Hemodialysis. J Am Soc Nephrol 26:1238-1247:2015

AJKD
Special Report

Diagnosis and Management of Iron Deficiency in CKD: A Summary of the NICE Guideline Recommendations and Their Rationale

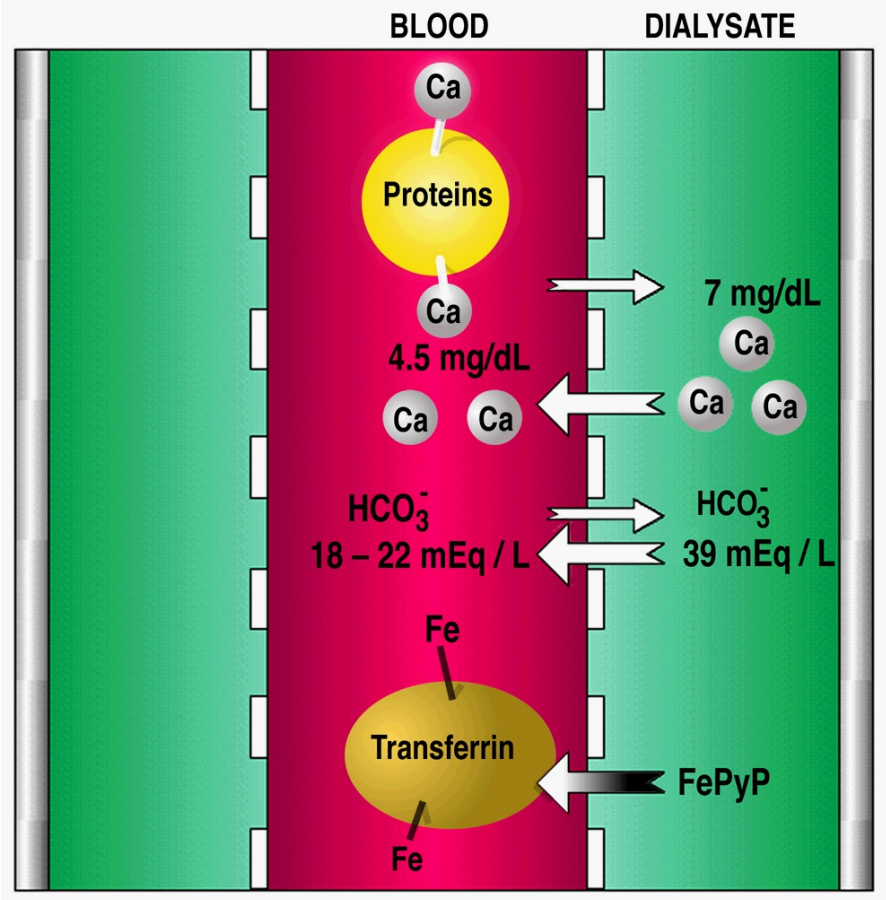
Laura E.K. Ratcliffe, MRCP,[1] Wayne Thomas, FRCPath,[2] Jessica Glen, MSc,[3] Smita Padhi, MBBS, MPH,[3] Ben A.J. Pordes, BSc,[3] David Wonderling, MSc,[3] Roy Connell, RN (Child), MSc,[4] Suzanne Stephens, MBBS, FRCPCH,[5] Ashraf I. Mikhail, MD, FRCP,[6] Damian G. Fogarty, MD,[7] Jan K. Cooper,[8] Belinda Dring, BSc, MPH,[4] Mark A.J. Devonald, FRCPE,[4] Chris Brown, MPharm,[6] and Mark E. Thomas, FRCP[9]

Am J Kidney Dis. 67(4):548-558.

- 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

Intradialysate Soluble Ferric Pyrophosphate Citrate (FPC)

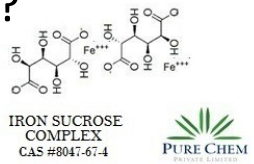
- Water soluble, no-carbohydrate shell, tightly complexed salt of Fe, electrostatically bonded to pyrophosphate
- Added to bicarbonate concentrate at each hemodialysis session
  - Dialysate with 110 µg/L iron
- Crosses the dialyzer membrane and donates iron directly to transferrin, bypassing hepcidin 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



