ANAEMIA IN CHRONIC KIDNEY DISEASE

INTRODUCTION

- Iron deficiency is a major contributory cause to the development of anaemia in chronic kidney disease (CKD) .[1]
- CKD patients suffer from both absolute and functional iron deficiency.[2]
- All CKD patients should be screened for anemia during the initial evaluation for CKD.[2]

1) Macdougall IC et al. Curr Opin Nephrol Hypertens. 2018 ;27(5):358-363.
2) Gvili AG et al. Acta Haematol 2019;142:44–50

PREVALENCE OF CKD AND ANEMIA IN CKD IN INDIA

- CKD prevalence in india 17% of the earth's population. [1]
- The prevalence of CKD is high both in rural and urban parts of India. [2]
- 78.9–96.5% patients suffer from anemia in CKD in later stages. [2]
- Diabetic nephropathy has the highest overall prevalence of anemia (75.9%). [2]

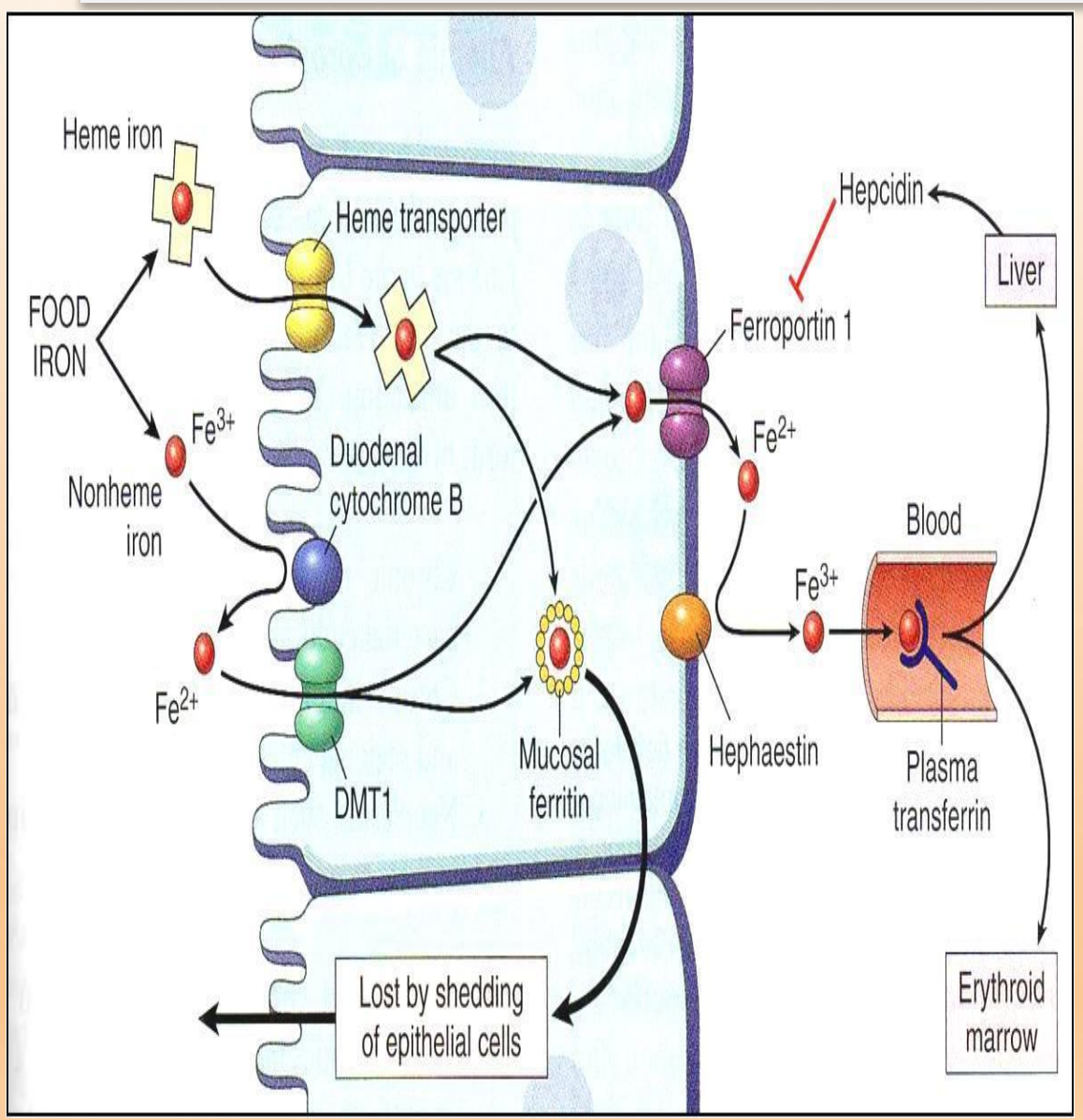
1) Varghese S et al. Clin J Am Soc Nephrol. 2018; 13: 802–804
2) Apsangikar P et al. Indian J Transplant 2018;12:30-4.

CAUSES OF IRON DEFICIENCY ANAEMIA

Condition/mechanism	Principal examples
Physiological (↑Requirement)	Growth spurt in adolescents, pregnancy
Reduced intake	Vegetarian/vegan diets, malnutrition, poverty
Gastrointestinal blood losses	Malignancies, peptic ulcer, erosive esophagitis/gastritis, hiatal hernia, diverticula, Hemorrhoids, inflammatory bowel diseases (Crohn's disease, ulcerative colitis), angiodysplasia, hereditary hemorrhagic telangiectasia (HHT, where frequent/massive epistaxis can also occur)
Genitourinary blood losses	Heavy menstrual bleeding (uterine fibromatosis, menorrhagia in women taking anticoagulants)
Intravascular hemolytic anemias	Paroxysmal nocturnal hemoglobinuria, autoimmune hemolytic anemias, microangiopathic hemolytic anemia, malfunctioning prosthetic heart valves
Malabsorption	Celiac disease, chronic gastritis (atrophic autoimmune or related to helicobacter pylori infection), gastrectomy, bariatric surgery
Developing countries, migrants	Parasitic infections (hookworm, schistosomiasis)
Genetic	IRIDA (iron refractory iron deficiency anemia)
Drugs	Non-steroidal anti-inflammatory drugs, antithrombotic drugs, proton pump inhibitors (PPI)
Coagulopathies	Von Willebrand disease, other forms
Miscellaneous	Munchausen or Lasthènje de Feriol Syndrome (factitious anemia), frequent blood donors, endurance athletes (march hemoglobinuria)

Girelli D et al. Int J Hematol.2018 ;107(1):16-30.

Intestinal Absorption of Conventional Iron



The absorption of the iron ion is in the duodenum and is mediated by **specific carriers.**

1. The iron ion enters the intestinal cells via the Transporter DMT1 (Divalent Metal Transporter 1).

2. Duodenal cytochrome b reduces the iron to the ferrous state of the intestinal lumen

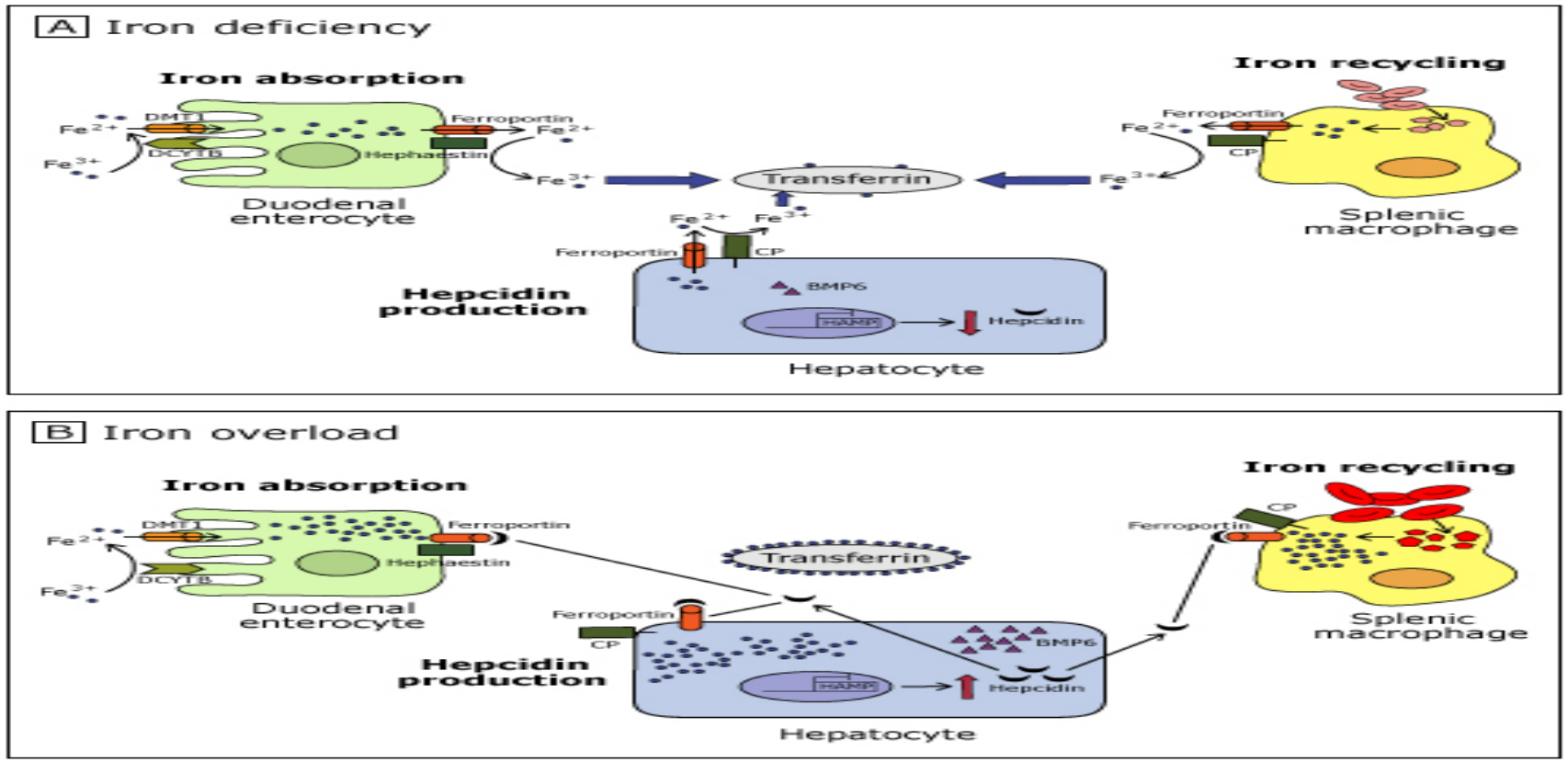
3. The iron absorbed is deposited in the ferritin and then transported across the basolateral membrane in the plasma.

4. The excretion to the bloodstream is mediated by **FERROPORTIN** in the basolateral membrane, regulated by hepcidin

Following Proteins (and Many More) Control the Iron Metabolism

- **Transferrin (Tf)**
- **Transferrin receptor (TfR)**
- **Ferritin (Ft)**
- **Hepcidin**
- **Iron regulatory protein 1 and 2 (IRP1 and IRP2)**
- **Divalent metal transporter 1 (DMT1, N**ramp2, DCT1, Solute carrier family 11, member 2 [SLC11A2]
- **Ferroportin** (Ireg1, SLC40A1, Mtp1)
- **Hephaestin**
- Ceruloplasmin
- HFE
- TFR2
- **Hemojuvelin**
- **Bone morphogenetic protein 6 (BMP6)**

Regulation of iron balance



The main cells implicated in systemic iron regulation are enterocytes, which absorb non-heme iron from the diet through DMT1; hepatocytes, which produce hepcidin according to the iron concentration; and macrophages, which release iron during the breakdown of hemoglobin from senescent red blood cells. Ferroportin exports iron from all of these cells into the circulation with the cooperation of a ferroxidase (hephaestin in enterocytes and ceruloplasmin [CP] in macrophages and hepatocytes) that oxidizes Fe^{2+} to Fe^{3+}.

(A) In iron deficiency there is increased iron absorption and recycling. Absorption of iron by enterocytes is facilitated by duodenal cytochrome b (DYCTB), an iron reductase. Hepcidin synthesis is suppressed. Ferroportin is free to export iron from macrophages and enterocytes, after which iron is bound to transferrin.

(B) In iron overload there is reduced iron absorption and recycling. Hepcidin production is high; its synthesis is stimulated by BMP6, which is induced by increased liver iron. Hepcidin released into the circulation binds ferroportin, and the complex is internalized and degraded, in turn blocking iron export into the circulation.

DMT1: divalent metal transporter; DCYTB: duodenal cytochrome B; CP: ceruloplasmin; BMP6: bone morphogenetic protein 6; *HAMP*: hepcidin antimicrobial peptide (gene encoding hepcidin).

