



HYPOPROLIFERATIVE ANEMIAS AND IRON METABOLISM

BHS course 18-11-2023



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ANEMIA : 3 MAJOR MECHANISMS

Defective production

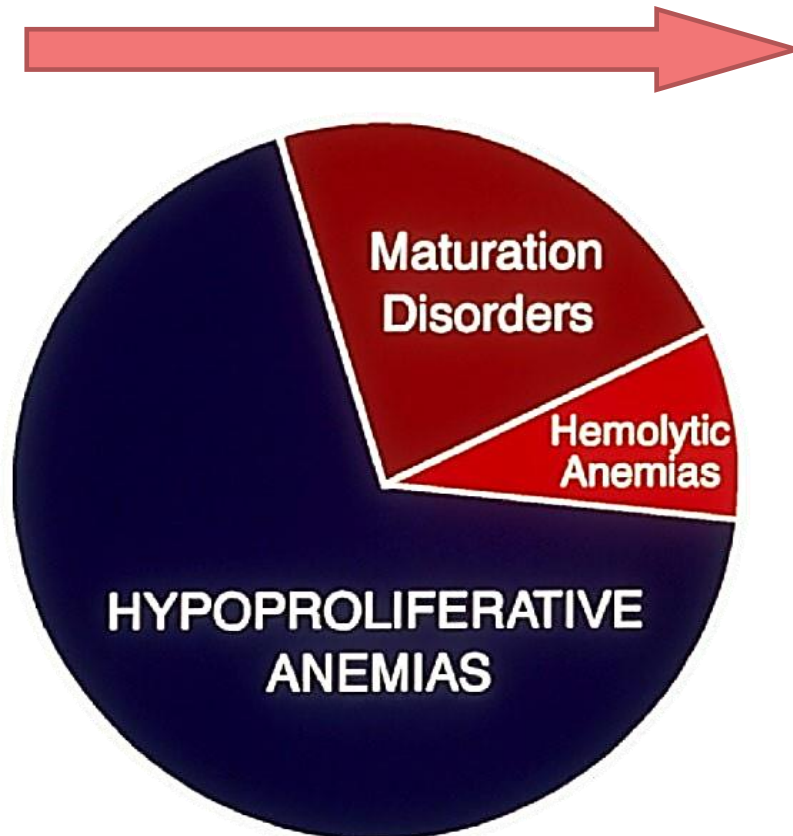
- Erythroid marrow
- Erythropoietin
- Iron

Defective maturation

- DNA (folate, B12, ...)
- Hb : *Globin / Heme*
- Myelodysplasia

Red cell loss

- Hemolysis
- Hemorrhage



Decreased erythroid precursors

- Marrow damage
SAA, chemoT, radioT, drugs, toxic agents
- Marrow replacement
myelofibrosis, tumor cells
- Erythroid inhibition
cytokines, Ab (PRCA), low hormones

Decreased Epo production

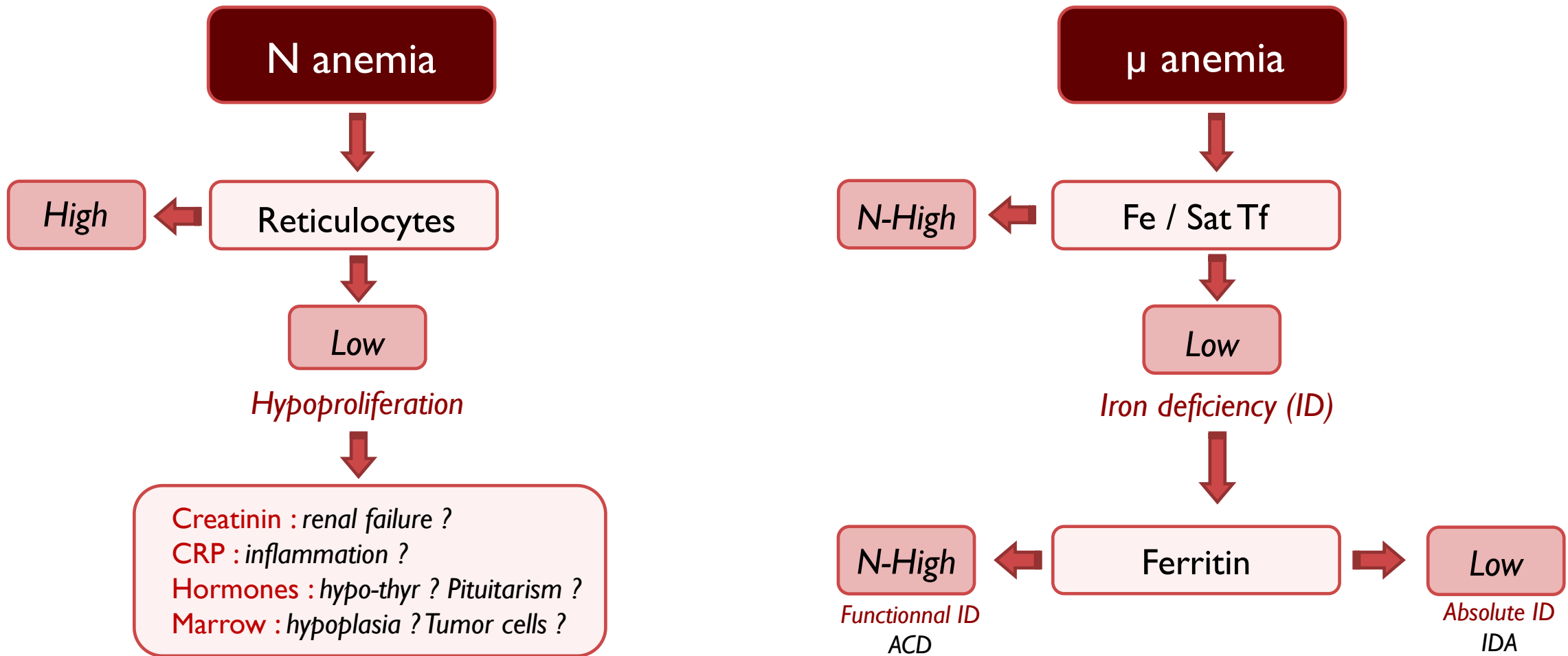
- Renal failure
- Others

Decreased iron availability

- Absolute : ID
- Functional : inflammation



HYPOPROLIFERATIVE ANEMIA : DIFFERENTIAL DIAGNOSIS



HYPOPROLIFERATIVE ANEMIA

Anemias due to defective erythroid
precursors



HYPOPROLIFERATIVE ANEMIA : DEFECTIVE ERYTHROID PRECURSORS

Normocytic normochromic, low retics

**+ Neutropenia
thrombocytopenia**

Marrow damage

- **Aplasia** : SAA
- **Hypoplasia** :
 - *Chemotherapy, radiotherapy*
 - *Toxic agents, irradiation, drugs*
 - *Idiopathic*

Marrow replacement

- **Myelofibrosis**
- **Tumor cells** : *Leukemia, Lymphoma – Myeloma, Solid tumors*

Anemia alone

Red cell hypoproliferation

- **Auto-immune** : *Pure red cell aplasia*
- **Cytokines** : *Inflammation (ACD)*
- **Hormonal** : *Hypopituitarism, Hypothyroidism, hypoadrenalism*



HYPOPROLIFERATIVE ANEMIA : **PRCA (I)**

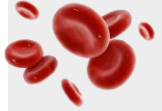
ETIOLOGY

Congenital :

- Diamond-Blackfan anemia

Acquired :

- Transient erythroblastopenia of childhood
- Idiopathic auto-immune
- Secondary chronic
 - Thymoma*
 - CLL*
 - Some solid tumors*
 - AI diseases (lupus, rheumatoid arthritis)*
 - Anti-Epo Ab (SC Eprex® in CRF)*
 - Biermer, B6 (pyridoxine) deficiency*
- Secondary transient
 - Parvovirus B19, CMV, HIV*
 - Dapsone, sulfasalazine, rifampicin*
 - Thiamphenicol, chloramphenicol*



HYPOPROLIFERATIVE ANEMIA : PRCA (2)

Biological features :

- Normocytic normochromic anemia
- Reticulocytes < 1%
- Normal WBC & platelets
- BM : *normocellular without erythroblasts*

Management :

- Transfusion
- Treat underlying condition
- Thymoma : *surgery*
- Parvovirus : *IV Ig*
- Immunosuppression : *steroids, ciclosporin, cyclophosphamide, ATG, azathioprim ...*

Prognosis :

15% spontaneous CR, 65% respond to IS, 50% relapse

HYPOPROLIFERATIVE ANEMIA

Anemias due to inadequate
endogeneous EPO

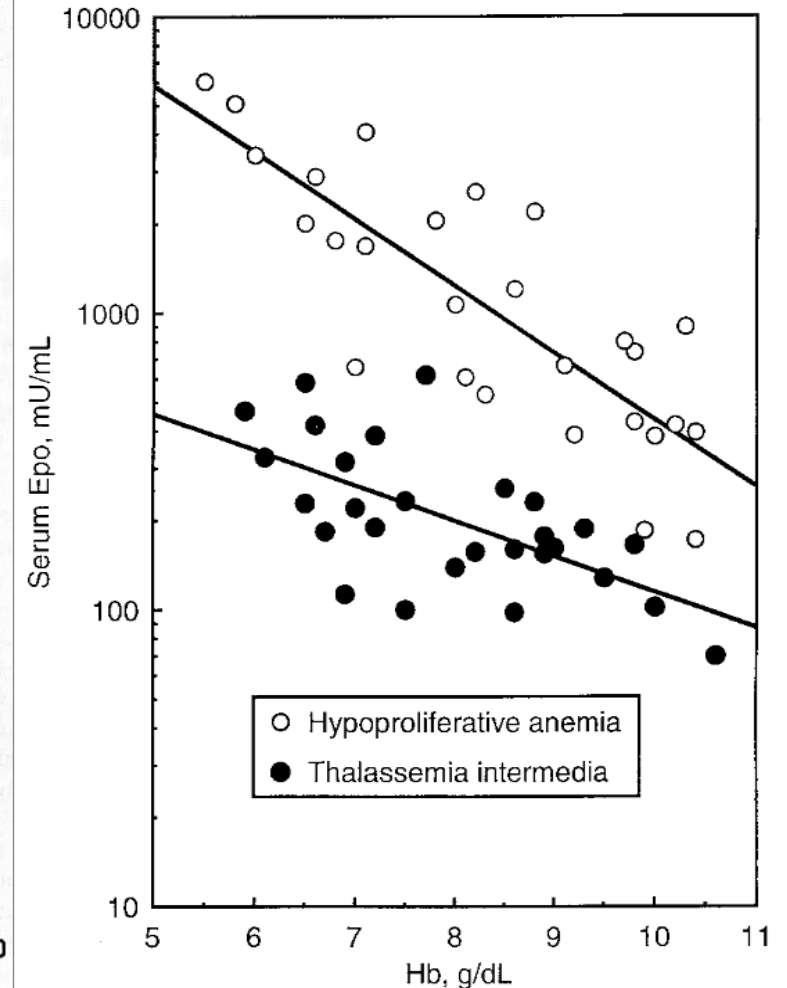
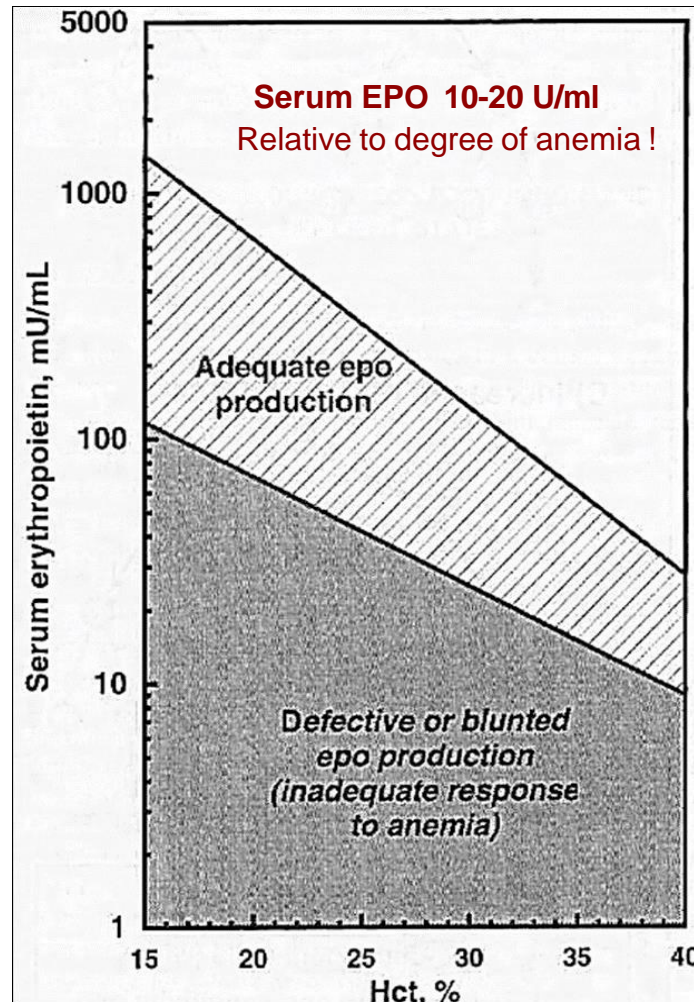