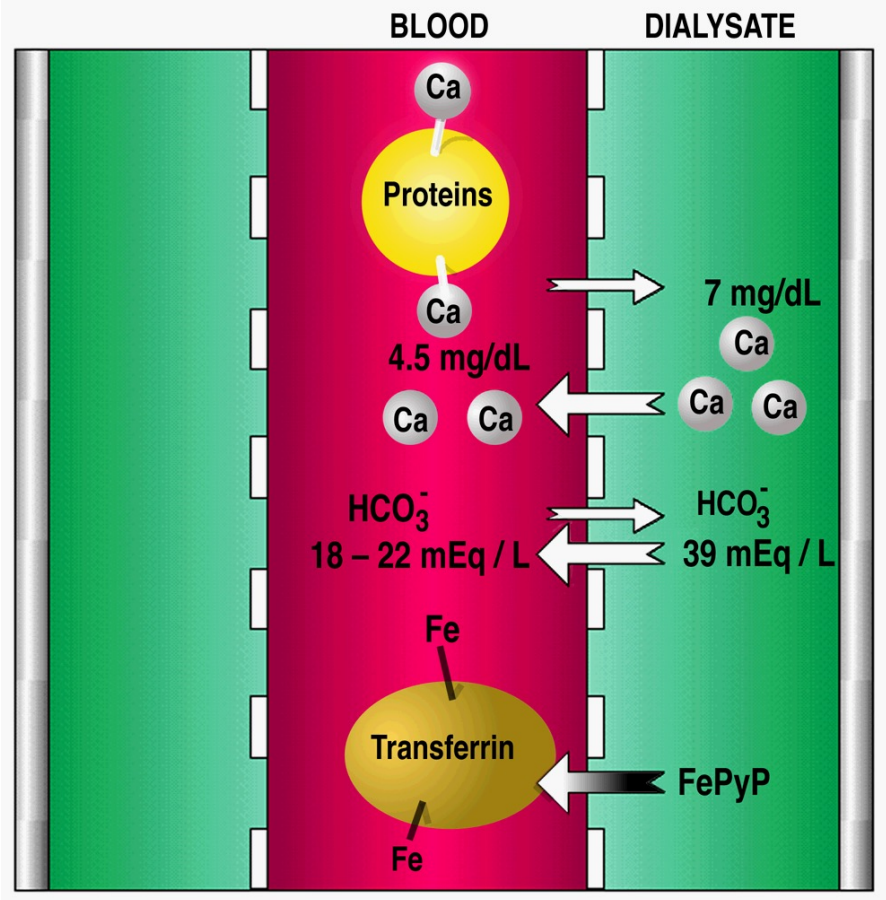
Courtesy of Dr. Ajay Gupta
via Dr. Brad Warady

Intradialysate Soluble Ferric Pyrophosphate Citrate (FPC)

- 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 rapidly bound to transferrin -> bone marrow, may avoid storage in reticuloendothelial system which contributes to iron overload



Courtesy of Dr. Ajay Gupta
via Dr. Brad Warady

Pharmacokinetics of ferric pyrophosphate citrate administered via dialysate and intravenously to pediatric patients on chronic hemodialysis

Raymond D. Pratt[1] · Sarah Grimberg[1] · Joshua J. Zaritsky[2] · Bradley A. Warady[3]

Pediatric Nephrology (2018) 33:2151–2159

- 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

Pharmacokinetics of ferric pyrophosphate citrate administered via dialysate and intravenously to pediatric patients on chronic hemodialysis

Raymond D. Pratt[1] · Sarah Grimberg[1] · Joshua J. Zaritsky[2] · Bradley A. Warady[3]