MECHANISM OF ANAEMIA IN CKD

Mechanism	**Outcome**
Renal Impairment	Decreased Erythropoietin production
Uremia	Bone marrow suppression Decreased RBC life span
Nutritional deficiency	Deficiency of Vitamin B12, folate or Iron
Secondary Hyperparathyroidism	Fibrosis of bone marrow Failure of erythropoiesis
Chronic Inflammation Increased inflammatory cytokines Increased hepcidin	Abnormal iron homeostasis and erythroid progenitor proliferation
Hypothyroidism	Reduced GFR Increased peripheral vascular resistance

Sing NP et al. API text book of medicine. 2017; 2 : 590-596

ANEMIA OF INFLAMMATION

In anemia of chronic disease, Hepcidin production is high and consequently

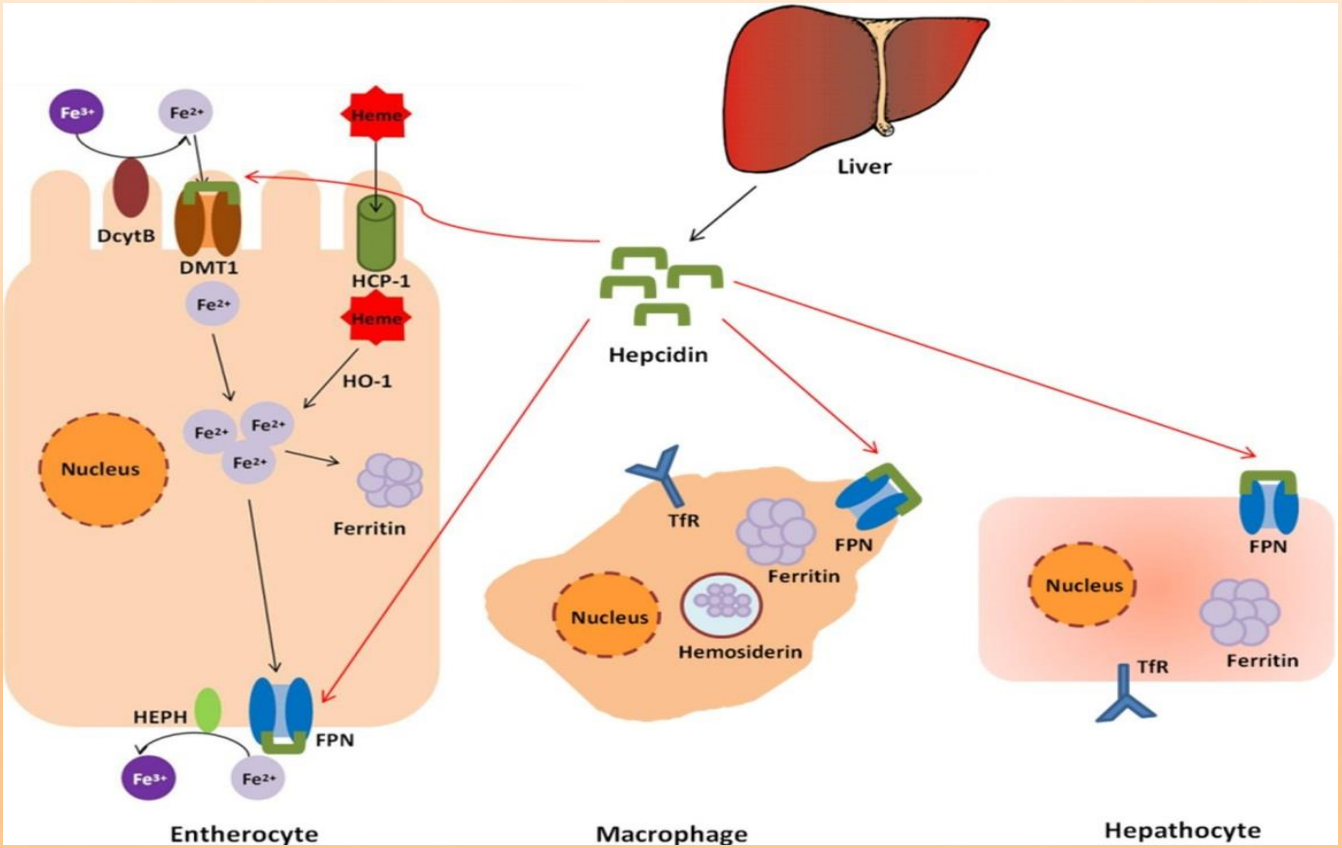
iron remains blocked in macrophages

intestinal absorption is inhibited

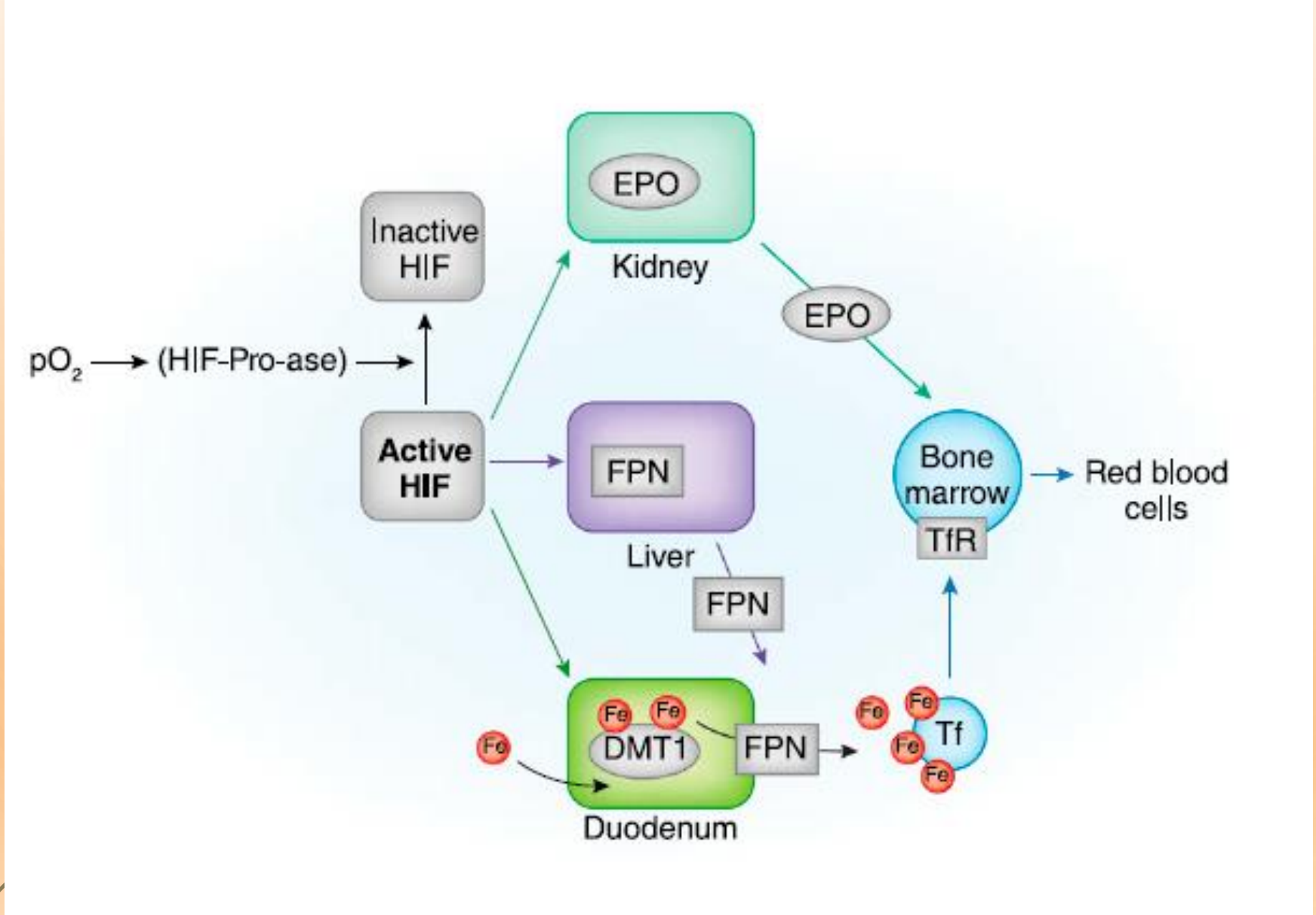
increased deposits of liver ferritin

IN THE COURSE OF INFLAMMATION, HEPCIDIN PREVENTS IRON TO REACH THE BONE MARROW

Inflammation → ↑ Hepcidin



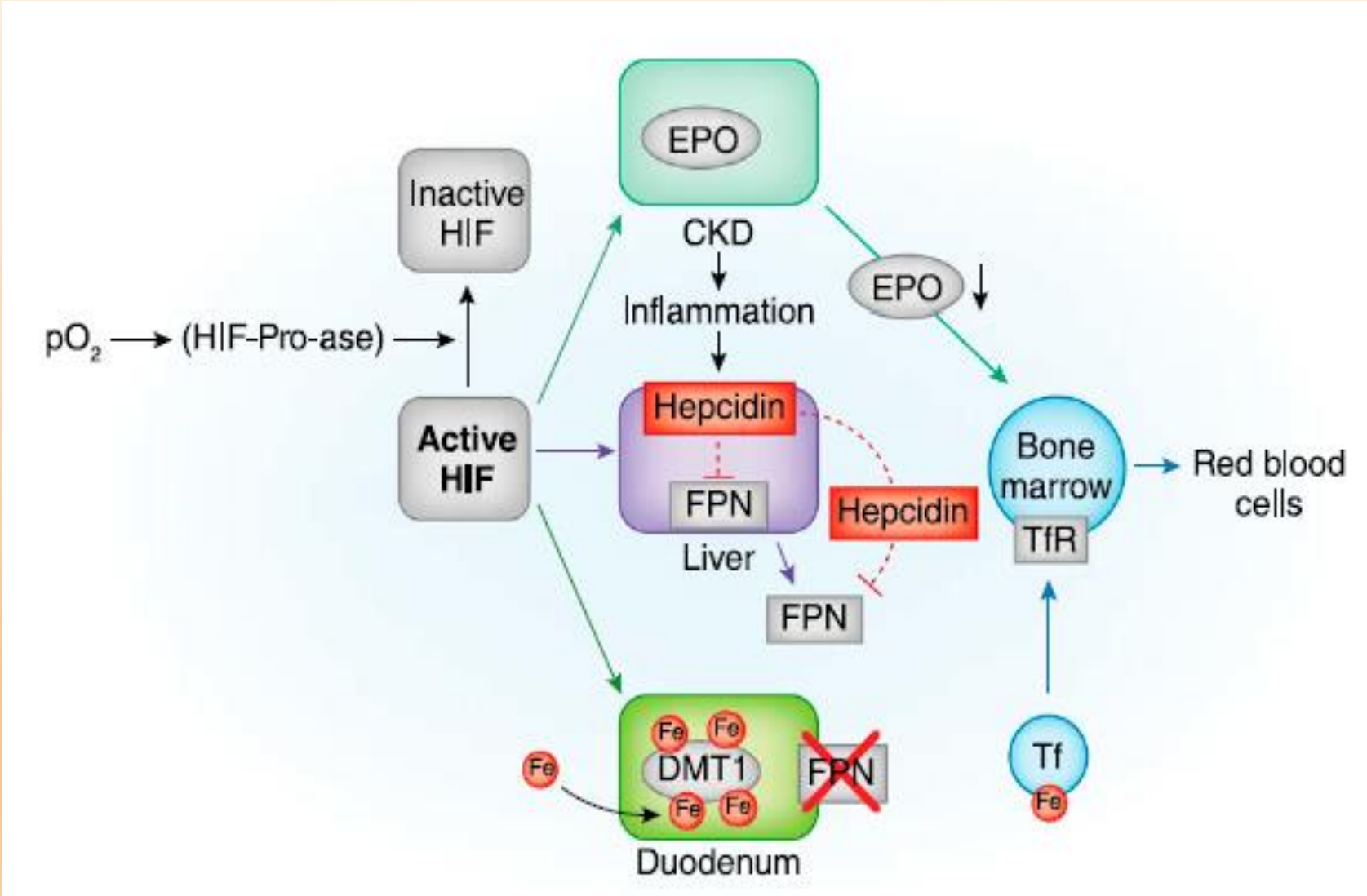
ANEMIA, ERYTHROPOIESIS, AND IRON ABSORPTION IN NORMAL SUBJECTS



HIF-Pro-ase hypoxia–inducible factor–prolyl–hydroxylases
HIF- hypoxia-inducible factor
EPO -Erythropoietin
FPN -Ferroportin
DMT 1 -Divalent metal transporter 1
TfR- transferrin receptor

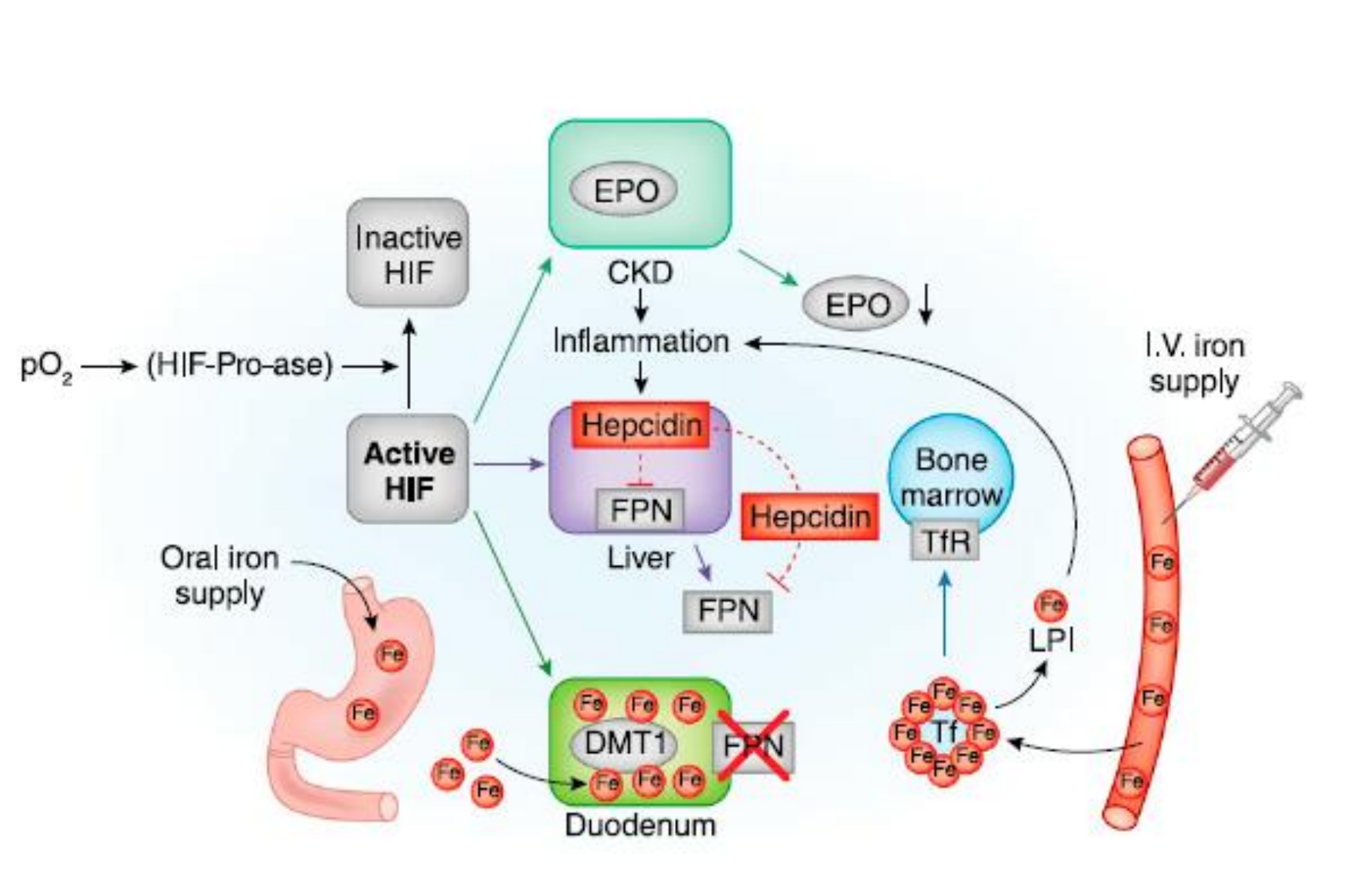
Locatelli F et al. Clin J Am Soc Nephrol. 2016;11(7):1269-80.