HYPOPROLIFERATIVE ANEMIA : **INADEQUATE ENDOGENEOUS EPO**

Normocytic normochromic, low retics

- Chronic renal disease
- Congestive heart failure
- Chronic inflammatory disease
- HIV infection
- Cancer
 - MM, lymphoma, some ST*
 - MDS : highly variable*
- Platinum-based chemotherapy
- Allogeneic HCT
- Premature infants
- Early pregnancy

Treatment = rHuEpo





HYPOPROLIFERATIVE ANEMIA

Anemias due to iron deficiency



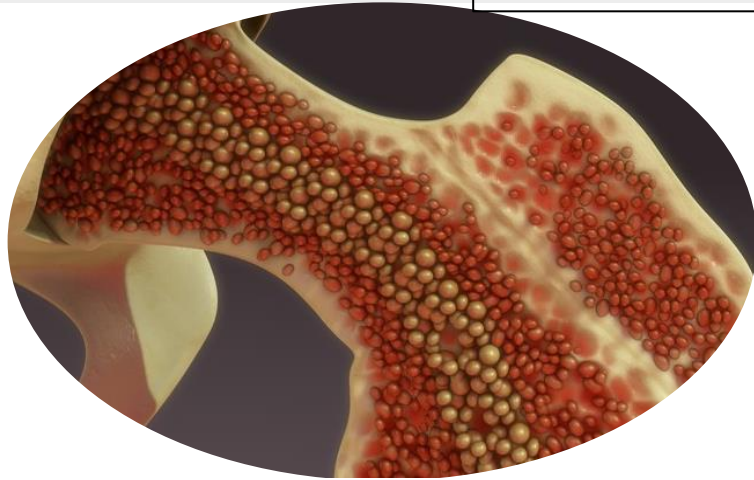
IRON METABOLISM

Regulation



IRON METABOLISM : IRON COMPARTMENTS & EXCHANGES

Total iron in the human body: 3000 - 5000 mg



**Bone marrow (300 mg)
RBC (2000 mg)**



Erythropoiesis

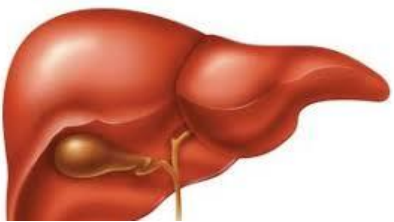
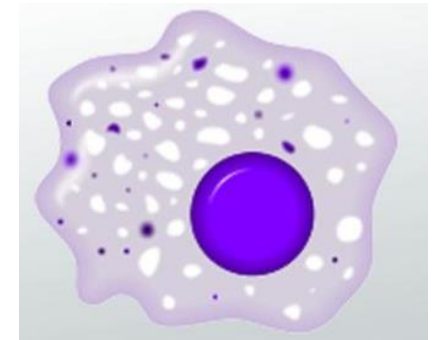
Erythrophagocytosis

Iron turnover in mg per day :
1 mg iron is lost per day

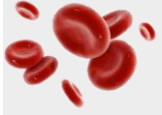
**Plasma iron bound to
Transferrin (3 mg)**

20-30 mg/day

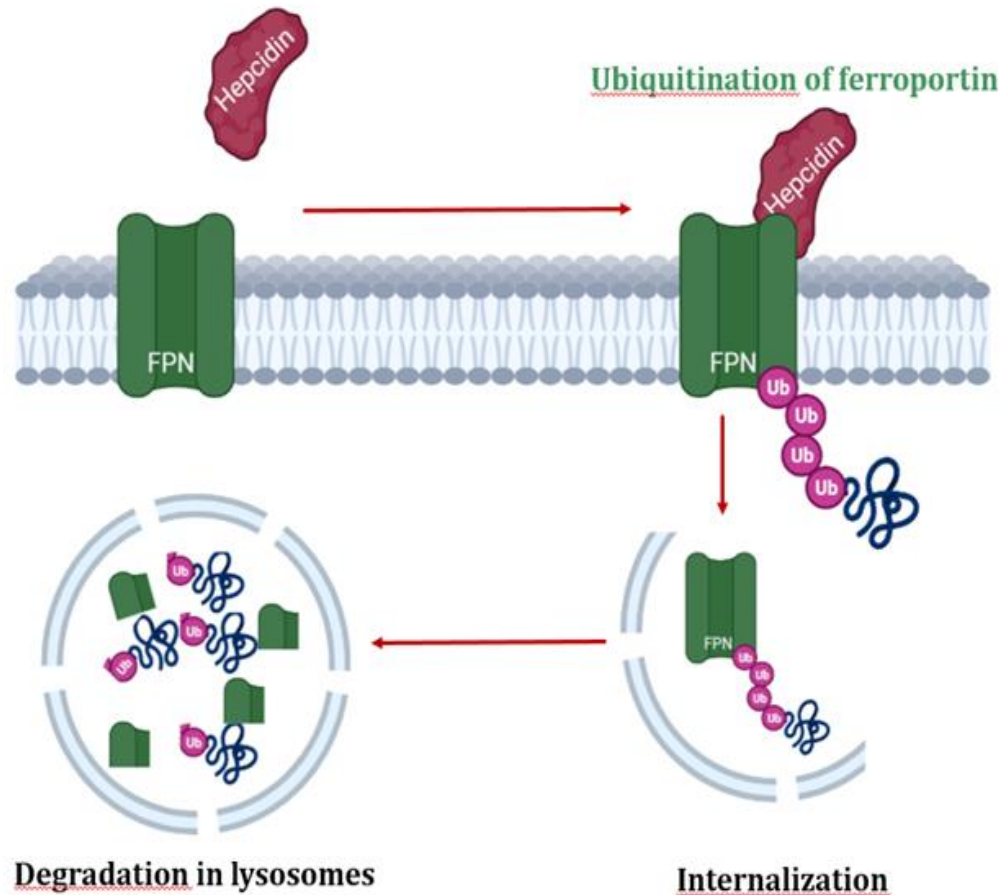
**Macrophages (200-
1800mg)**



Hepatocytes (100-1200 mg)