Pediatric Nephrology (2018) 33:2151–2159

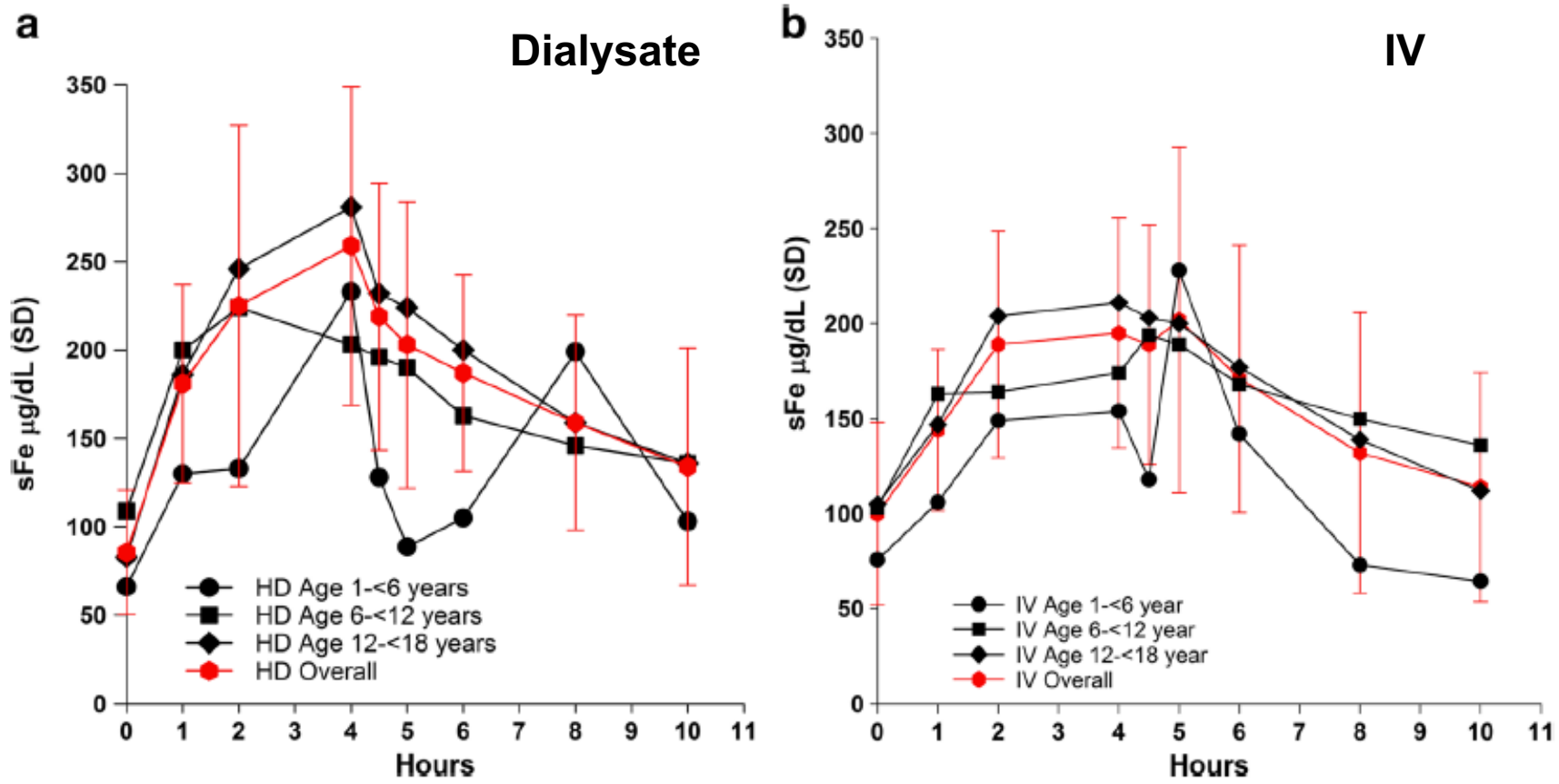


Fig. 1 Mean concentration-time plots for serum total iron (sFe) after administration of ferric pyrophosphate citrate (FPC) via hemodialysis (HD) at a concentration of 2 µM (110 µg/L) iron (**a**) and after intravenous (IV) administration of 0.07 mg Fe/kg of FPC by age group (years) and overall (**b**)

JOHNS HOPKINS CHILDREN'S CENTER

Pharmacokinetics of ferric pyrophosphate citrate administered via dialysate and intravenously to pediatric patients on chronic hemodialysis

Raymond D. Pratt[1] · Sarah Grimberg[1] · Joshua J. Zaritsky[2] · Bradley A. Warady[3]