ANEMIA, ERYTHROPOIESIS, AND IRON ABSORPTION IN CHRONIC KIDNEY DISEASE



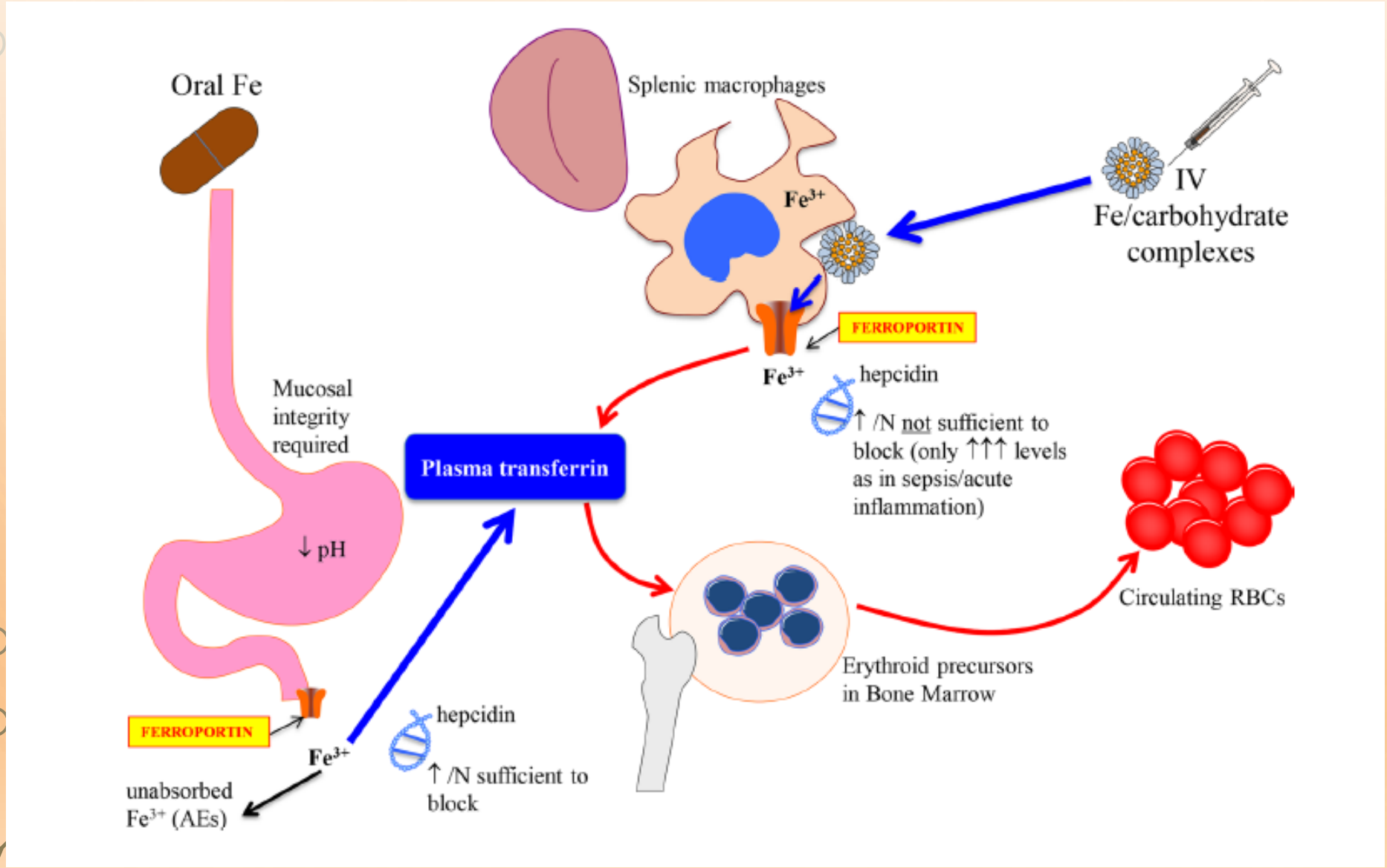
Locatelli F et al. Clin J Am Soc Nephrol. 2016;11(7):1269-80.

IRON SUPPLY IN CHRONIC RENAL FAILURE



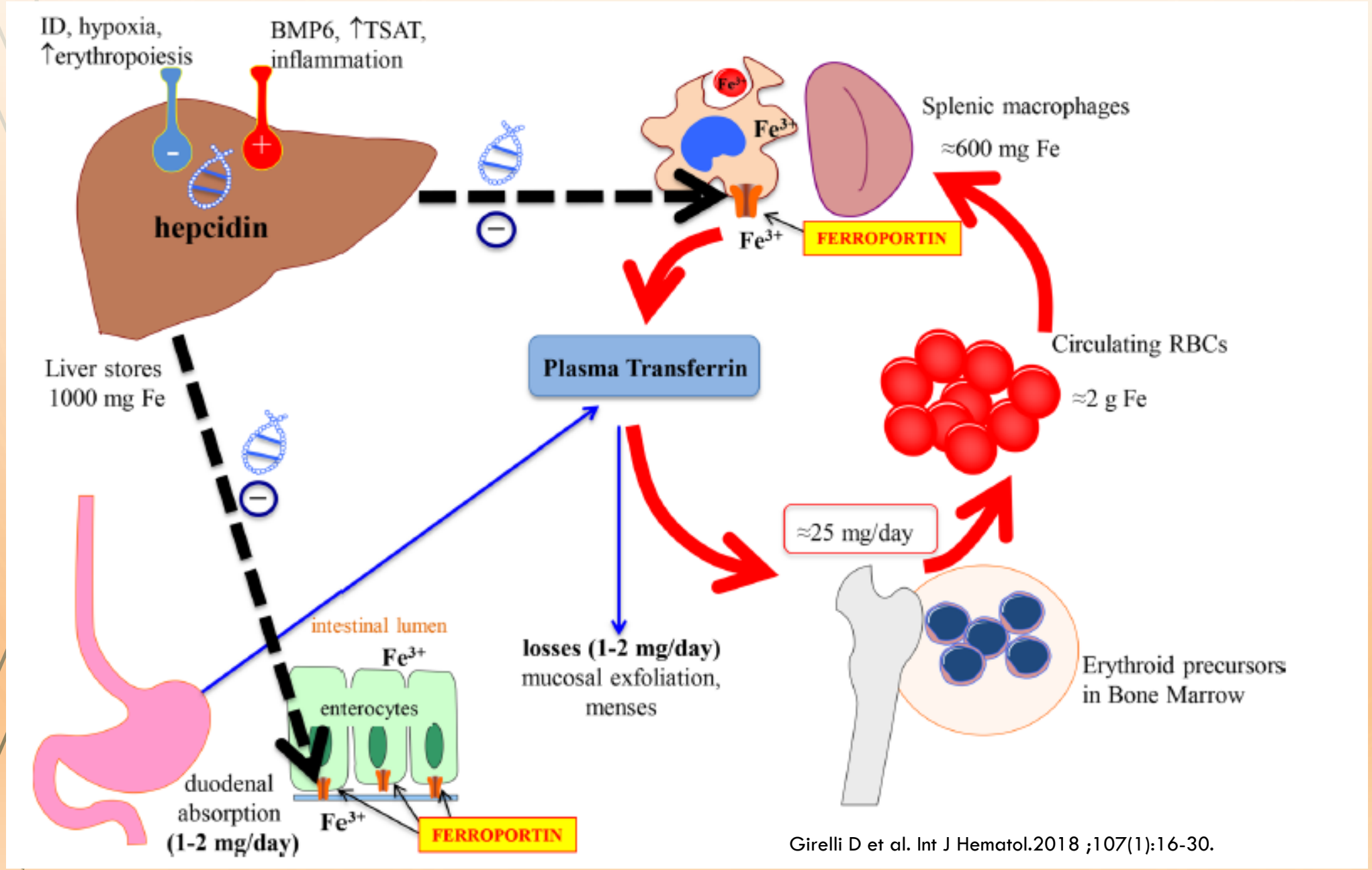
Locatelli F et al. Clin J Am Soc Nephrol. 2016;11(7):1269-80.

PHARMACOKINETIC BETWEEN ORAL AND IV IRON



Girelli D et al. Int J Hematol.2018 ;107(1):16-30.

SYSTEMIC IRON METABOLISM



Girelli D et al. Int J Hematol.2018 ;107(1):16-30.

ID- Iron Deficiency

BMP-6 Bone morphogenetic protein-6

TSAT –Transferrin Saturation

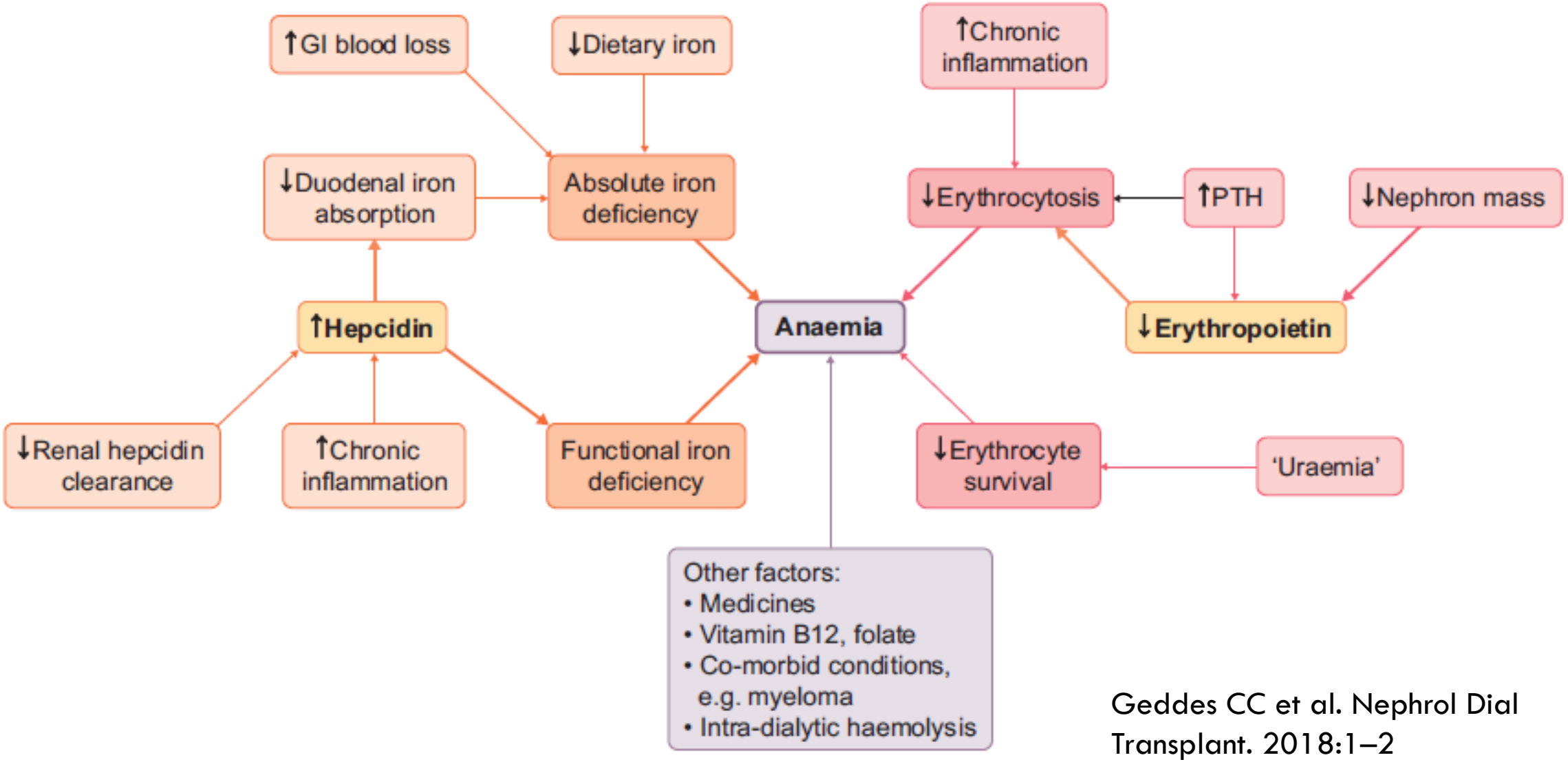
PATHOPHYSIOLOGY

- Hepcidin levels are increased in chronic kidney disease and negatively correlated with the glomerular filtration rate (GFR) .
- The mechanisms responsible for this phenomenon in CKD include