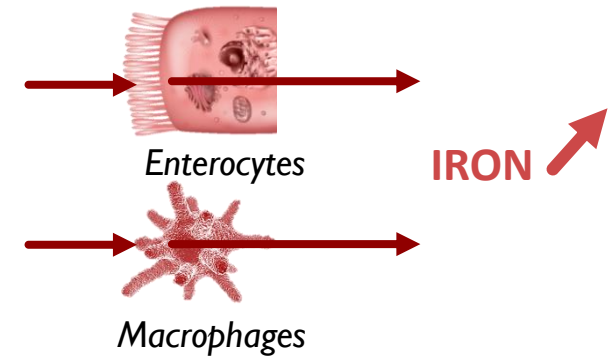


HEPCIDIN : REGULATOR OF IRON METABOLISM FUNCTION



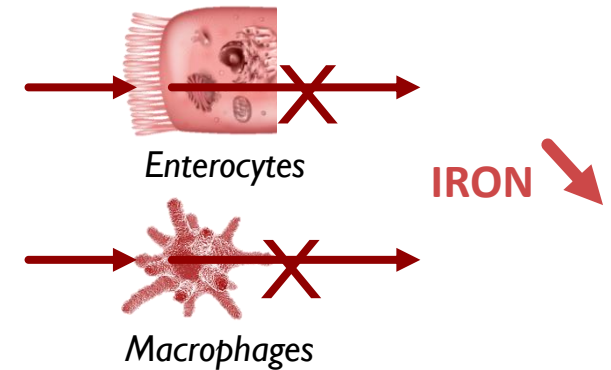
Hypoxia
Erythropoiesis
Iron deficiency

HEPCIDIN ↓



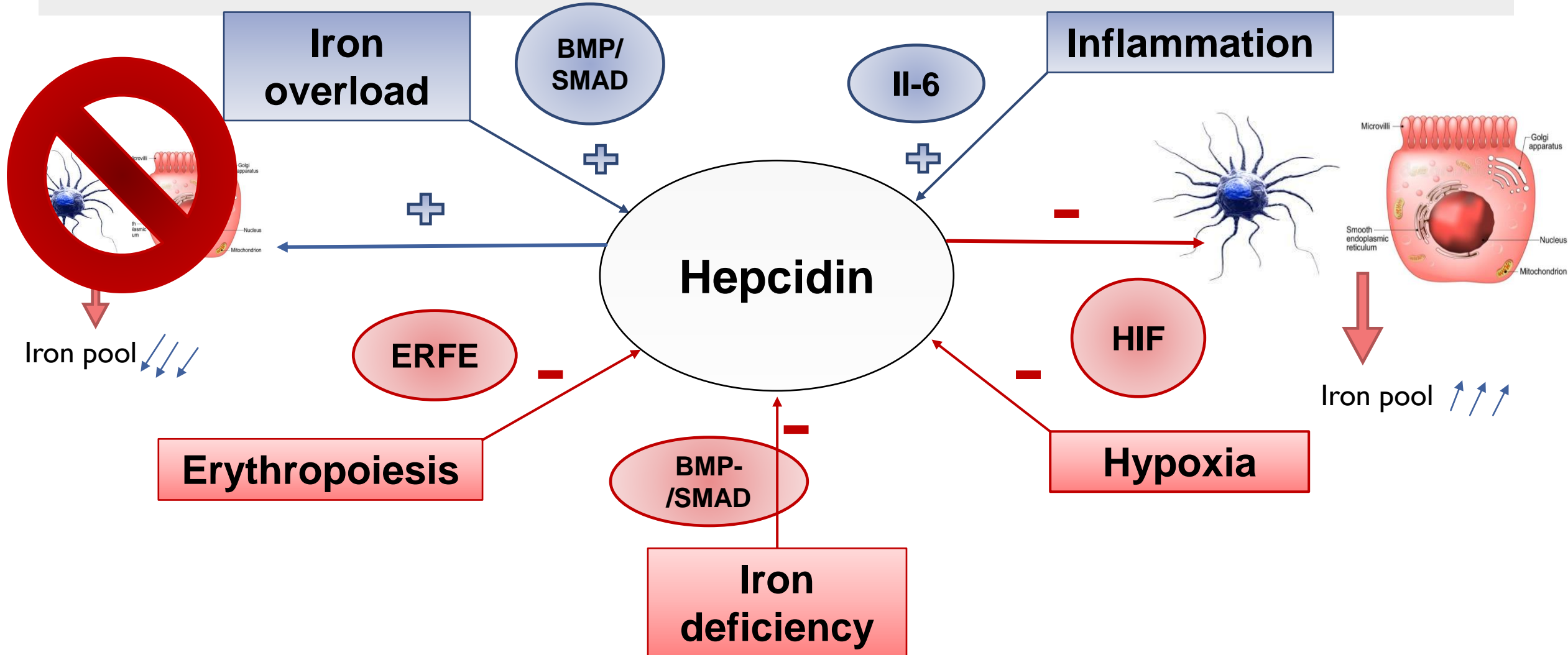
Inflammation
Iron overload

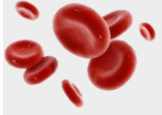
HEPCIDIN ↑



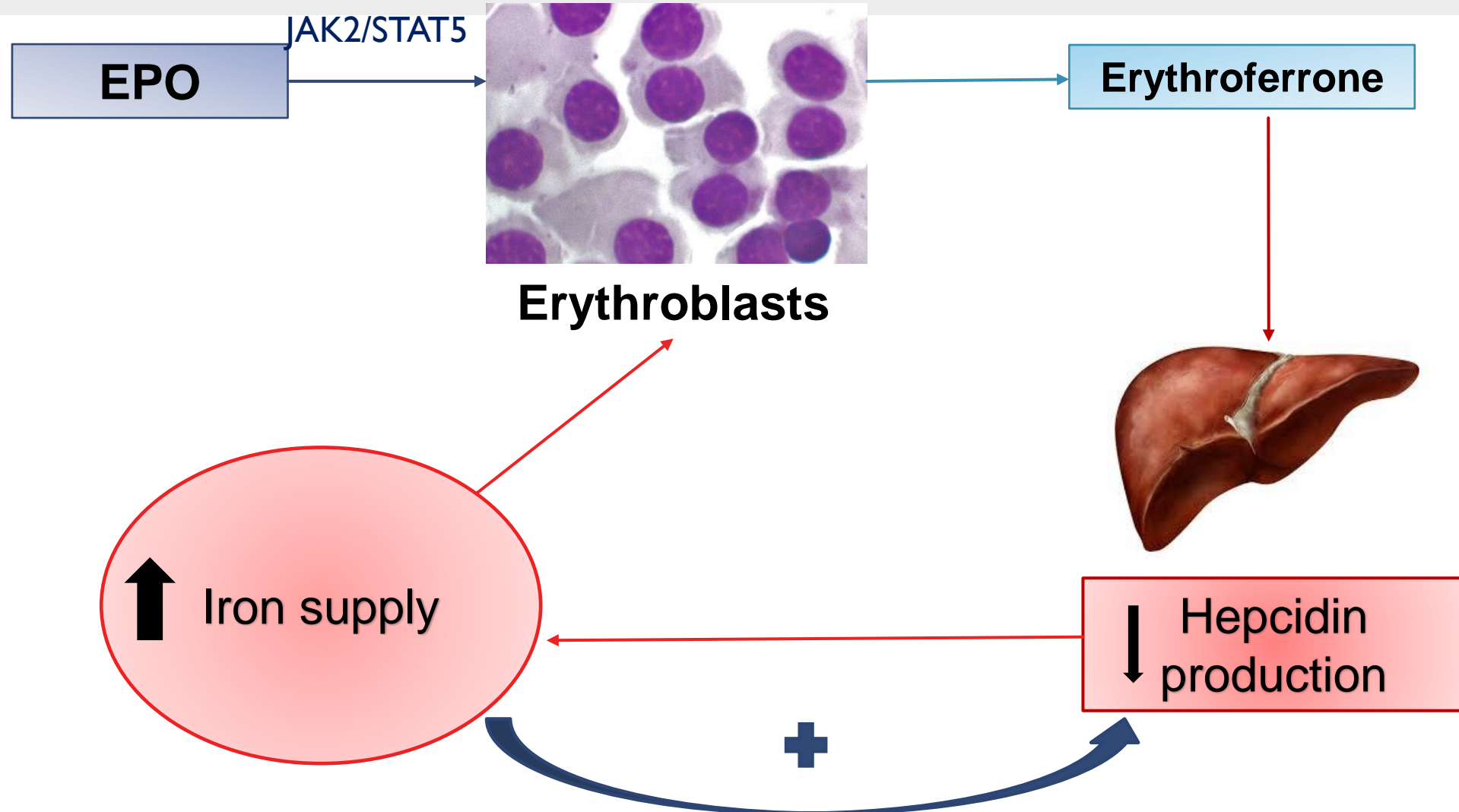


REGULATION OF HEPCIDIN PRODUCTION





REGULATION OF ERYTHROPOIESIS : EPO-ERFE-HEPCIDIN





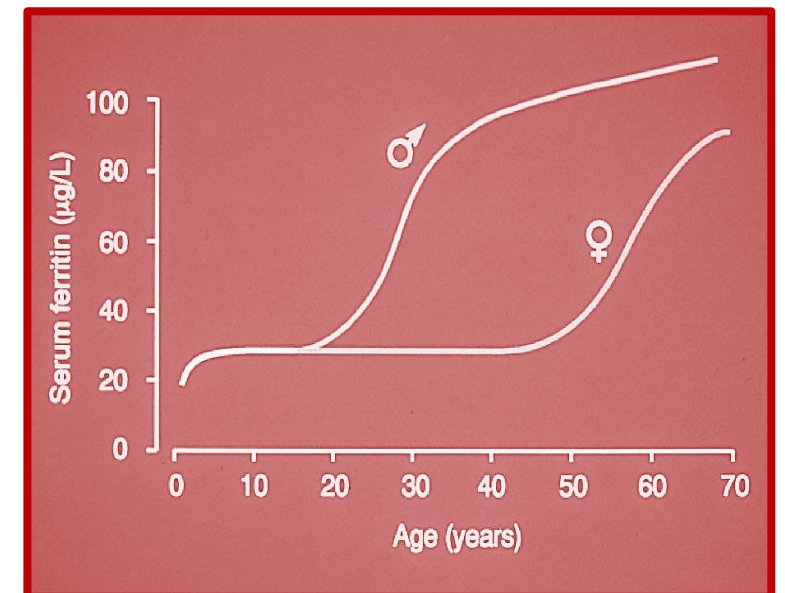
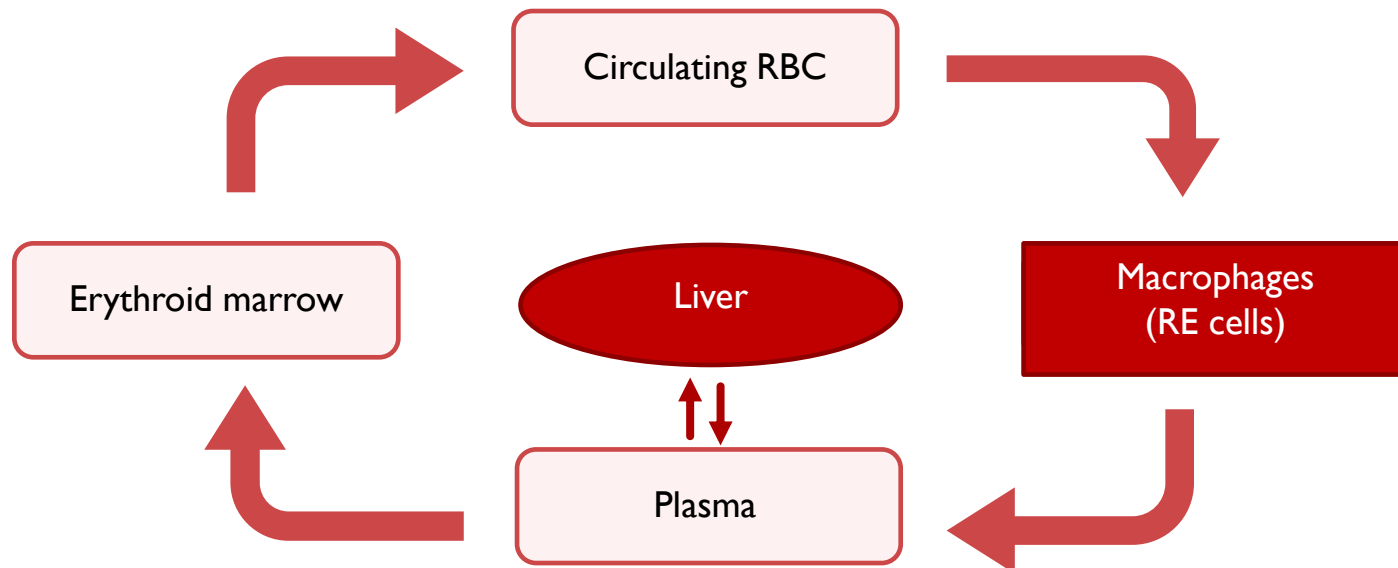
IRON METABOLISM

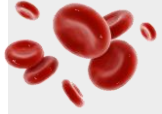
Iron parameters



FERRITIN : **SERUM FERRITIN**

- Iron stores (macrophages & hepatocytes) **1 $\mu\text{g/L}$ = 120 $\mu\text{g/kg}$ storage iron**
- Low ferritin **< 20 $\mu\text{g/L}$ (12-30 according to assay)**
→ **100% specific for iron deficiency**
- Normal range varies with age and sex
- No circadian variation





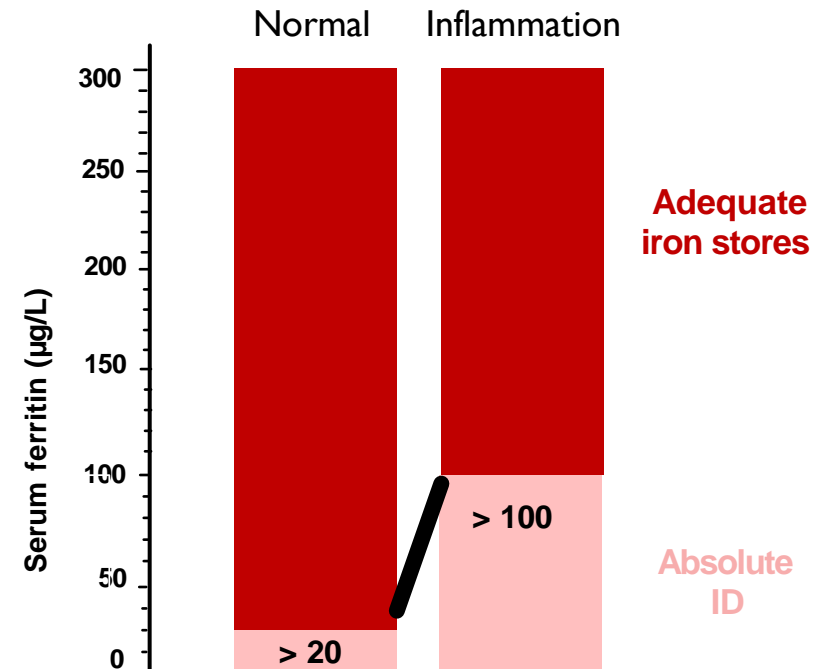
FERRITIN : SERUM FERRITIN INTERPRETATION

Conditions with falsely elevated serum ferritin :

- Inflammation (including cancer)
 - Lower limit = 100 (40–120) $\mu\text{g/L}$*
 - Lower levels = absolute ID in cancer*
- Liver damage
- Severe renal failure (lower limit 40–100 $\mu\text{g/L}$)
- Some types of cancer (e.g. neuroblastoma)
- Hyperthyroidism
- Poorly controlled diabetes mellitus (ferritin glycosylation)
- Hyperferritin-cataract syndrome
- Benign hyperferritinemia ?