Pediatric Nephrology (2018) 33:2151–2159

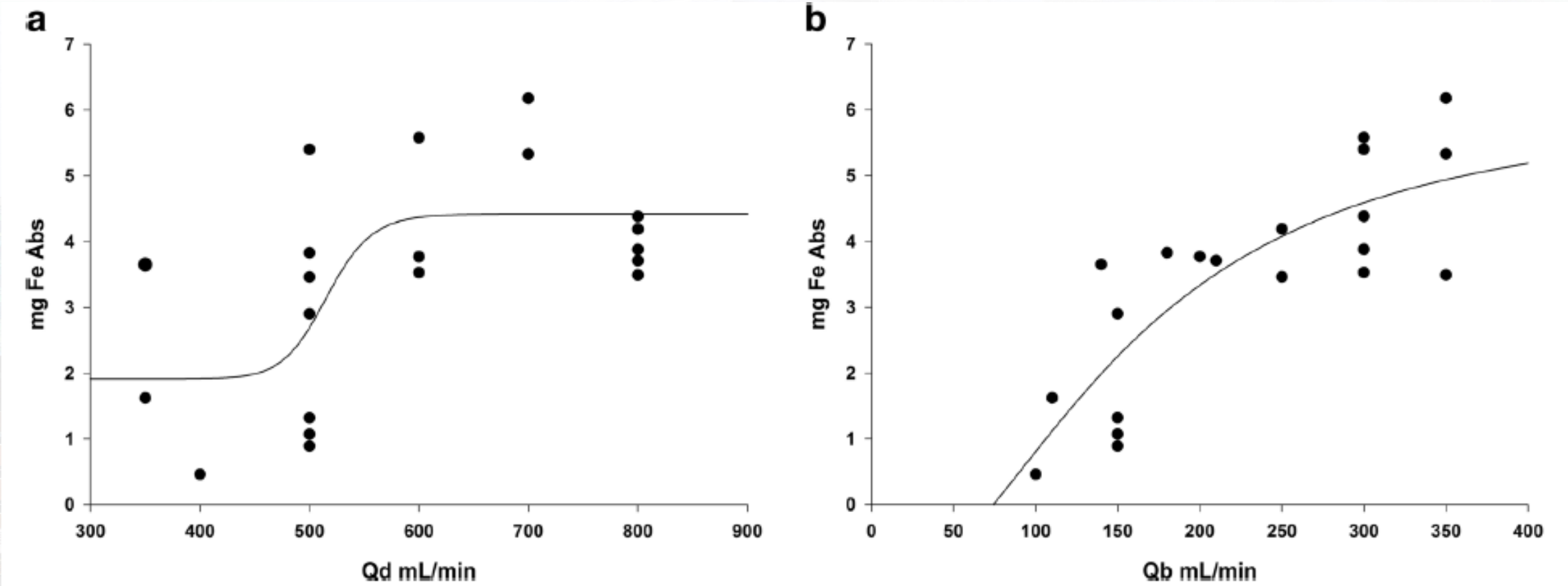


Fig. 3 Amount of iron (Fe) administered during hemodialysis (HD) by dialysate flow rate (Qd) (**a**) and blood flow rate (Qb) (**b**). Regression lines are fitted by nonlinear regression in SigmaPlot V14.0

Pharmacokinetics of ferric pyrophosphate citrate administered via dialysate and intravenously to pediatric patients on chronic hemodialysis

Raymond D. Pratt[1] · Sarah Grimberg[1] · Joshua J. Zaritsky[2] · Bradley A. Warady[3]

Pediatric Nephrology (2018) 33:2151–2159

Table 2 Baseline-corrected noncompartmental pharmacokinetic parameters of serum total iron in pediatric patients after administration of ferric pyrophosphate citrate intravenously and via dialysate

Route of administration	Pharmacokinetic parameter[a]		
	C_{max} (µg/dL)	AUC_{last} (h µg/dL)	$t½$ (h)
Intravenous ($N=21$)	114 (53.7)	419 (101.6)	1.60 (190.1)[b]
Via dialysate ($N=20$)	166 (54.3)	682 (82.9)	1.98 (60.6)[c]

AUC_{last} area under the serum concentration-time curve from time zero to the time of the last quantified concentration, *C_{max}* maximum drug concentration in serum, *CV%* percent coefficient of variation, *$t½$* terminal phase half-life

[a] Values are reported as geometric mean (geometric CV%)

[b] $n=8$

[c] $n=10$

- 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

Pharmacokinetics of ferric pyrophosphate citrate administered via dialysate and intravenously to pediatric patients on chronic hemodialysis

Raymond D. Pratt[1] · Sarah Grimberg[1] · Joshua J. Zaritsky[2] · Bradley A. Warady[3]

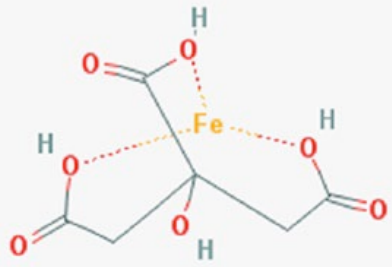
Pediatric Nephrology (2018) 33:2151–2159

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 designed and planned but not completed