1. Reduced renal clearance
2. Increased inflammatory cytokines
3. Reduced erythropoietin levels

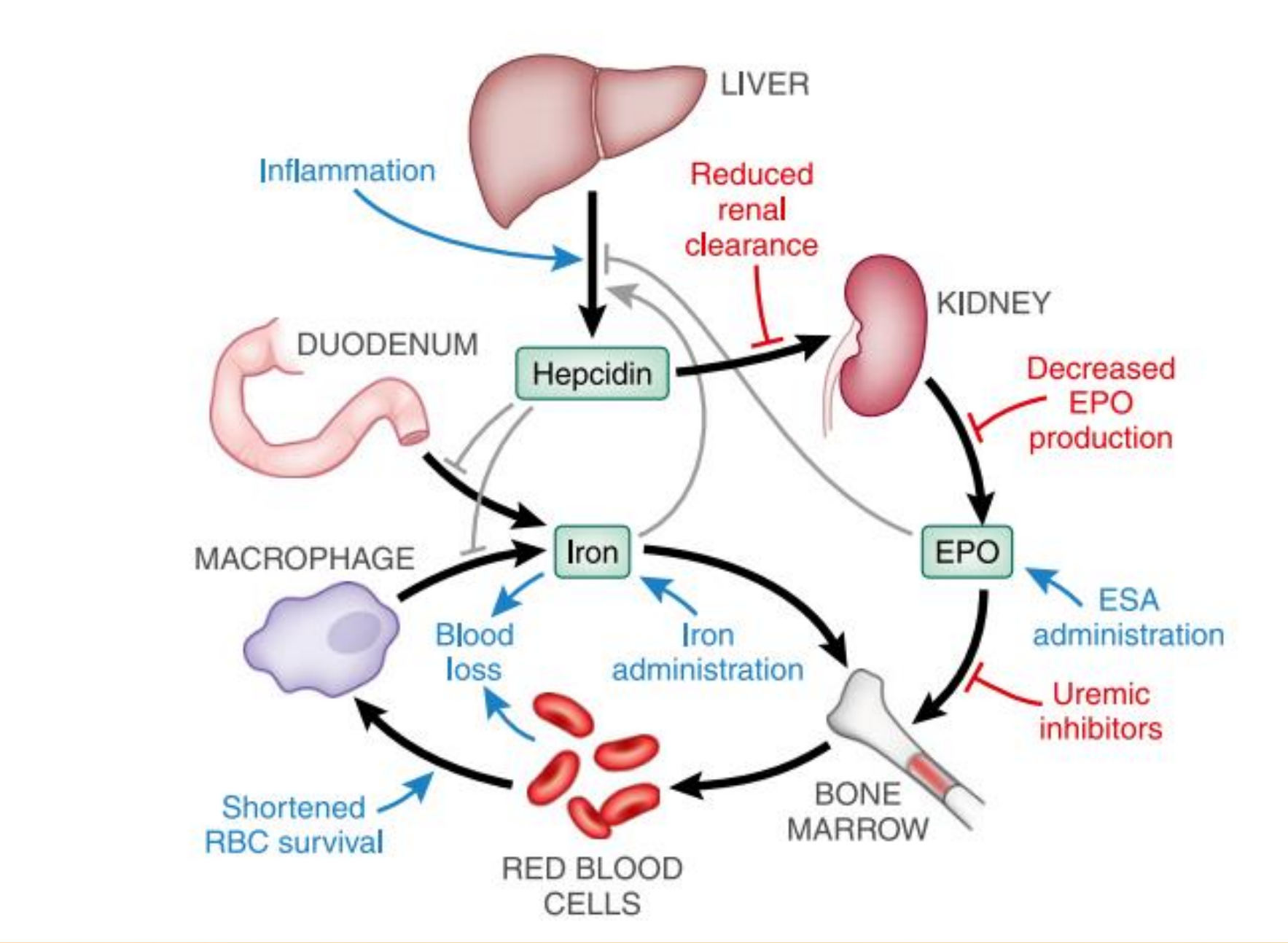
Gvili AG et al. Acta Haematol 2019;142:44–50

FACTORS AFFECTING PATHOPHYSIOLOGY



Geddes CC et al. Nephrol Dial Transplant. 2018:1–2

MECHANISMS OF ANAEMIA IN CKD



Babit JL et al. J Am Soc Nephrol.2012;23: 1631–1634.

HYPOXIA-INDUCIBLE FACTORS (HIF)

- HIFs are proteins that play a pivotal role in the signal transduction leading to Erythropoietin production.
- The HIF complex consists of either HIF-1a or an oxygen-sensitive HIF-2a subunit that associates with a constitutively expressed HIF-1b subunit.
- Human renal fibroblasts, under hypoxic conditions, activate only HIF-2a and not HIF-1a.
- HIF-2a, in the absence of hypoxia, is hydroxylated at 2-proline residues by prolyl-hydroxylases

Coyne DW et al Kidney International Supplements.2017; 7: 157–163

HIF PATHWAY

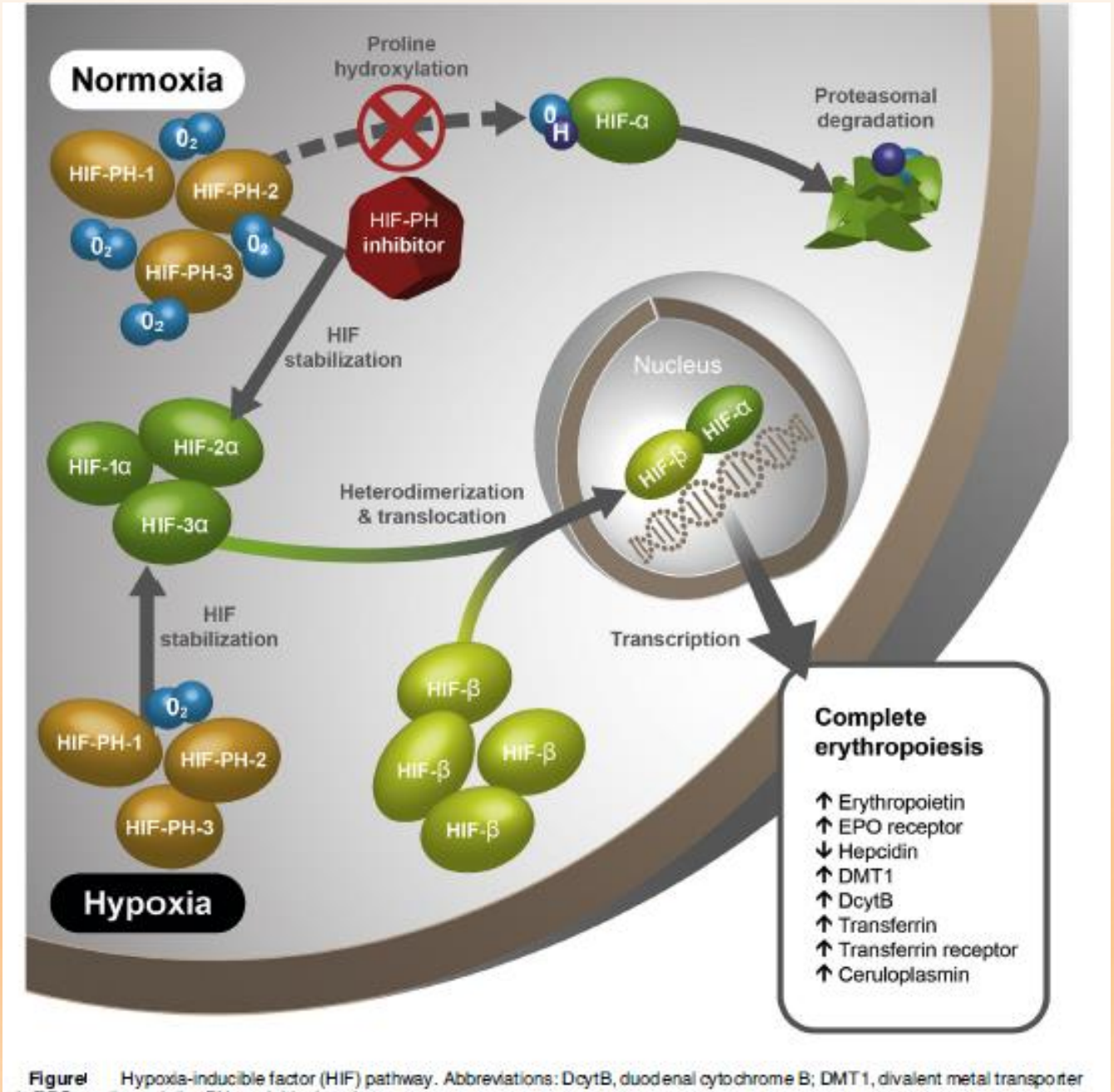


Figure1 Hypoxia-inducible factor (HIF) pathway. Abbreviations: DcytB, duodenal cytochrome B; DMT1, divalent metal transporter 1; EPO, erythropoietin; PH, prolyl hydroxylase.

Gupta N et al. Am J Kidney Dis. 69(6):815-826

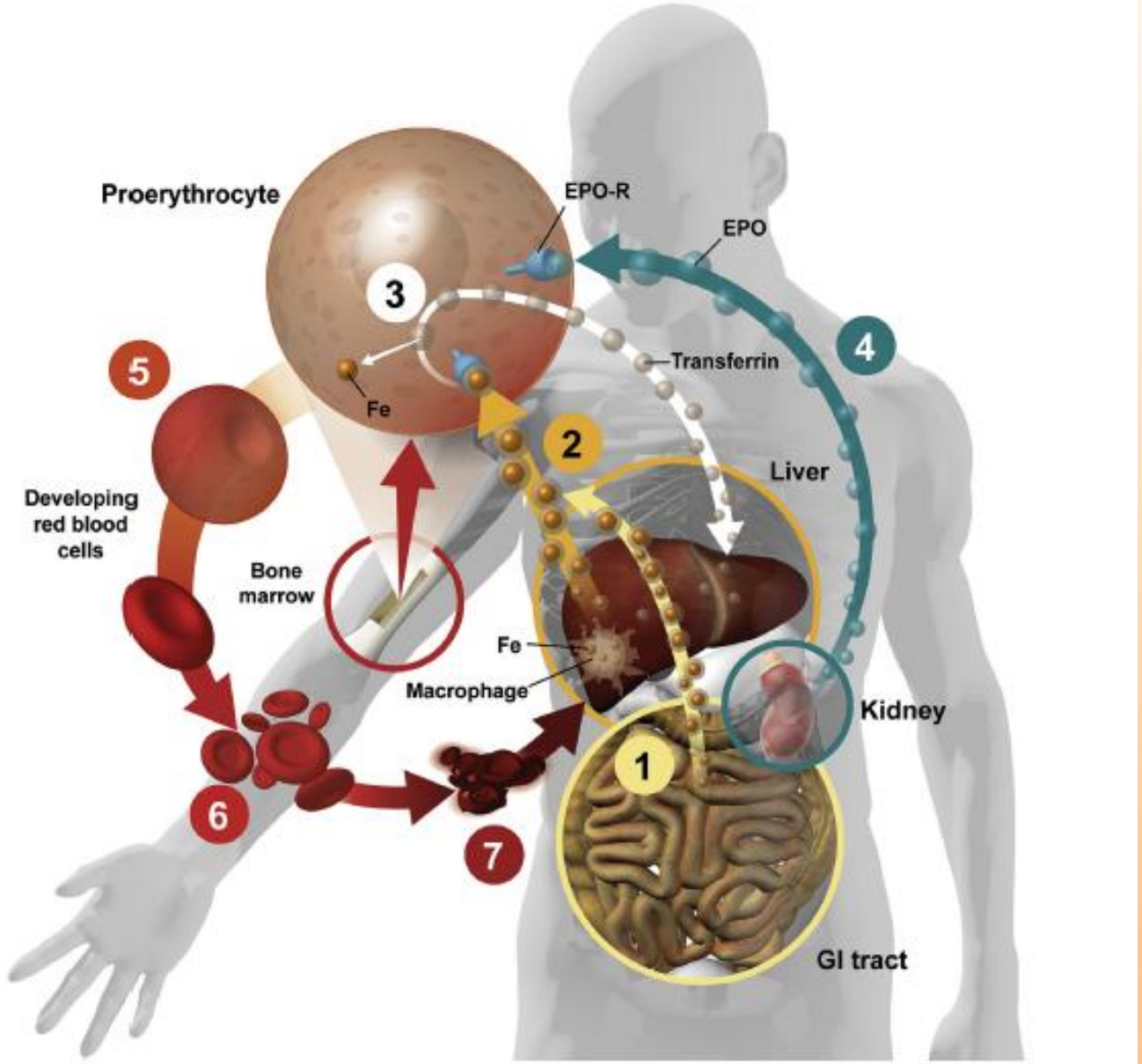


Figure Erythropoietic effects of hypoxia-inducible factor (HIF). (1) HIF upregulates divalent metal transporter 1 (DMT1) and duodenal cytochrome B (DcytB) to increase intestinal iron (Fe) absorption; (2) transferrin transports Fe to transferrin receptors in the bone marrow; (3) Fe is released from transferrin into the developing erythrocyte; (4) HIF upregulates the erythropoietin (EPO) receptor (EPO-R) and endogenous EPO production; (5) HIF upregulates transferrin receptor, increasing iron uptake by proerythrocytes; (6) HIF promotes the formation of fully functional mature erythrocytes replete with hemoglobin (Hb); (7) after a lifespan averaging approximately 120 days, exhausted erythrocytes are scavenged in the liver and the Fe is returned for reuse. Abbreviation: GI, gastrointestinal.

Gupta N et al. Am J Kidney Dis. 69(6):815-826

Recommendations Of Iron Usage

2012 KDIGO guidelines recommend iron therapy during administration of ESAs if the following conditions are present

✓An increase in hemoglobin concentration

✓or a decrease in ESA dose is desired

✓TSAT ≤30 percent and ferritin ≤500 ng/mL

http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf

GUIDELINES ON EVALUATION OF ANAEMIA

- **Screening for anaemia**

1. At least annually in patients with CKD G3.
2. At least twice a year in patients with CKD G4–5 not on dialysis.

- **Haemoglobin (Hb) Levels**

1. Less than 110 g/L (less than 105 g/L if younger than 2 years) or
2. Develop symptoms attributable to anaemia.

- **Renal function**

1. CKD should be considered when the glomerular filtration rate (GFR) is <60 ml/min/1.73m2.
2. More likely if the GFR is <30 ml/min/1.73m2 (<45/min/ 1.73m2 in patients with diabetes) and no other cause e.g. blood loss, folic acid or vitamin B12 deficiency.

Mikhail et al. BMC Nephrology (2017) 18:345

GUIDELINES ON EVALUATION OF ANAEMIA

- **Baseline Investigations**
- Complete blood count
- Absolute reticulocyte count (if indicated).
- Test to determine iron status:
- Transferrin saturation and serum ferritin levels
- Plasma/serum C-reactive protein (CRP).