Absolute ID = no iron stores

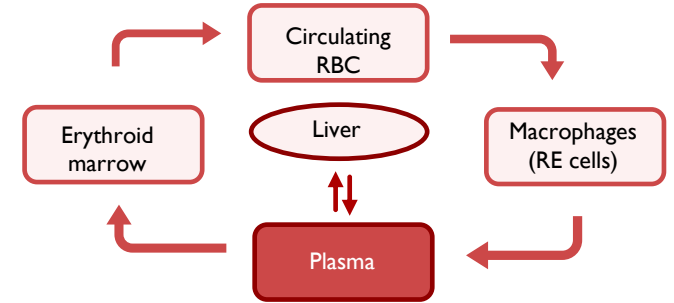
FERRITIN **< 20 $\mu\text{g/L}$ in normal individual**
< 100 $\mu\text{g/L}$ in cancer patient





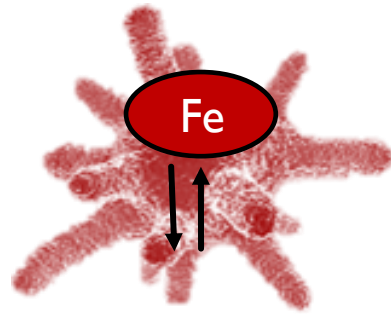
TRANSFERRIN SATURATION : **NORMAL**

SeFe	8-30 $\mu\text{mol/L}$
Tsat	20-45 %



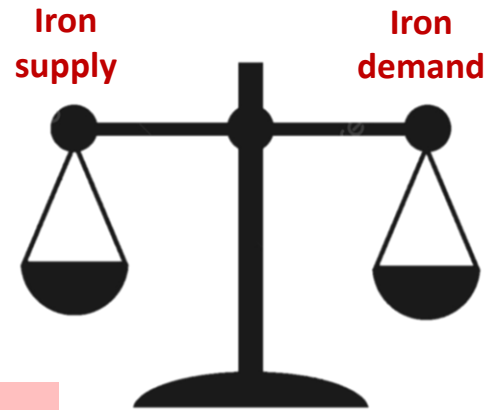
Red blood cells

Senescent RBCs taken-up by macrophages



Macrophages

Recycling and storage of iron from red blood cells



Plasma Transferrin

Dynamic equilibrium of transferrin saturation

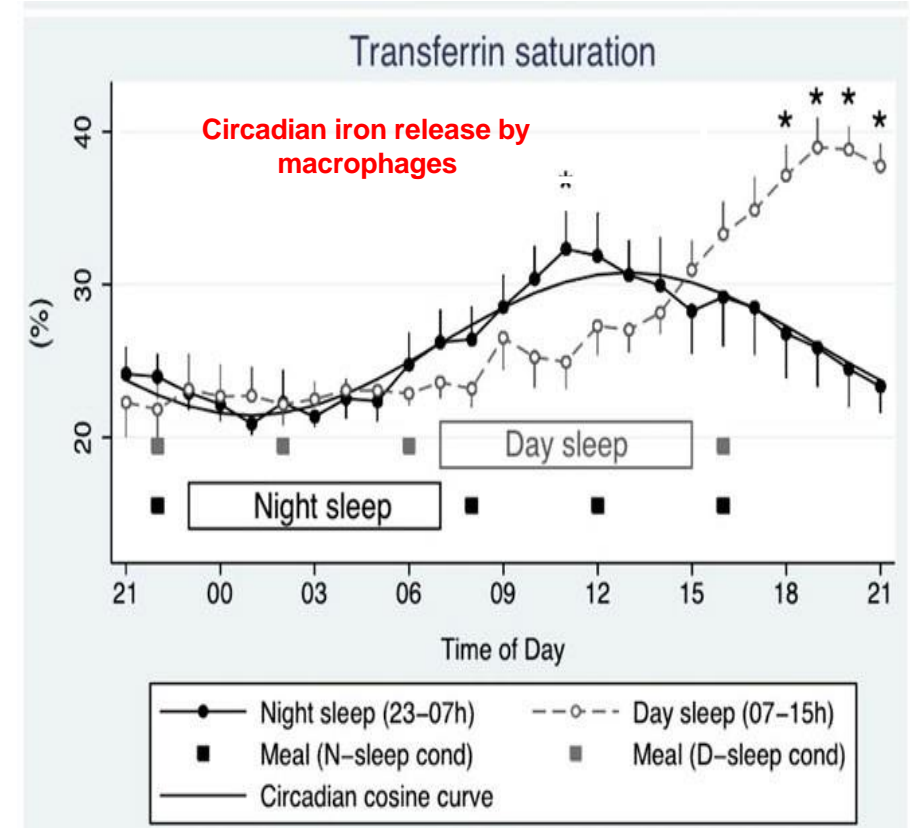
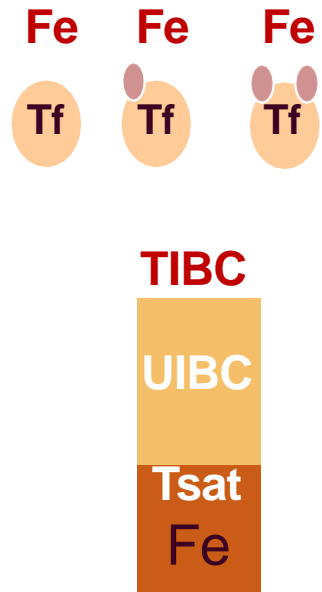
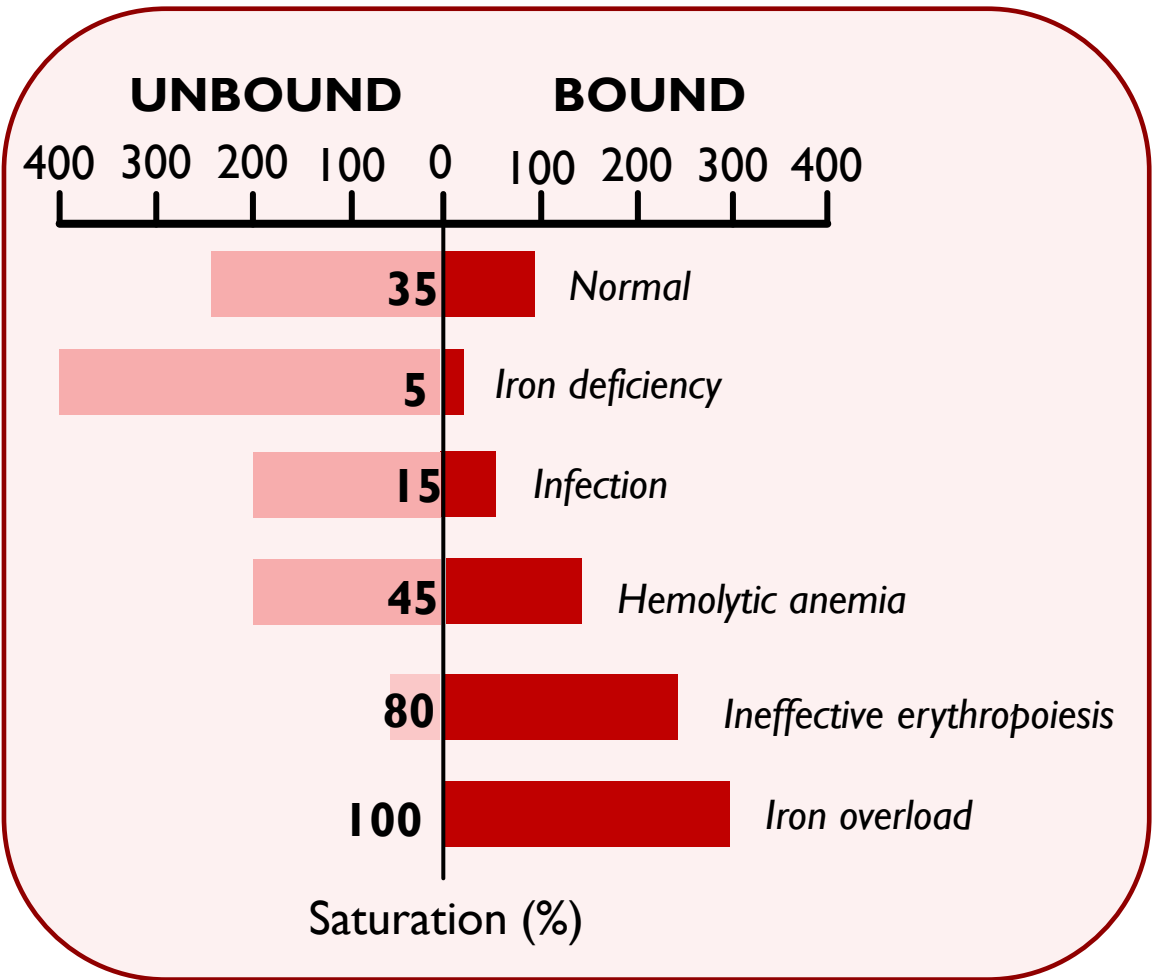