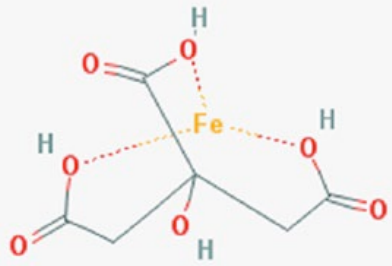
Ferric Citrate

- 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



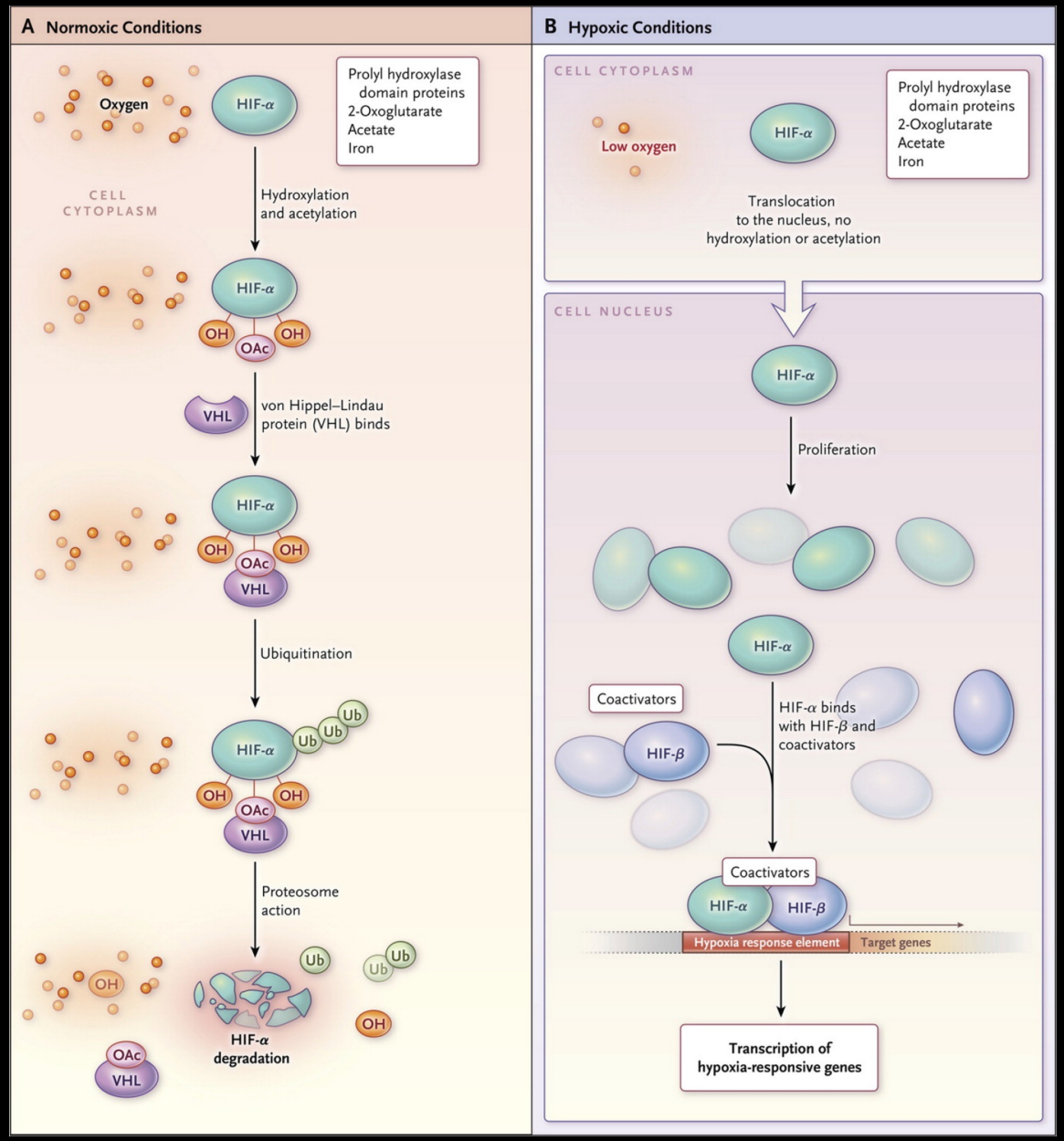
rHuEPO- and iron-independent anemia therapy?

- rHuEPO revolutionized treatment of anemia of kidney disease
  - Improved quality of life
  - Reduction in transfusion, allosensitization, iron overload
- Practice patterns for ESA dosing have evolved over the past decades
  - Safety concerns based on adult trials
    - US FDA black box warning 2011, narrowing Hgb range on treatment
  - Recognition of role of disordered iron metabolism

rHuEPO- and iron-independent anemia therapy?

- HIF-PHIs
  - More physiologic stimulation of erythropoietin pathway AND effects on iron metabolism pathway

Figure 2



Normoxia: HIF-α is rapidly (1/2-life 5 min) hydroxylated and degraded by the HIF prolyl hydroxylase enzymes

Hypoxia: HIF-α translocates to nucleus, binds HIF-β, activates hypoxia response element, EPO transcribed

HIF-PHIs treat anemia by stabilizing HIF and stimulating endogenous EPO production