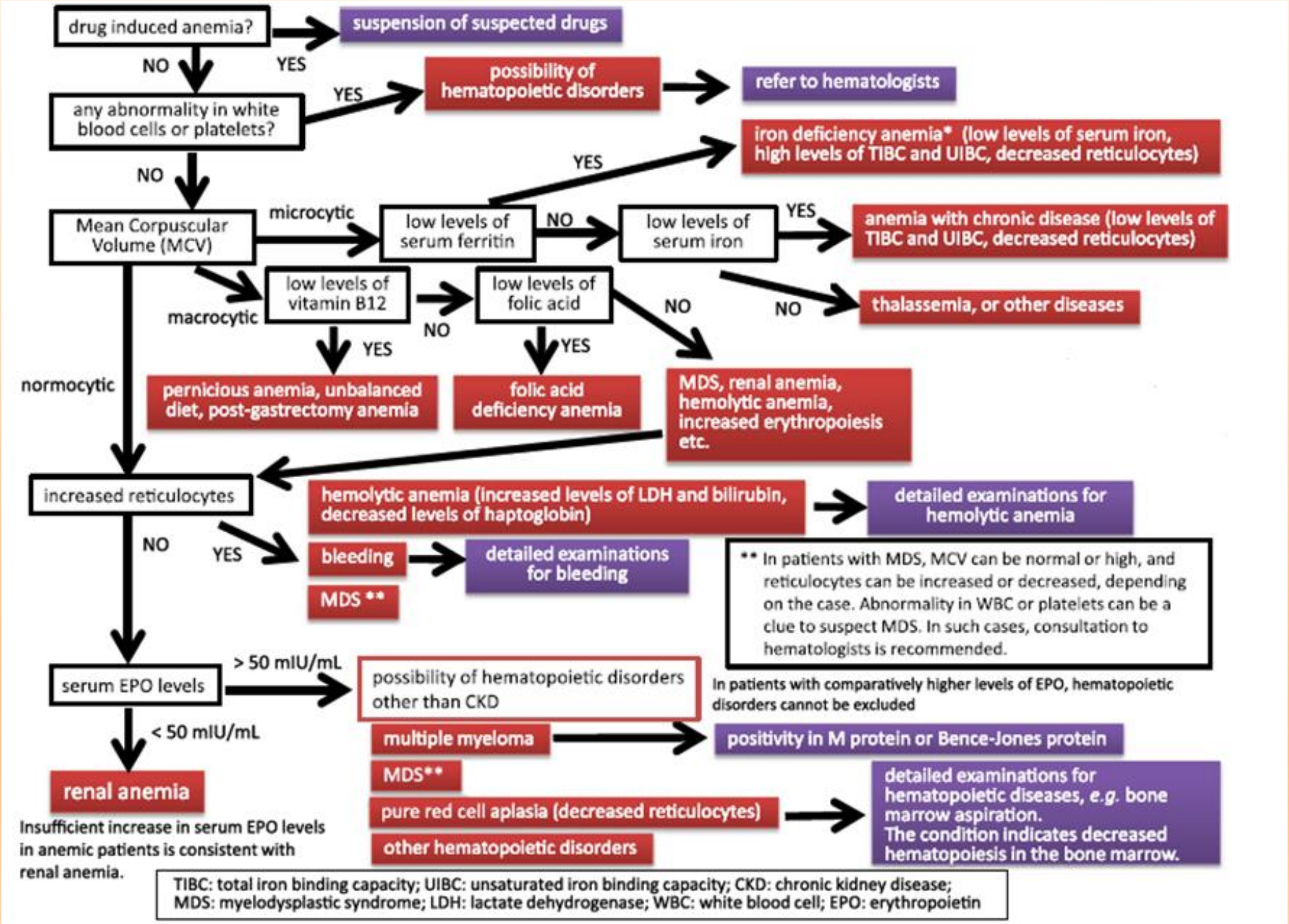
Mikhail et al. BMC Nephrology. 2017; 18:345

BASELINE INVESTIGATIONS IN SELECTED CASES

- Serum B12 and serum folate concentrations.
- Tests for haemolysis (plasma/serum levels of haptoglobin, lactate dehydrogenase, bilirubin, Coombs' test).
- Plasma/serum and/or urine protein electrophoresis.
- Hb electrophoresis.
- Free light chains and bone marrow examination

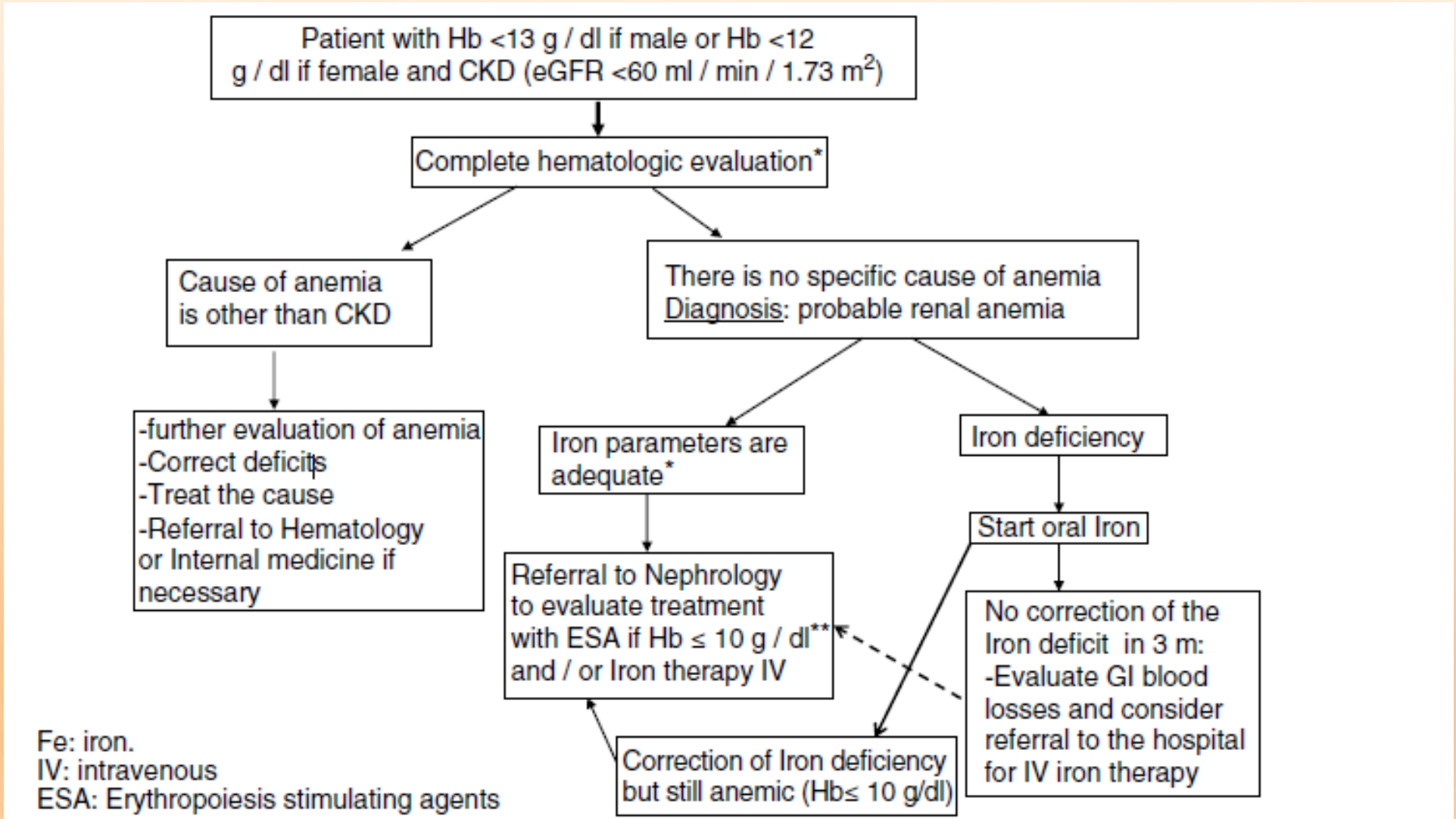
Mikhail et al. BMC Nephrology (2017) 18:345

DIAGNOSTIC CHART OF ANAEMIA IN CKD



Yamamoto et al. Renal Replacement Therapy.2017;3(36)-1-46

ALGORITHM FOR ANAEMIA IN CKD



Cases A et al. Nefrologia. 2018;38:8–12.

TREATMENT OF RENAL ANEMIA

- Androgens started to be used to treat anemia of end-stage renal disease in 1970. [1]
- The approval of recombinant human erythropoietin in 1989 drastically shifted the treatment of renal anemia. [1]
- The first recombinant Human Erythropoietin , epoetin alfa, was manufactured in the US for dialysis patients in 1989. [2]

1) Nakhoul G et al. Cleve Clin J Med. 2016 Aug;83(8):613-24.
2) Zadeh KK et al. Am J Nephrol. 2017 ; 45(3): 235–247

ERYTHROPOIESIS STIMULATING AGENTS

Generation	Drug	Approval
First Generation	Epoetin alfa	1989
	Epoetin Beta	1990
	Epoetin omega	1990
Second Generation	Epoetin Beta	1997
	Darbepoetin alfa	2001
Third Generation	Epoetin delta	2002
	Methoxy polyethylene glycol	2007
	epoetin beta (biosimilar)	2007
	Epoetin alfa (biosimilar)	2007
	Epoetin zeta (biosimilar)	2009
	Epoetin theta	

Zadeh KK et al. Am J Nephrol 2017;45:235–247

ERYTHROPOEITIN RESISTANCE

- The National Kidney foundation - Kidney Disease Outcomes Quality Initiative defined the hyporesponsiveness to erythropoietin as the presence of at least one of the following three conditions:
- i) a significant decrease in Hb level at a constant ESAs dose
- ii) a significant increase in the ESAs dose requirement to preserve a target Hb level
- iii) a failure to raise the Hb level to values higher than 11 g/dL despite an ESAs dose equivalent to erythropoietin greater than 500 IU/kg/week

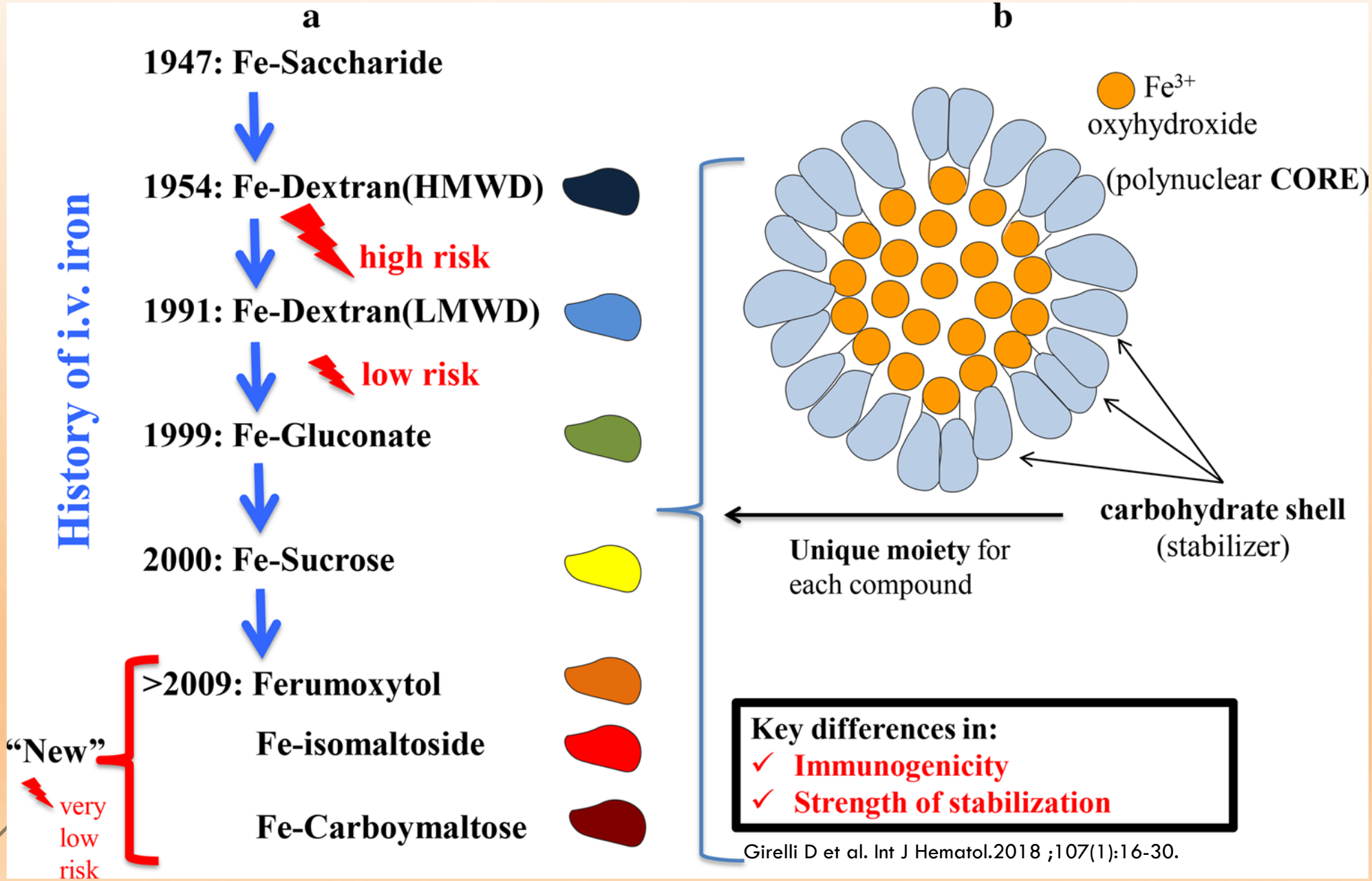
Rattanasomapattikul et al. Nephrol Dial Transplant. 2013; 28(7): 1936–1945..