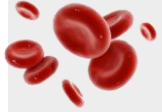
Marrow

Sufficient iron available for erythropoiesis



TRANSFERRIN SATURATION : PATHOLOGY & CIRCADIAN RYTHM



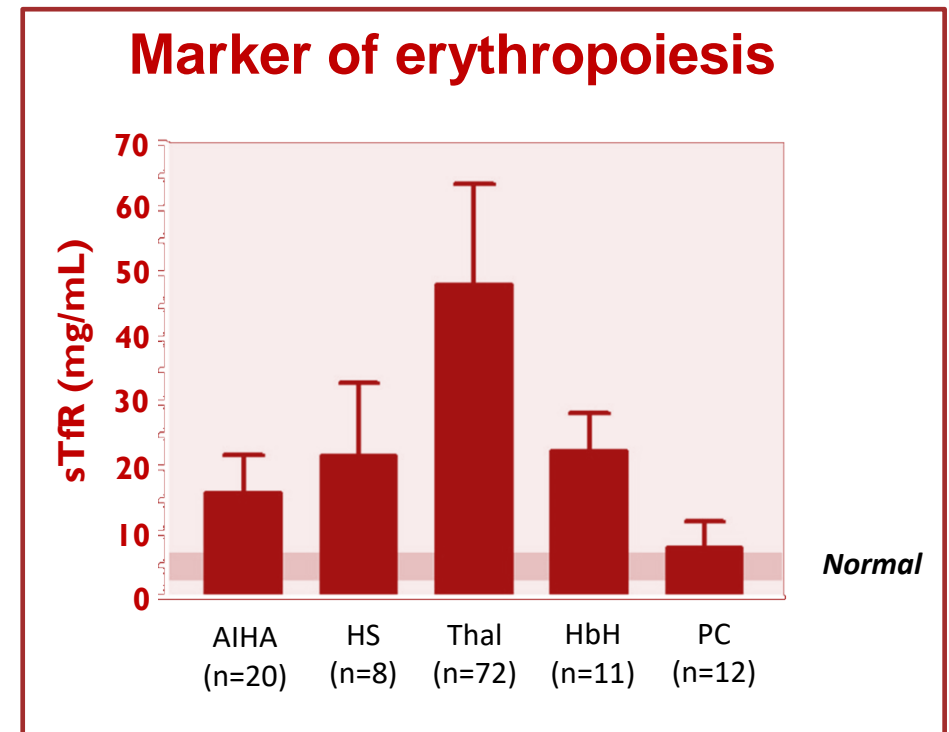
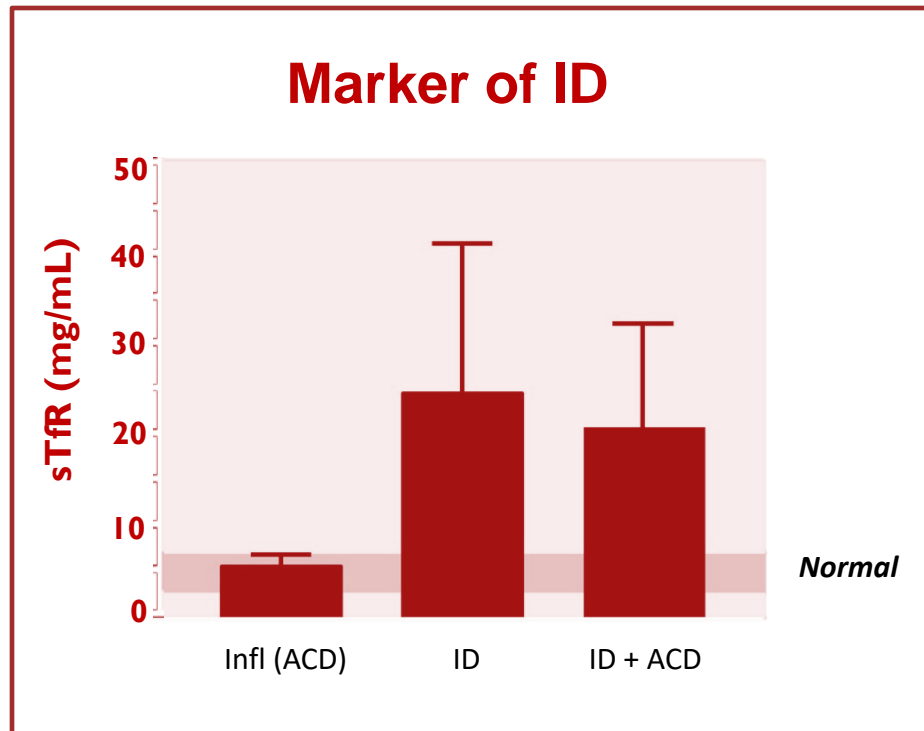


TRANSFERRIN SATURATION : (FUNCTIONAL) IRON DEFICIENCY



SOLUBLE TRANSFERRIN RECEPTOR : *INFL* vs. *ID* vs. *COMBINED INFL+ID*

sTfR 3-7 $\mu\text{g/l}$





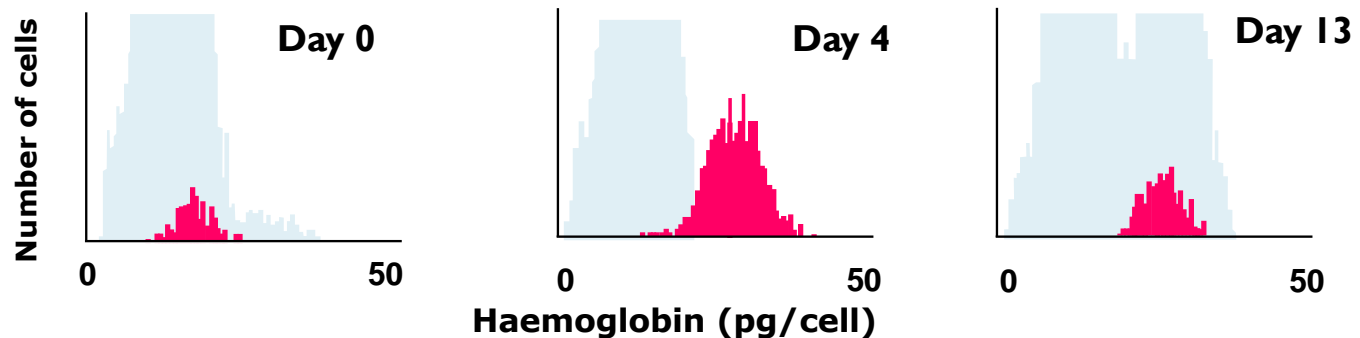
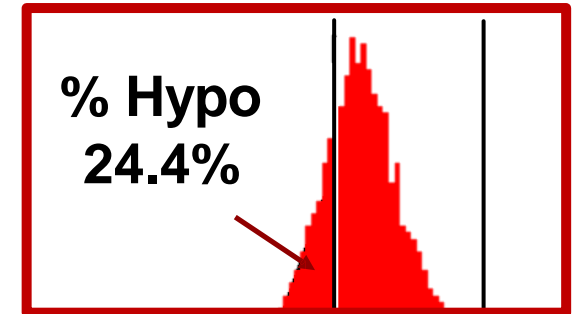
RBC INDICES : % HYPO & CHR

Hypochromic erythrocytes :

- Normal : < 5%
- ID erythropoiesis : > 5-10%
→ long term indicator of ID erythropoiesis (RBC lifespan : 120 d)

HB content of reticulocytes (CHr) :

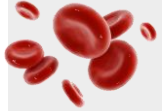
- Normal : 28-32 pg
- ID erythropoiesis : < 28 pg
→ short term indicator of ID erythropoiesis (Retic lifespan : 4 d)



MCH
CHr

HYPOPROLIFERATIVE ANEMIA

Anemias due to **absolute** iron
deficiency



IRON DEFICIENCY ANEMIA : SYMPTOMS AND SIGNS DUE TO ANEMIA

- Pallor (nailbeds, mucous membranes, palmar creases, conjunctivae)
- Asthenia, fatigue when exercising
- Exercise dyspnea (**hyperventilation**)
- Palpitations, forceful systolic murmur, forceful apical impulses, hyperactive heart sounds (**increased cardiac pace/output**)
- Edema (**sodium retention**)
- Weakness, dizziness, syncope (**loss of vasomotor regulation**)
- Loss of appetite, indigestion (**GI hypoxia**)
- Insomnia, headache, inability to concentrate, disorientation (**CNS hypoxia**)
- Angina, claudication, severe GI / CNS symptom (**localized ischemia**)



IRON DEFICIENCY ANEMIA : SYMPTOMS AND SIGNS DUE TO ID

- **Pregnancy** : prematurity
- **Infancy** : impaired psychomotor development
- **Childhood** : altered scholastic performance, attention deficit
- Asthenia, muscular weakness
- Cardiac failure
- Nail anomalies : flattening, koilonychia
- Atrophy of lingual papillae, angular stomatitis, dysphagia
- Gastritis, achlorhydria
- Pica : pagophagia
- Impairment of cell-mediated immunity and bacterial killing (*no increased risk of infection, protection against malaria*)
- Increased absorption of toxic cations (Pb, Cd, Al...)
- Thrombocytosis



IRON DEFICIENCY : ETIOLOGY

Decreased iron intake :

- Inadequate diet : malnutrition, vegetarianism
- Impaired intestinal absorption :

Stomach : *achlorhydria (PPI, H2 blockers...)*
gastrectomy, duodenal bypass, bariatric surgery autoimmune atrophic gastritis, H. Pylori infection pica

Duodenum : *celiac disease*
chronic inflammation, CKD, cancer : hepcidin
genetic IRIDA (iron-resistant IDA) : hepcidin

Increased iron requirements

- Childhood (prematurity, growth)
- Pregnancy
- EPO therapy

Increased iron losses

Blood
losses

Limited
supply

Increased
needs



IRON DEFICIENCY : ETIOLOGY - INFANT

Decreased total body iron at birth

- Prematurity
- Twins
- low birth weight (< 2.5 kg)
- early clamping of cord
- feto-maternal hemorrhage

Growth

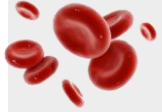
- particularly in premature infants

Inadequate diet

- cow's milk, unsupplemented formula
- Pica

Blood losses

- occult GI hemorrhage (milk allergy, Meckel's diverticulum)



IRON DEFICIENCY : ETIOLOGY – BLOOD LOSSES

Organic pathology

- **Gastrointestinal** →
- Gynecologic (excessive menstrual flow)
- Urinary (hematuria, hemoglobinuria)
- Cutaneo-mucous (telangiectasia)
- Pulmonary (alveolar hemorrhage)

Disorders of hemostasis, anticoagulants

Runner's anemia

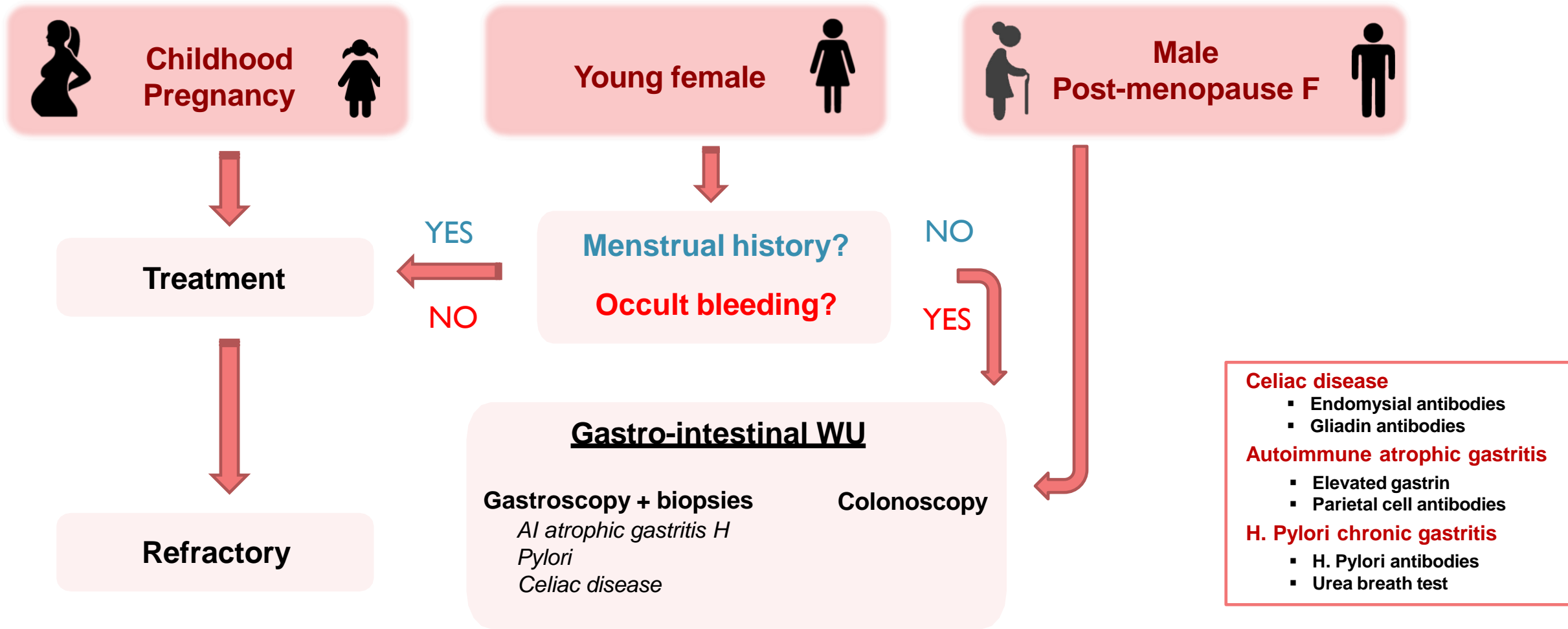
Blood donation, blood tests, hemodialysis