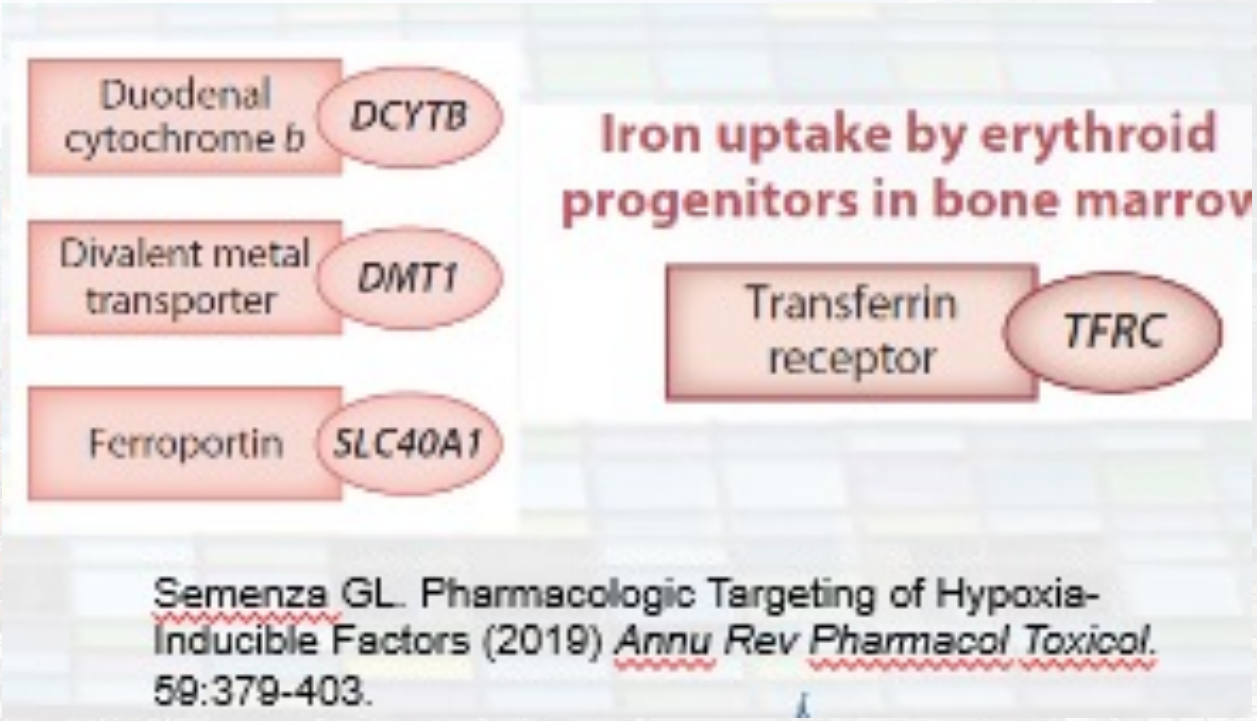
American Journal of Kidney Diseases 2018 71, 423-435DOI: (10.1053/j.ajkd.2017.09.026)

Proc. Natl. Acad. Sci. USA
Vol. 88, pp. 5680–5684, July 1991
Genetics

Hypoxia-inducible nuclear factors bind to an enhancer element located 3′ to the human erythropoietin gene

GREGG L. SEMENZA, MARY K. NEJFELT, SUZIE M. CHI, AND STYLIANOS E. ANTONARAKIS

Center for Medical Genetics, Departments of Pediatrics and Medicine, The Johns Hopkins University School of Medicine, Baltimore, MD 21205



Semenza GL. Pharmacologic Targeting of Hypoxia-Inducible Factors (2019) *Annu Rev Pharmacol Toxicol.* 59:379-403.

- In addition to controlling erythropoietin production, HIFs promote transcription of several iron metabolism and transport genes

JOHNS HOPKINS CHILDREN'S CENTER

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
    - Can induce production of erythropoietin by the liver
  - Avoidance of injections at home!

HIF-PHIs

- Clinical efficacy studies *in adults* have demonstrated decreases in both ferritin and hepcidin levels
  - Suggesting reduction in iron-restricted erythropoiesis

Pediatric trials?

- July 2021 – US FDA voted against roxadustat approval
  - Not superior to epoetin alfa in risk of major adverse cardiovascular events
- March 2022 – FDA issued a complete response letter for vadadustat
  - Concern for vascular access thrombosis in dialysis patients
  - Liver injury
- Accepted new drug application for daprodustat – Feb 2023

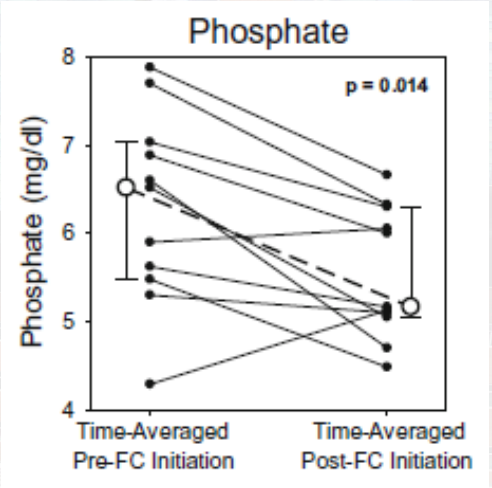
QUESTIONS?