RISK FACTORS

- Absolute or functional iron deficiency
- Gastrointestinal blood loss
- Hemolysis
- Inflammation , Infection
- Neoplastic diseases
- Malnutrition, Folic acid and vitamin B12 deficiencies
- Inadequate dialysis
- Hyperparathyroidism
- ACE inhibitors and ARBs
- Anti-erythropoietin antibodies
- Genetic polymorphisms

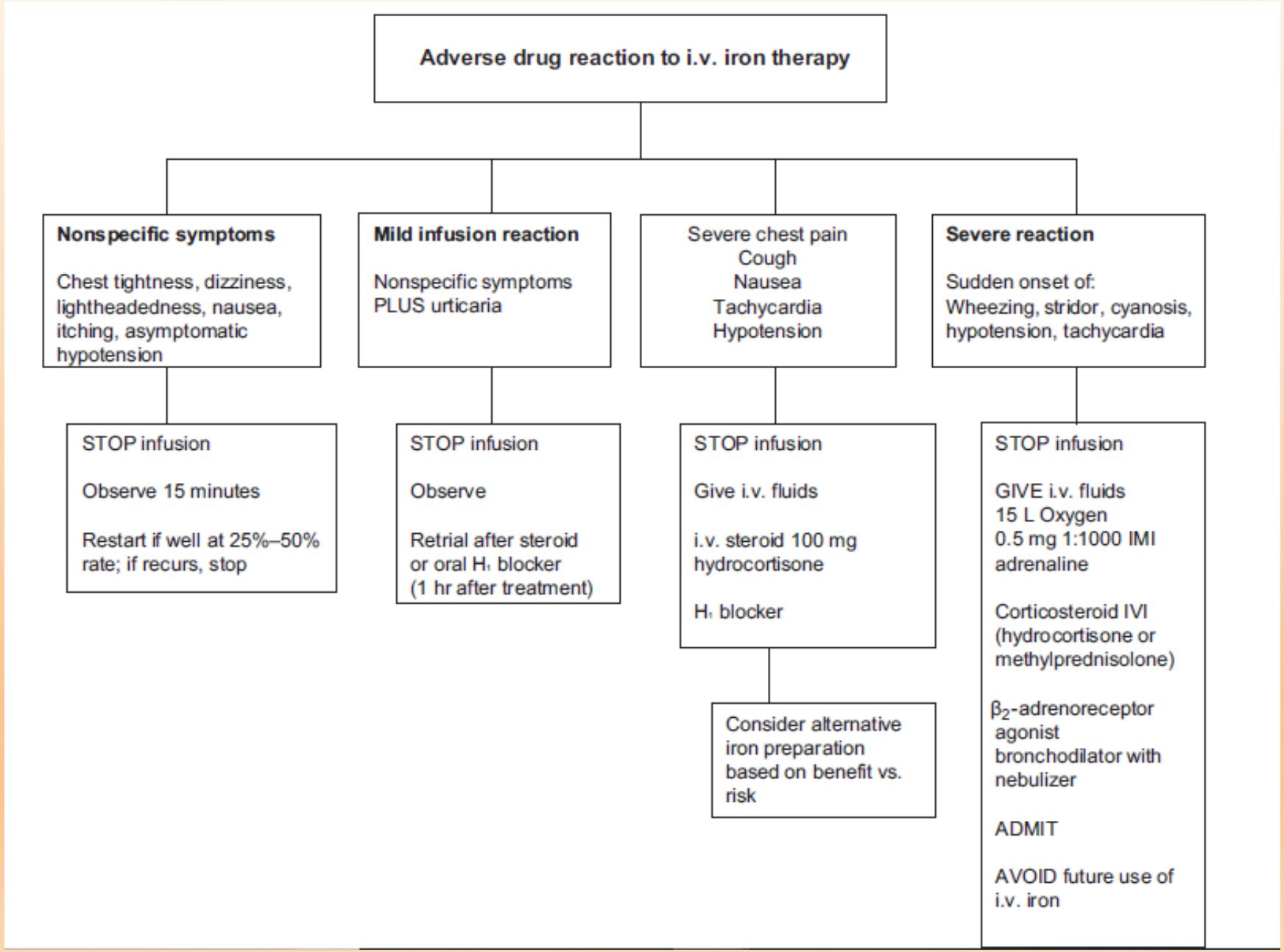
Alves MT et al. rev bras hematol hemoter. 2015 ; 37 (3):190–197

INTRAVENOUS IRON PREPARATIONS



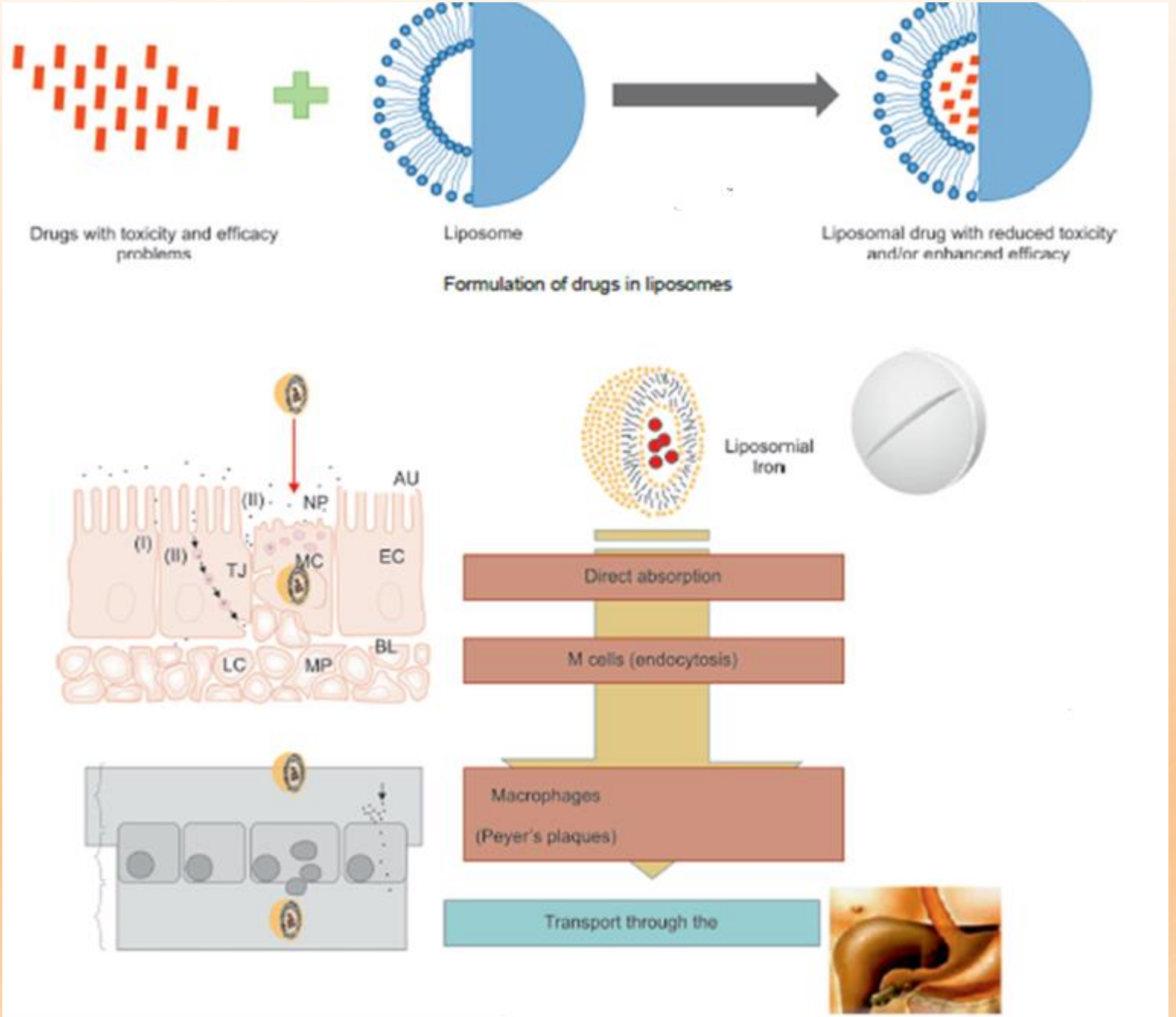
Girelli D et al. Int J Hematol.2018 ;107(1):16-30.

ADVERSE DRUG REACTION TO IRON THERAPY



Macdougall IC et al. Kidney Int. 2016;89(1): 28-39.

LIPOSOMAL IRON ABSORPTION



Malhotra J et al. World J Anemia 2017;1(4):1-6.

Liposomal Technology

1

Phospholipid

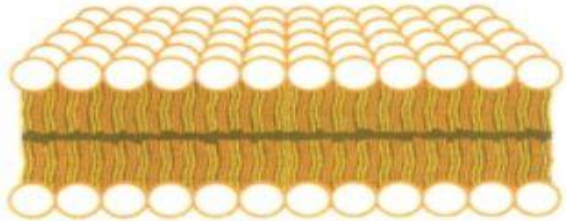
Head
Hydrophilic

Tail
Hydrophobic

2

Phospholipid bilayer

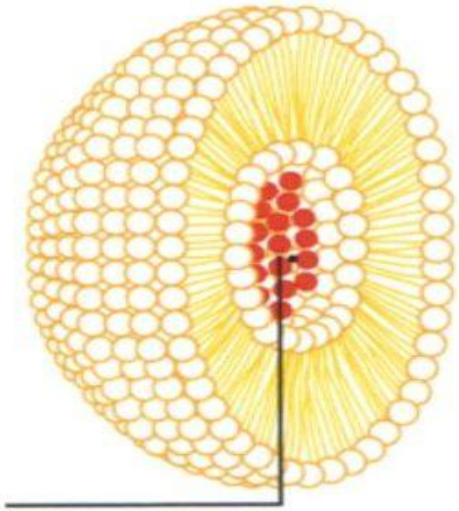
Phospholipid bilayer is similar to cell membrane



3

Liposomes

The lipid capsule (bilayer) contains and carries Iron avoiding the direct contact of Iron and mucosa

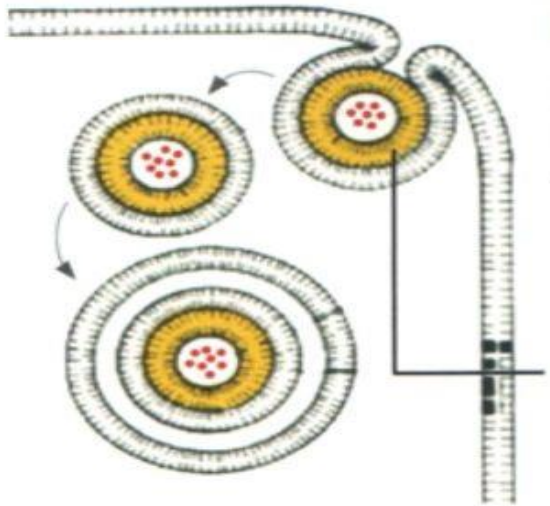


Ferric Pyrophosphate

4

Endocytosis

Engulfing intact liposome into the nucleus of cells



Liposome during endocytosis

Iron

The iron carried by phospholipid bilayer, is DIRECTLY ABSORBED similar to chylomicrons, it reaches the lymph and is carried to the liver

LIPOSOMAL ORAL IRON

- Liposomal Iron is a highly bioavailable ferric pyrophosphate carried inside a phospholipid bilayer membrane.
- This is produced mainly from sunflower lecithin.

- It is tasteless. It ensures maximum tolerability and absence of side effects commonly associated with oral iron therapy.

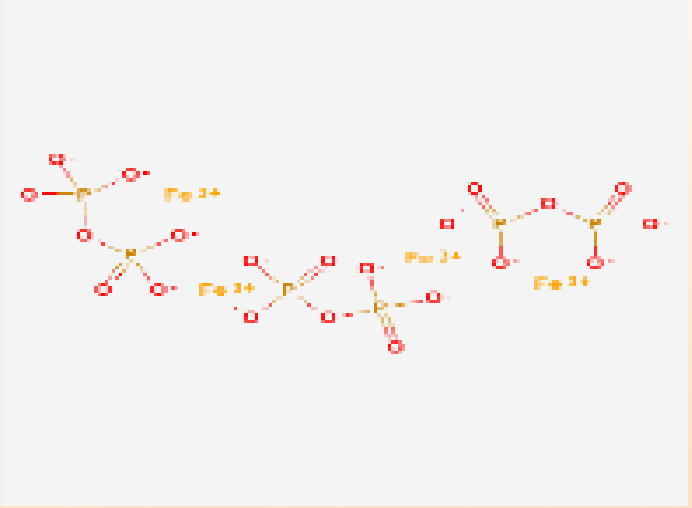
- It bypasses the extremely restrictive, normal intestinal barriers of iron absorption.

- Hence it achieves much higher plasma iron concentration, compared to usual oral iron compounds.

ADVANTAGES WITH LIPOSOMES

- Suitable for delivery of hydrophobic, hydrophilic and amphipatic drugs and agents
- Chemically and physically well characterized entities
- Biocompatible
- Suitable for controlled release
- Suitable to give localized action in particular tissues.
- uitable to administer via various routes

IRON PYROPHOSPHATE



- The presence of the pyrophosphate group increases the affinity of iron to Transferrin
- In inflammatory states where Ferritin is saturated, the iron pyrophosphate readily reaches Transferrin and is then transported to the marrow.

Johnson-Wimbley TD *Therap Adv Gastroenterol*. 2011 May; 4(3): 177–184.
Pisani A et al. Nephrol Dial Transplant;2015: 30(4):645-52

ADVANTAGES WITH LIPOSOMAL IRON

1) Simple adsorption which increases local concentration of liposomal contents at intestinal membrane with resultant absorption by diffusion or transporters

2) Endocytosis with subsequent breakdown of liposomal membrane by intracellular lysosomes;

3) Fusion of lipid bilayer to plasma membrane with release of contents in to the cytoplasm;

4) Exchange of lipids between liposomal bilayer and plasma cell membrane causing liposomal bilayer instability with subsequent release of contents intracellularly

Biniwale P et al . Open J Obs and Gynecol. 2018;8(11):993.

INDICATIONS FOR LIPOSOMAL IRON

- **Iron Deficiency Anemia**
- **Inflammatory Bowel Disease**
- **Chemotherapy-related Anemia**
- **Chronic Kidney Disease-related Anemia**
- **Celiac Disease**

Malhotra J et al. World J Anemia 2017;1(4):1-6.