Self-induced bleeding

Hiatal hernia
Peptic ulcer
Corticosteroids, NSAIDs
Vascular anomaly
Milk allergy in infants
Hookworm (ankylostomiasis), schistosomiasis
MICI (ulcerative colitis)
Diverticulosis
Cancer
Hemorrhoid



IRON DEFICIENCY : WORK-UP





IRON DEFICIENCY : PREVENTION PREGNANCY

First half of pregnancy

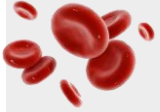
- Multiparity
- Twin or multiple pregnancy
- Low socio-economical status
- Diet low in meat and ascorbic acid
- Ferritin < 80-100 µg/L
- Adolescent
- Chronic blood loss, menorrhagia, blood tests, aspirin

Second half of pregnancy

- All women

60 mg elemental iron daily

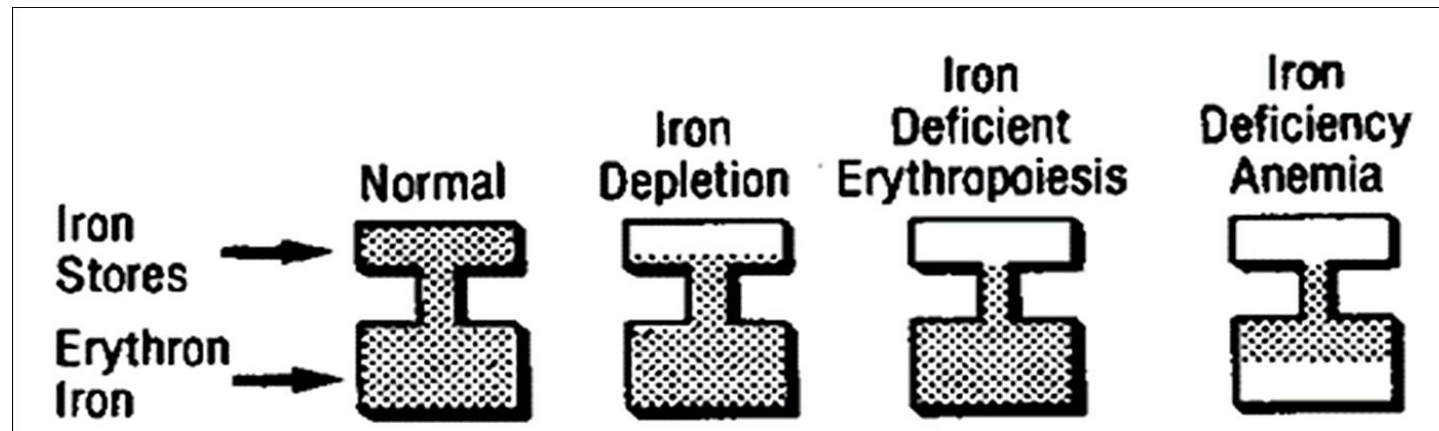
120 mg elemental iron qod



IRON DEFICIENCY : WU & TREATMENT

Two simultaneous tasks :

- **Diagnosis & treatment of underlying cause**
- **Treatment of iron deficiency**
 - (1) *Correction of anemia*
 - (2) *Restoration of adequate iron stores : ferritin > 100 µg/L*
 - (3) *Prevention of relapse (in some cases)*





IRON DEFICIENCY : TREATMENT – ORAL IRON

Ferrous salts >< Ferric salts not absorbed (well tolerated)

Better absorbed when given between meals in 1 single dose

Better tolerated when given with meals in divided doses

Dose :

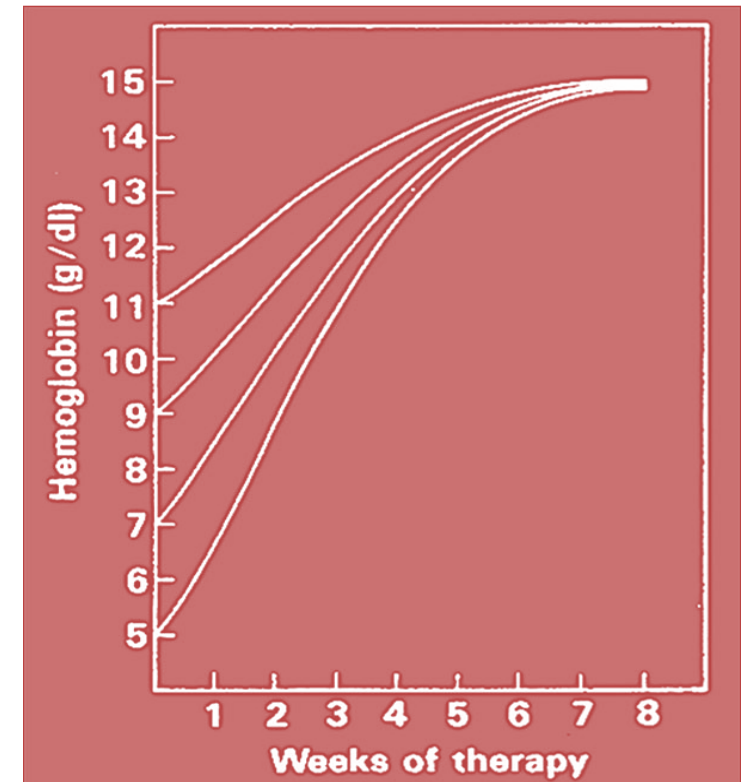
- *ID anemia : 200 mg elemental iron per day*
- *ID without anemia : 60-120 mg on alternate days (longer duration)*

Duration : 3-6 months

- *1-3 months for correction of anemia*
- *2-3 additional months for restoration of iron stores*

Side effects : gastric intolerance, diarrhea, constipation, black stools

Absorption decreased with inflammation, renal failure, cancer, achlorhydia, gastric surgery, gastritis, celiac disease





IRON DEFICIENCY : TREATMENT – ORAL IRON

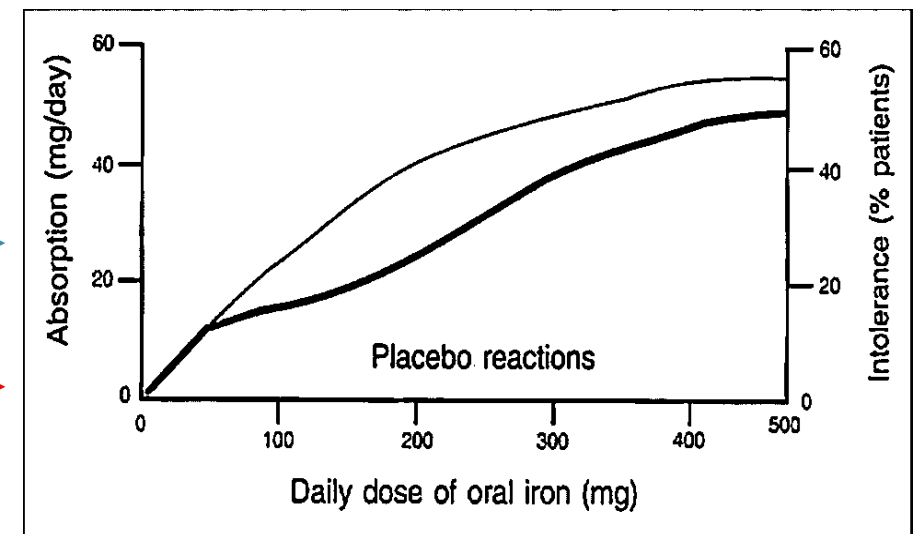
Gluconate : Losferron[®] : 3 x 1 / d = 80 mg Fe

Sulfate : Tardiferon[®] : 3 x 1 / d = 80 mg Fe
Fero-Gradumet[®] : 2 x 1 / d = 105 mg Fe
Fero-Grad 500[®] : 2 x 1 / d = 105 mg Fe
(+ ascorbate)

Pidolate : Biofer[®] = 14 mg Fe !!! : NO !

—————→
Ferrous Fe : YES !

—————→
Ferric Fe : NO !
(Ferricure[®])