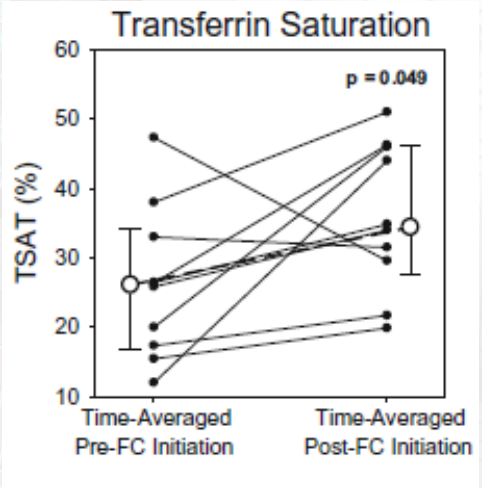
Clinical experience with the use of ferric citrate as a phosphate binder in pediatric dialysis patients

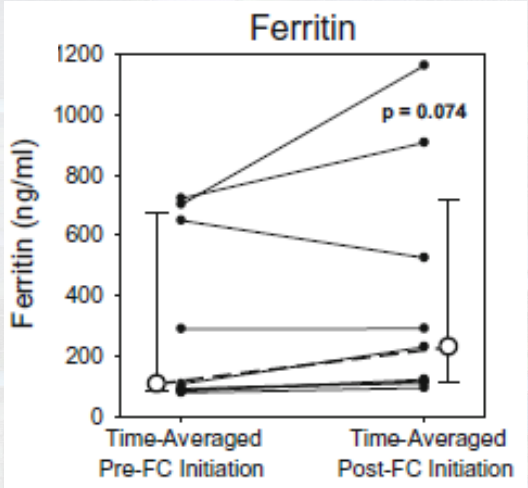
Mark R. Hanudel[1] · Marciana Laster[1] · Georgina Ramos[1] · Barbara Gales[1] · Isidro B. Salusky[1]

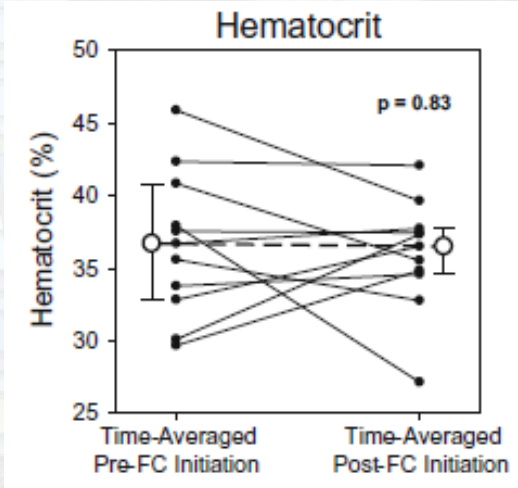
Pediatr Nephrol (2018) 33:2137–2142

- 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









Pharmacokinetics of ferric pyrophosphate citrate administered via dialysate and intravenously to pediatric patients on chronic hemodialysis

Raymond D. Pratt[1] · Sarah Grimberg[1] · Joshua J. Zaritsky[2] · Bradley A. Warady[3]

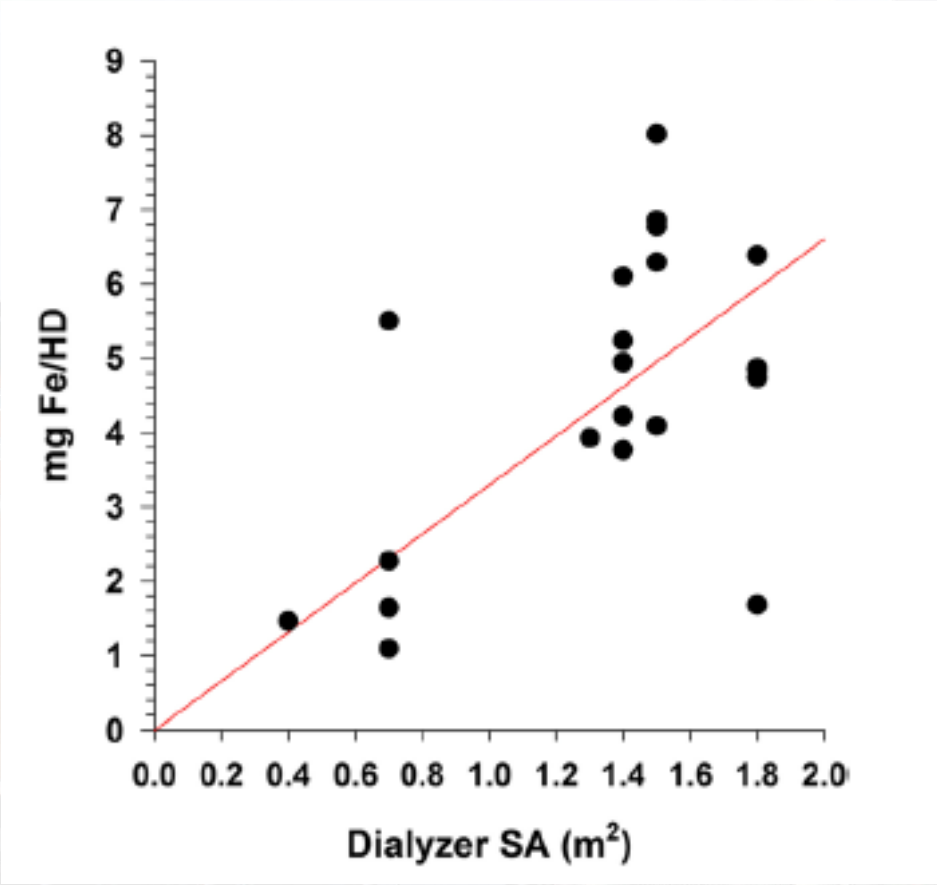
Pediatric Nephrology (2018) 33:2151–2159