Efficacy of Liposomal Iron in Patients with anemia of inflammation

INTESTINAL ABSORPTION

The liposome bypasses the block in intestinal absorption induced by hepcidin. liposomal iron follows a different way of uptake through M cells

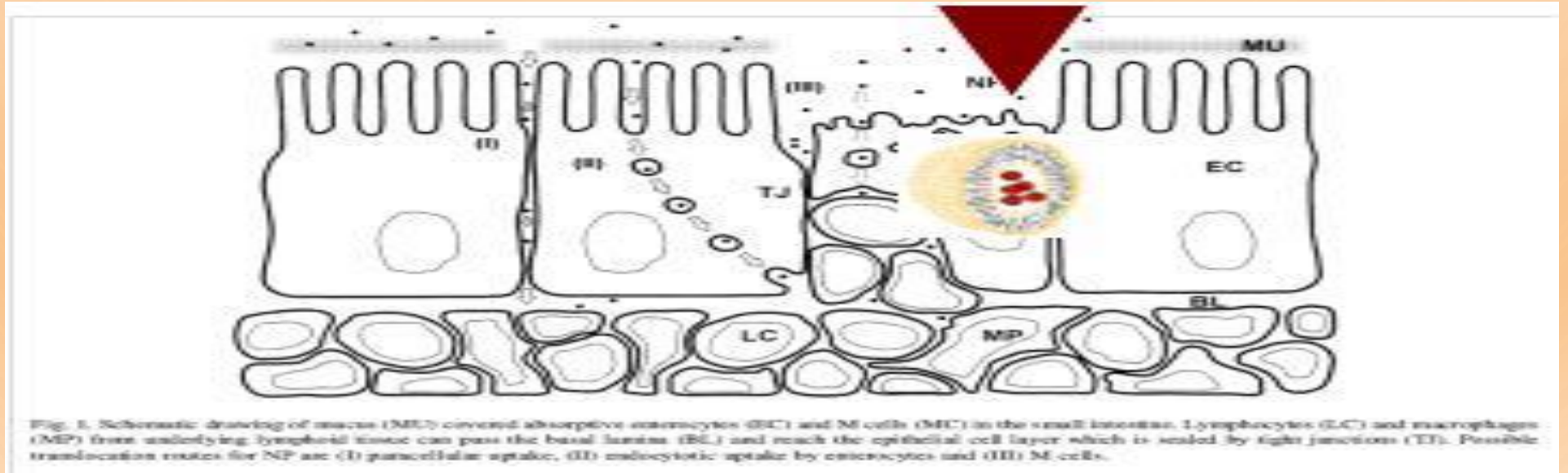
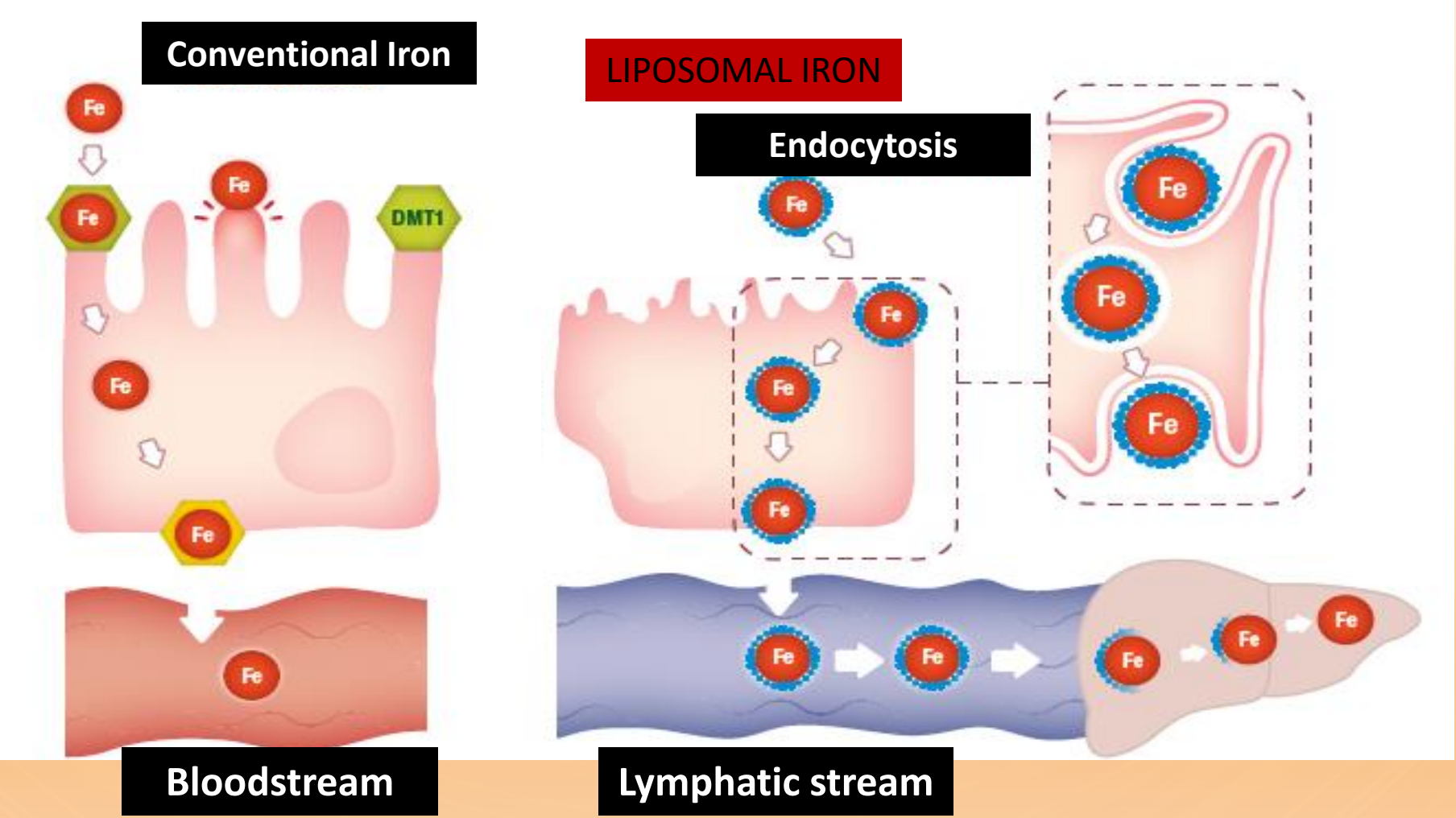


Fig. 1. Schematic drawing of mucus (MU) covered absorptive enterocytes (EC) and M cells (MC) in the small intestine. Lymphocytes (LC) and macrophages (MP) from underlying lymphoid tissue can pass the basal lamina (BL) and reach the epithelial cell layer which is sealed by tight junctions (TJ). Possible translocation routes for NP are (I) paracellular uptake, (II) endocytotic uptake by enterocytes and (III) M cells.

Liposomal Iron Absorbtion



Liposomal Iron: Clinical Trials

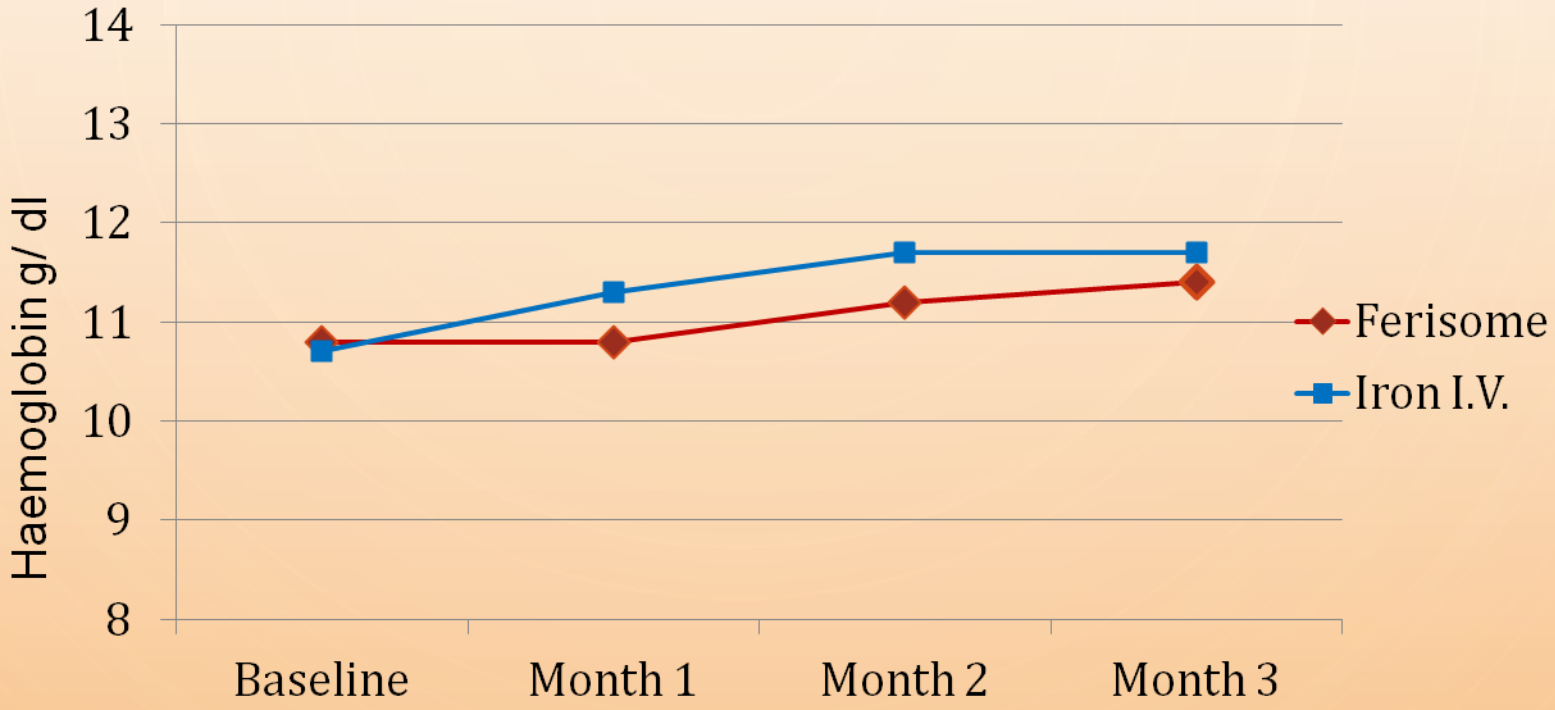
ORAL LIPOSOMAL IRON VS IV IRON FOR IRON DEFICIENCY ANAEMIA IN CKD PATIENTS

- **Methods:**
- Randomized study of 99 CKD patients (stage III to V) with IDA
- **Inclusion:**
- Hb≤12 g/dL, Ferritin≤100 ng/mL, TSAT≤25%
- **Treatment**
- Oral liposomal iron 30 mg/day or a total dose of 1000 mg of IV iron gluconate (125 mg iv weekly) for 3 months

Pisani A et al. Nephrol Dial Transplant;2015: 30(4):645-52

RESULTS

EFFECTS OF I.V. AND ORAL LIPOSOMAL IRON ON HAEMOGLOBIN



Pisani A et al. Nephrol Dial Transplant;2015: 30(4):645-52

RESULTS

Oral Liposomal Iron Vs IV Iron For IDA in CKD Patients

	Baseline	Month 1	Month 2	Month 3
Ferritin (ng/mL)				
Ferisome	71.4 ± 23.7	79.5 ± 26.4	84 ± 25.4	85.5 ± 31.3
I V iron	67.7 ± 31.6	145 ± 47.8	195 ± 51.2	238.5 ± 49.7
TSAT (%)				
Ferisome	16.5 ± 2.2	17.0 ± 3.1	18.1 ± 2.4	18.3 ± 4.3
I V iron	17.0 ± 2.1	19.3 ± 4.2	20.1 ± 5.6	21.5 ± 5.2

CONCLUSION:

Oral liposomal iron is safe and efficacious alternative to IV iron for the treatment of IDA in CKD patients.

Pisani A et al. Nephrol Dial Transplant;2015: 30(4):645-52

STUDY - 4

Liposomal Iron is superior to iron sulphate in Anemia Of Chronic Inflammatory Disease

Giulio Giordano
Fondazione “G. Paolo II”, Campobasso - Italy

21 women with anemia of chronic inflammatory diseases (SLE, Connective tissue disorders and Fibromyalgia) were treated for 3 months

Group A (N= 9)

Liposomal Iron 60 mg

Mean values

- **Hb 8.5 g/dl**
- **TSAT <20%,**
- **CRP 18 mg/l**

Group B (N= 12)

Ferric sulfate 210 mg

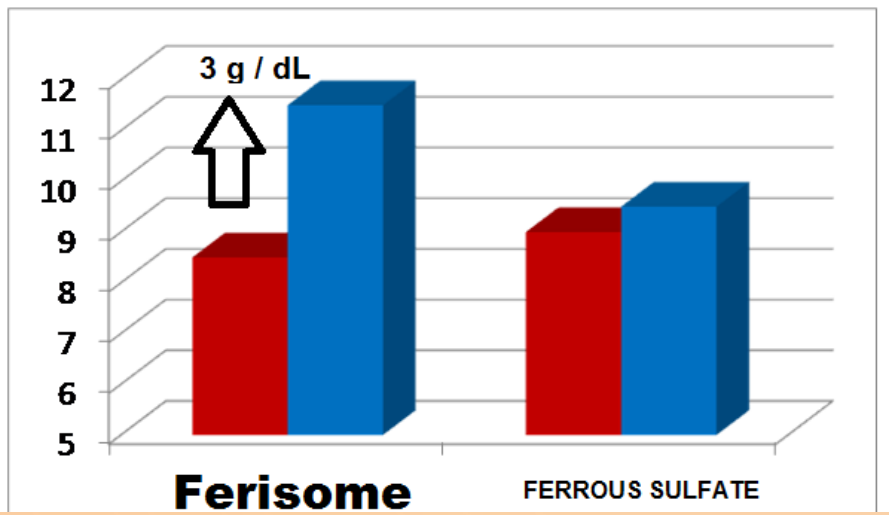
Mean values

- **Hb 9 g/dl**
- **TSAT<20%**
- **CRP 15 mg/l**

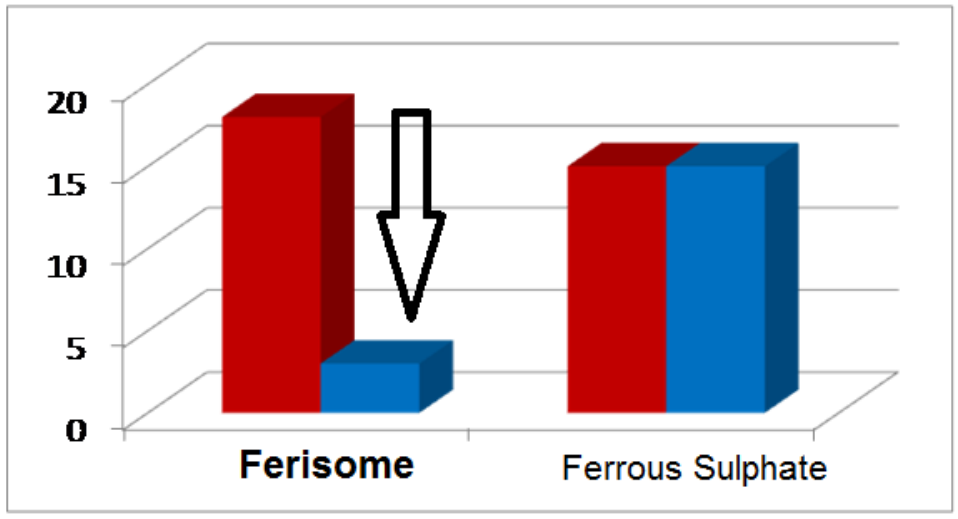
Presented as Abstract at 44th Congress 2013 of Italian Society of Hematology