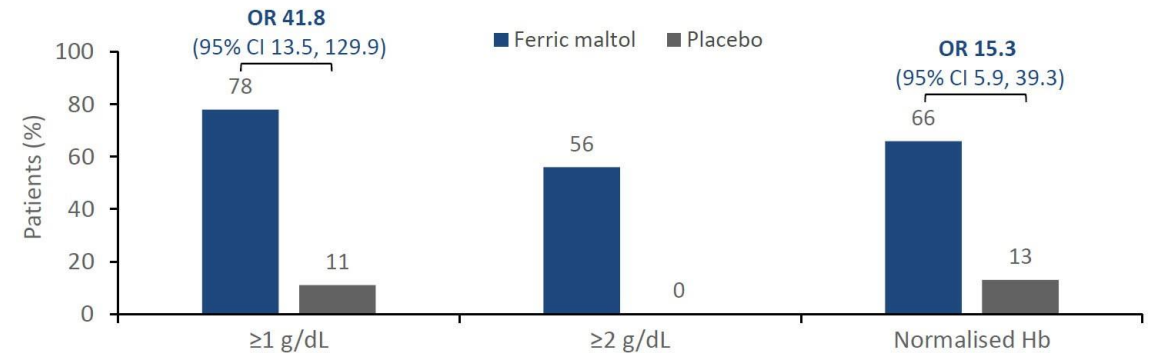
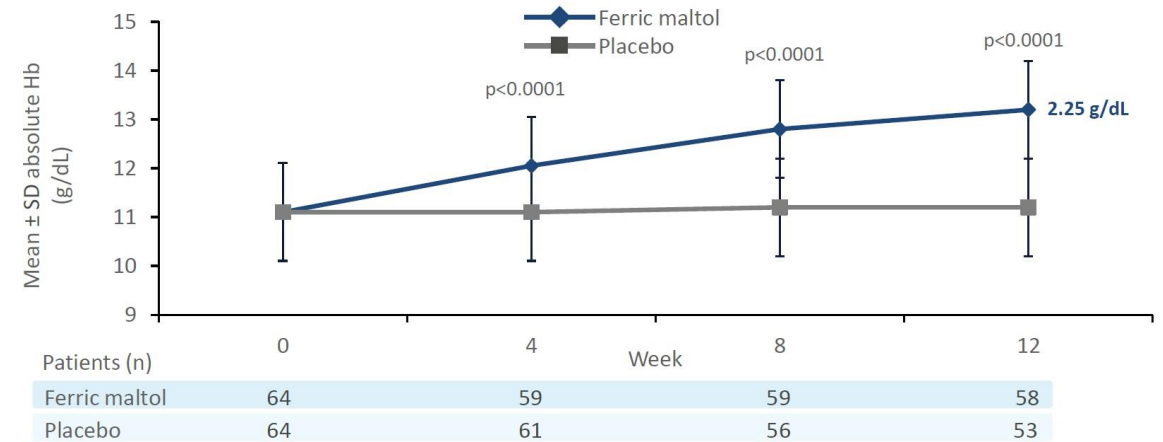
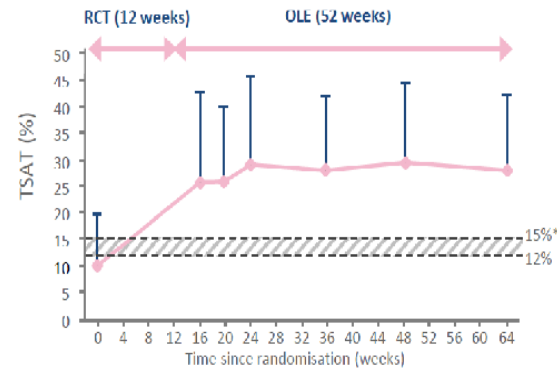
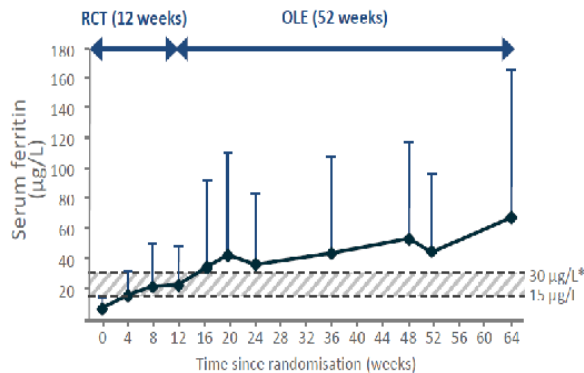


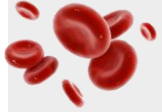
IRON DEFICIENCY : TREATMENT – FERRIC MALTOL (FERACCRU®)

Randomized trial in IBD patients

- IBD in remission or mild/moderate activity
- Ferritin < 30 µg/L
- Hb ≥ 9.5 g/dL & < 13.0 (M) or < 12.0 (F) g/dL
- Failure of ≥ 1 oral iron therapy

Ferric maltol 30 mg or placebo BID





IRON DEFICIENCY : TREATMENT – FAILURE OF ORAL IRON

EXPLANATIONS

Diagnosis or treatment not optimal

- Incorrect diagnosis
- Inadequate prescription (dose and form)
- Non-compliance / intolerance

Too high requirements

- Losses > supplements (Rendu-Osler)
- Intense erythropoiesis (ESA therapy)

Iron malabsorption

- Achlorhydia, gastritis (atrophic, HP), celiac disease, gastric surgery
- Inflammation (cancer, infection, auto-immune, CKD...)
- IRIDA (genetic)

ALTERNATIVES

Optimize oral iron therapy

Parenteral iron : IV, not IM !



IRON DEFICIENCY : TREATMENT – IV IRON

Iron sucrose

200-300 mg IV in 1 H, qw x 3

Iron carboxymaltose

1000 mg IV in 15 min

Hemoglobin iron deficit: $(\text{Hb normal} - \text{patient's Hb [g/dL]}) \times \text{weight (kg)} \times 2.4$

Where: Normal Hb = 15 (M) or 13 (F)

$2.4 = 0.0034 \times 0.07 \times 1000$ (Fe=0.34% of Hb, blood mass = 7% of weight)

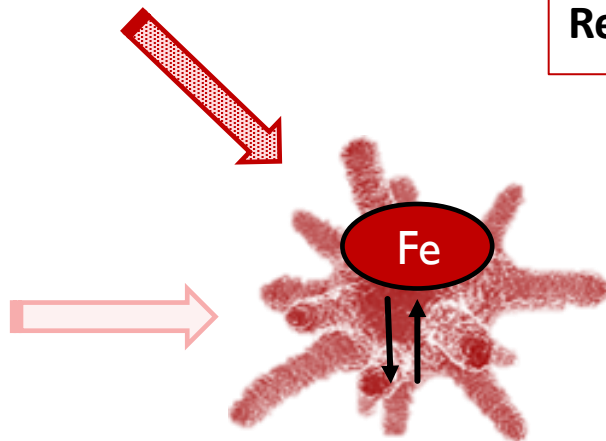
Example : men 70 kg with Hb = 8 gr/dL

$(15 - 8) \times 70 \times 2.4 = 1176 \text{ mg} + 500 \text{ mg} = 1676 \text{ mg}$

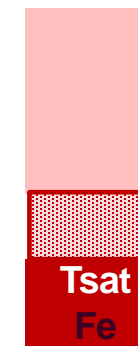
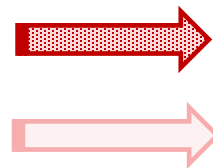
Reserve iron deficit: 500 mg



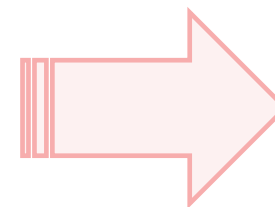
Red blood cells



Macrophages



Plasma



Marrow



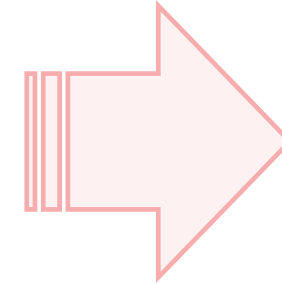
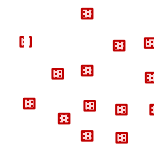
IRON DEFICIENCY : TREATMENT – SAFE IV IRON ADMINISTRATION

Do not exceed recommended dose (compound-specific)

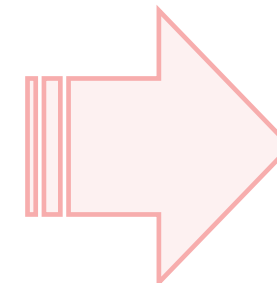
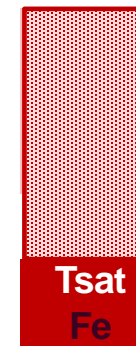
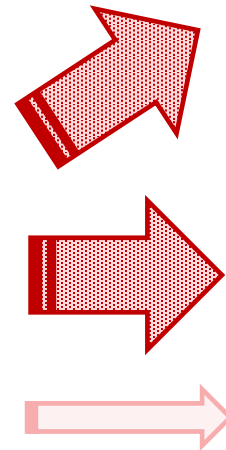
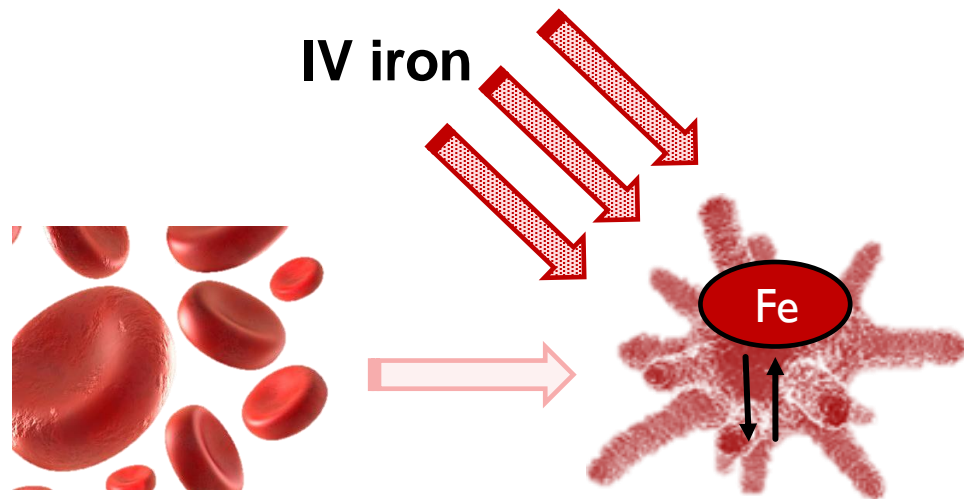
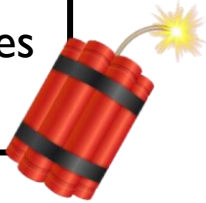
Withhold IV iron:

- On the days of chemotherapy (anthracyclins)
- During infection
- If TS > 40-50% or ferritin > 1,000 µg/L
- If severe liver dysfunction

Acute reactions / Organ damage



Endothelium
Hepatocytes
& others



Red blood cells

Macrophages

Plasma

Marrow

HYPOPROLIFERATIVE ANEMIA

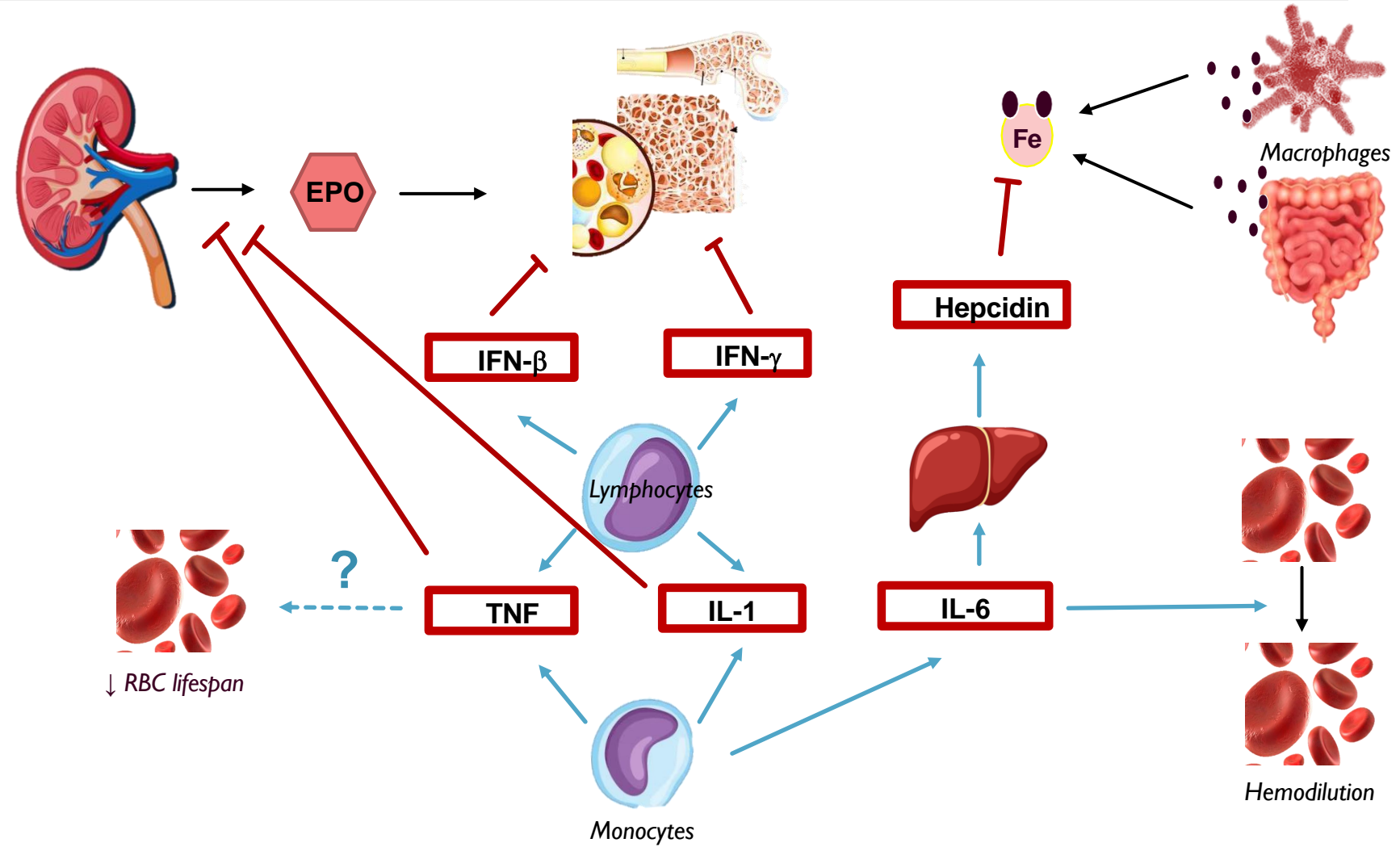
Anemias due to **functional** iron
deficiency