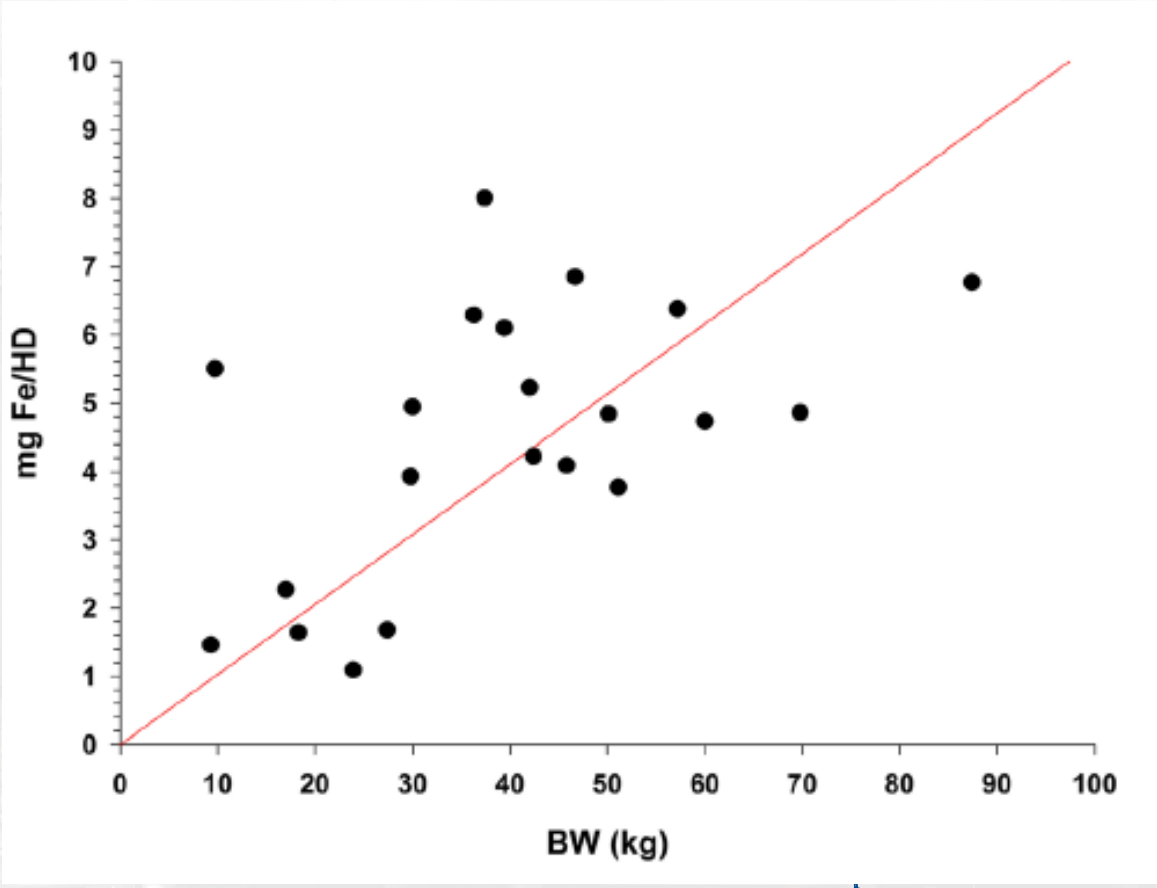
- Study Design
  - Multicenter, open-label, two-period, single dose study
  - 2 week screening period followed by two sequential FPC treatment sessions
    - Single 0.07 mg/kg dose in D5W as a continuous IV infusion throughout the HD session
    - FPC added to dialysate to deliver a final dose of 110 µg/L throughout the HD session

Pharmacokinetics of ferric pyrophosphate citrate administered via dialysate and intravenously to pediatric patients on chronic hemodialysis

Raymond D. Pratt[1] · Sarah Grimberg[1] · Joshua J. Zaritsky[2] · Bradley A. Warady[3]

Pediatric Nephrology (2018) 33:2151–2159





JOHNS HOPKINS CHILDREN'S CENTER