RESULTS

Hemoglobin



CRP levels



Increase in Hb levels in patients treated with Liposomal Iron

Significant reduction in CRP levels in patients treated with Liposomal Iron

STUDY-4: CONCLUSIONS

- **Liposomal iron :**
  - **Increased Hemoglobin levels and reduction in markers of inflammation were achieved in women with chronic inflammatory diseases.**
  - **Effective and safe with better tolerability compared to ferrous sulfate.**

STUDY - 5

Intravenous Iron Vs Oral Liposomal Iron In Patients With Refractory Anemia Treated With ESA Alpha

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1 Department of Oncology, University Cattolica - Campobasso,

2 Department of Oncology, University of Messina, 3 Cardiovascular Diseases,

4 Hospital Management, University Cattolica - Campobasso

MASCC/ISOO 2011 International Symposium, June 23-25, 2011, Athens, Greece
The 11th International Symposium on Myelodysplastic Syndromes, Edinburgh, UK, May 18-21, 2011
EHA 16th congress, June 9-12, 2011, London
G. Giordano *et al. Leukemia Research 2011 (1)* 35; S137
43° congresso nazionale SIE, 16-19 October2011, Napoli, Italy

STUDY - 5

IV Iron Vs Oral Liposomal Iron

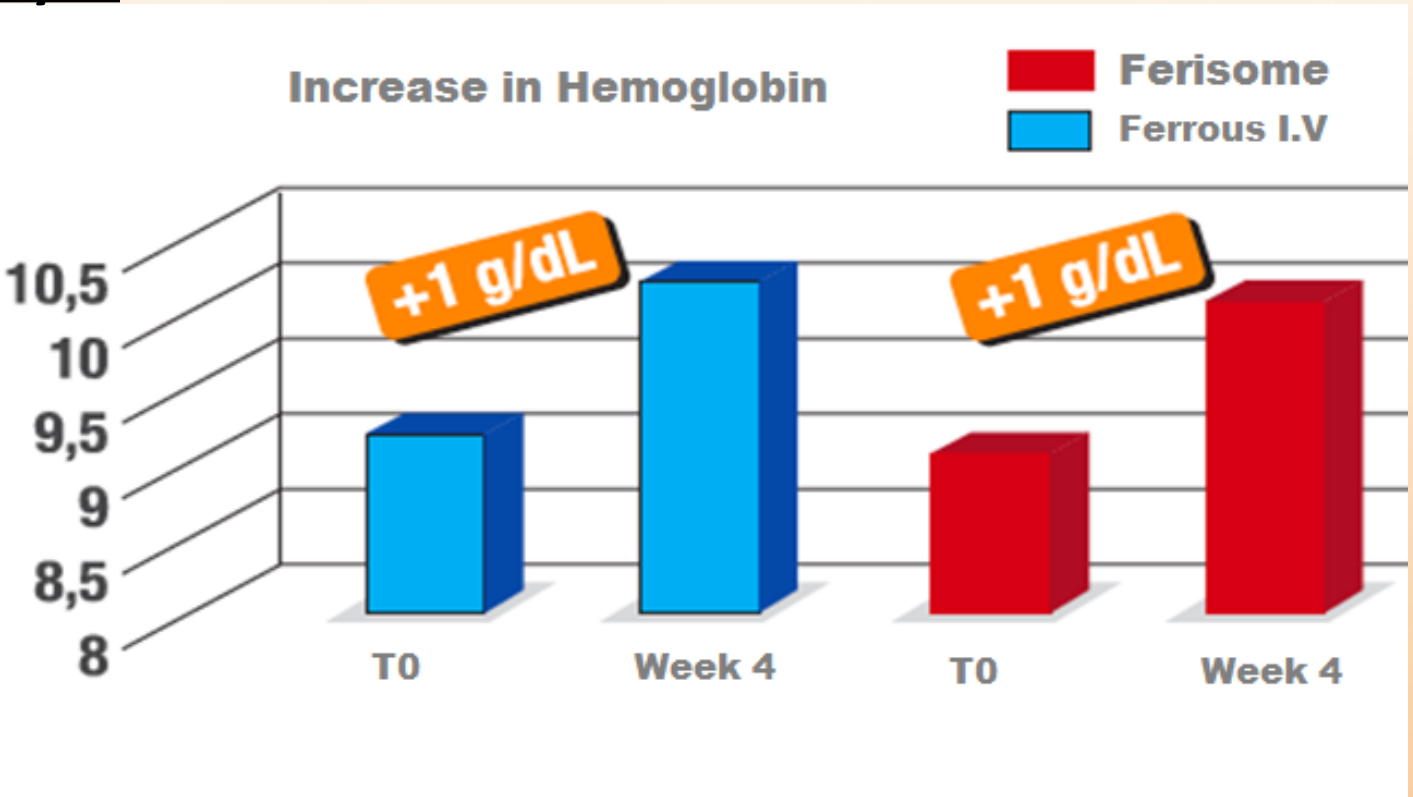
24 patients with refractory anemia: (Myelodysplastic syndrome)

- **Group A**
  - **Sodium iron gluconate**
  - 62.5 mg **iv**
  - **EPO alfa** 40000 U sc/Week
  - **Folic acid** 7.5mg/day PO
  - **Vitamin B12** 400mg/day PO
  - **Mean value Hb 9 g/dl**

- **Group B**
  - **Oral Liposomal iron pyrophosphate 14mg, 2 caps OD**
  - **Epo alfa** 40000 U sc/week
  - **Folic Acid** 7.5mg/per day orally
  - **Vitamin B12** 400mg/per day orally
  - **Mean value Hb 8.8 g/dl**

RESULTS

Study 5



- The oral liposomal iron is **safe , feasible** and **non inferior** to intravenous iron therapy in patients of refractory anemia.

IV Iron Is Not All That Safe

- Dialysis Outcomes and Practice Patterns Study (DOPPS)
- Included 32,435 patients
- Increased mortality associated with IV iron, in selected patients getting >300 mg iron per month

Bailie GR *et al.* Kidney Int. 2015;87(1):162-8.

Treatment of Anemia of Chronic Diseases

Oral or Intravenous administration of Iron ?

- With conventional oral iron, the absorption is a problem
- With IV iron there is risk of toxicity

IRON THERAPY: ISSUES

- Oral Iron :
  - Safe and economical
  - Poor gastrointestinal absorption
  - High rates of non compliance and side effects.

- IV iron :
  - May accelerate kidney damage
  - Promote infections by supplying iron to pathogens
  - Enhance atherosclerosis by generating oxidative stress
  - Cause endothelial damage
  - Anaphylaxis

Pisiani et al. Nephrol Dial Transplant;2014: 1–8

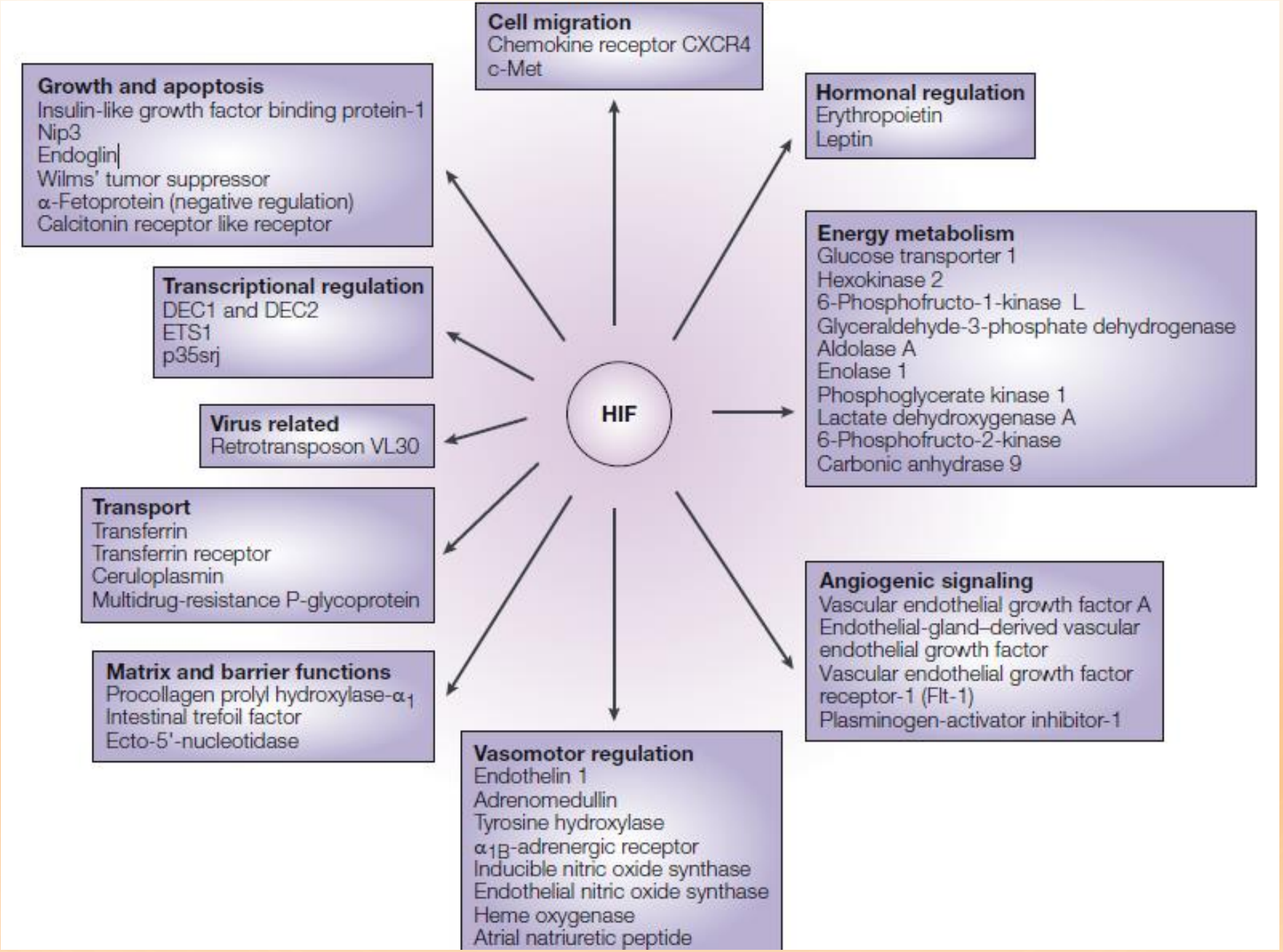
POTENTIAL NEGATIVE EFFECTS OF INTRAVENOUS IRON

- Pro-oxidant - might increase oxidative stress, infections, mortality, tumor growth.

- Non-ESRD patients – Nephrotoxicity?
  - Transient increase in induced proteinuria and albuminuria with iron sucrose.
  - Ferric gluconate showed significant increases in lipid peroxidation.

Auerbach M. Am J Hematol. 2008; 83: 580–588

NEWER TARGETS FOR ANAEMIA IN CKD



Coyne DW et al Kidney International Supplements.2017; 7: 157–163

AGENTS THAT STIMULATE ENDOGENOUS ERYTHROPOIETIN

CLASSIFICATION OF ERYTHROPOIESIS STIMULATING AGENTS

- ***Exogenous EPO:***

1. Epoetin and analogues
2. EPO-mimetic agents

Agents that stimulate endogenous EPO :

1. Prolyl-hydroxylase inhibitors (PHIs)
2. GATA inhibitors

Agents with other mechanisms of action:

1. Anti-hepcidin agents
2. Anti-activin agents

LATEST OPTIONS IN ANAEMIA TREATMENT IN CKD

1) Recombinant activin type-II receptor (ActRIIA)-IgG-Fc fusion proteins

Sotatercept and Luspatercept.

- Mechanism: trapping the ActRIIA ligands that inactivate the transforming growth factor-beta (TGFbeta) family and inhibit erythroid precursors.
- Indications:

  Myelodysplastic syndromes, metastatic solid tumours and beta thalassemia

Jelkmann W. Curr Opin Nephrol Hypertens 2018; 27:351–357

HIF STABILISERS OR PROLYL HYDROXYLASE 2 INHIBITORS

Drugs: Roxadustat, Daprodustat, Vadadustat, and Molidustat. [1]

Mechanism: increasing endogenous Erythropoietin by stabilizing the cellar hypoxia inducible factor (HIF). HIF stabilization helps improve iron metabolism by suppressing hepcidin levels and promotes iron absorption. [2]

Disadvantage: induction of tumour cell proliferation in hypoxic conditions using HIF signalling, HIF activation could mediate resistance to chemotherapy and radiation. [2]

1) Coyne DW et al. Kidney Int Suppl. 2017 ; 7(3): 157–163
2) Hasegawa S et al. Curr Opin Nephrol Hypertens 2018; 27:331–338

GATA (ERYTHROID TRANSCRIPTION FACTOR) INHIBITORS

- Erythropoiesis control by HIF-2 is negatively regulated by GATA which inhibits EPO expression in the liver and kidneys.
- There are 4 subtypes of GATA and GATA-2 acts most potently on the regulation EPO synthesis.
- In vitro experience has shown that its oral administration reverses the decrease in haemoglobin, reticulocytes and improve inflammation-induced erythropoiesis

Lopez Gomez JM et al. Nefrologia. 2016;36 (3):232–236

ANTI HEPCIDIN AGENTS

- Antagonizing hepcidin ameliorate anemia among persons with CKD.
- Inhibiting hepcidin production by using antisense oligonucleotides or silencing messenger RNA transcribed from the hepcidin gene is strategy to alleviate anemia.
- Lexaptepid increases serum iron levels and transferrin saturation in subjects who have previously developed an increase in hepcidin induced by endotoxaemia

Lopez Gomez JM et al. Nefrologia. 2016;36 (3):232–236

ANTI-ACTIVIN AGENTS

- Activin is a protein formed by 2 similar monomers bound by disulphide bonds, which belongs to the TGF- superfamily.
- It is mainly produced in the ovarian follicles and gonads, function is to regulate the menstrual cycle by controlling FSH secretion.
- Activin receptor type IIA antagonist Sotatercept produces a dose-dependent improvement in haemoglobin levels

Lopez Gomez JM et al. Nefrologia. 2016;36 (3):232–236

SUMMARY

- Anemia of renal disease is a common condition that is mainly caused by a decrease in erythropoietin production by the kidneys.
- Anemia of renal disease is associated with significant morbidity such as increased risk of left ventricular hypertrophy, myocardial infarction, and heart failure.