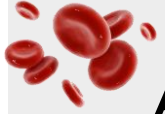


ANEMIA OF INFLAMMATION : PATHOGENESIS

Table 1. Underlying Causes of Anemia of Chronic Disease.

Associated Diseases	Estimated Prevalence* percent
Infections (acute and chronic)	18–95 ⁸⁻¹⁰
Viral infections, including human immunodeficiency virus infection	
Bacterial	
Parasitic	
Fungal	
Cancer†	30–77 ^{9,12-14}
Hematologic	
Solid tumor	
Autoimmune	8–71 ^{5,9,15,16}
Rheumatoid arthritis	
Systemic lupus erythematosus and connective-tissue diseases	
Vasculitis	
Sarcoidosis	
Inflammatory bowel disease	
Chronic rejection after solid-organ transplantation	8–70 ¹⁷⁻¹⁹
Chronic kidney disease and inflammation	23–50 ²⁰⁻²²

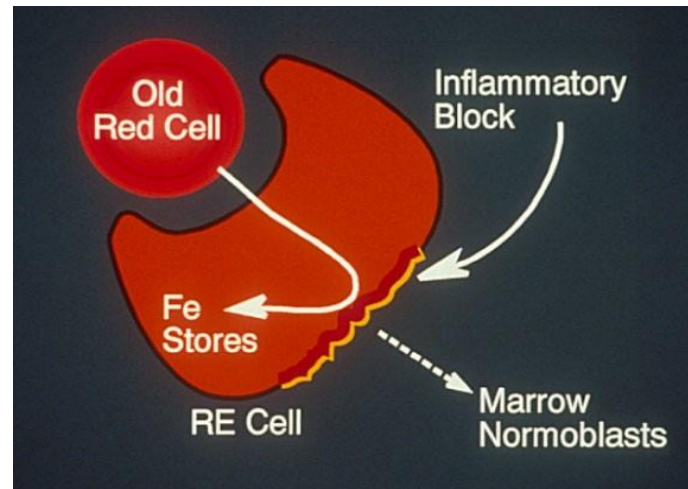




ANEMIA OF INFLAMMATION : FUNCTIONAL ID = ANEMIA OF CHRONIC DISEASE (CD)

ID erythropoiesis despite N-↑ iron stores

- Impaired iron absorption (1 mg/d)
- Reduced storage iron release (25 mg/d)



FID

- Normochromic normocytic anemia **short duration**
- Hypochromic microcytic anemia **long duration**
- ↓ SeFe & Tsat
- N (>100 µg/L)-↑ Ferritin

40-45% of cancer patients

Henry et al, Proc ASCO 2004

- Serum ferritin < 100 µg/L : **17%**
- TS < 20% : **57%**
- TS < 20% & ↑ serum ferritin : **46%**

Beguin et al, Blood 2009

- 481 adult cancer patients with CIA
- ID at baseline (ferritin <100 and/or TSAT <20%)
170 / 379 = 45 %

Ludwig et al, Ann Oncol 2013

- 1528 adult cancer patients
- ID at baseline (TSAT <20%) : **43%**



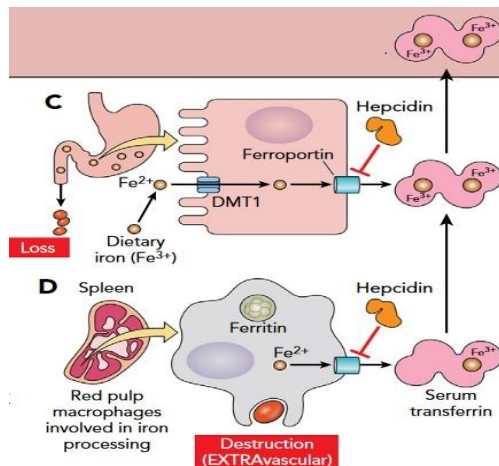
ANEMIA IN CANCER PATIENTS : PATHOGENESIS

Anemia of cancer (AOC)

Bone marrow infiltration

ACD :

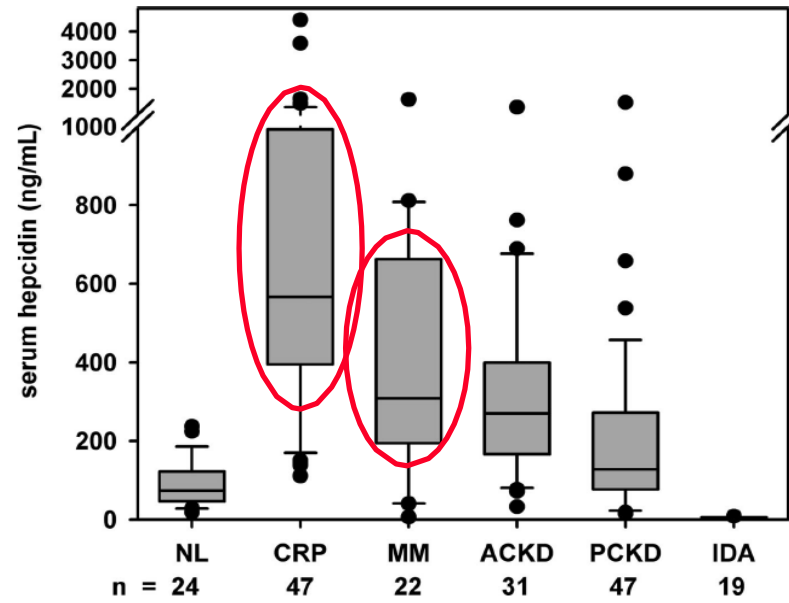
- Hemodilution
- Decreased RBC survival
- Decreased RBC production
 - Defective Epo production*
 - Inhibition of erythropoiesis*
 - Iron sequestration*



Treatment-induced anemia

Chemotherapy (CIA)

Radiotherapy



Anemia due to other causes

Increased RBC loss

- Hemodilution (spleen, hyper-γ...)
- Hemolysis (AIHA, μ-angiopathic...)
- Hemophagocytosis
- Hypersplenism
- Bleeding (GI, gynecologic...)

Impaired RBC production

- Nutrition. defic. (B12, folate...)
- Iron deficiency
- Renal dysfunction
- Marrow impairment (MDS, BM necrosis, PRCA...)

Gilreath, Blood 136:801, 2020
Ganz, Blood 112:4292, 2008

NL = normal
CRP = inflammation, MM = multiple myeloma,
ACKD & PCKD = adult & pediatric CKD (not dialyzed)
IDA = ID anemia,



EPO THERAPY

In cancer patients



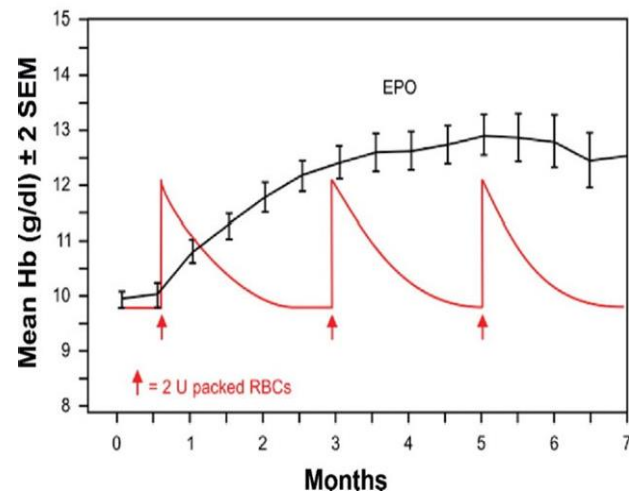
EPO THERAPY IN CANCER : **BENEFITS**

Progressive response

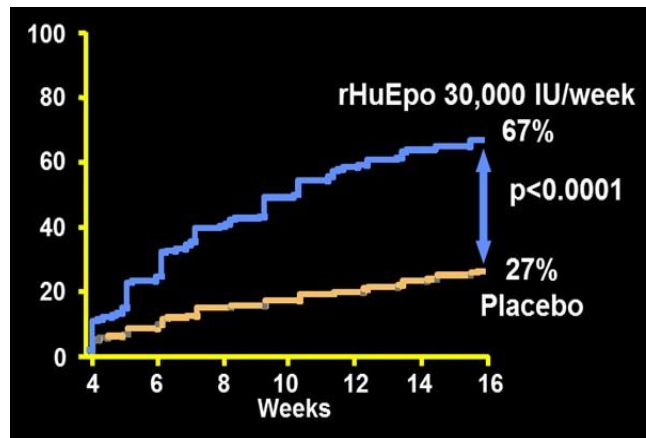
2/3 patients respond

Fewer transfusions

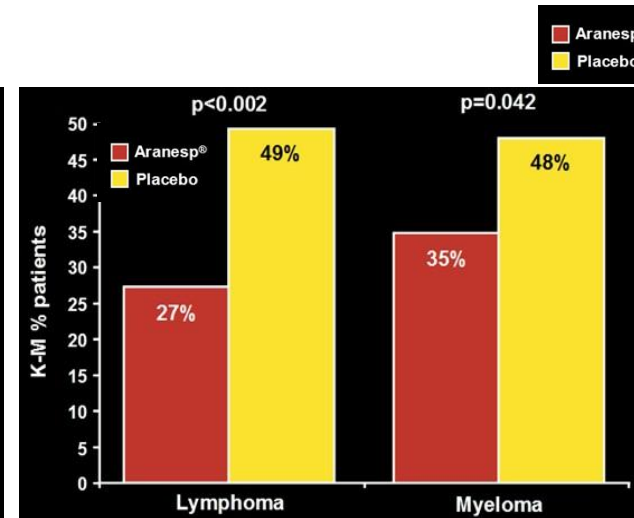
Improved QoL



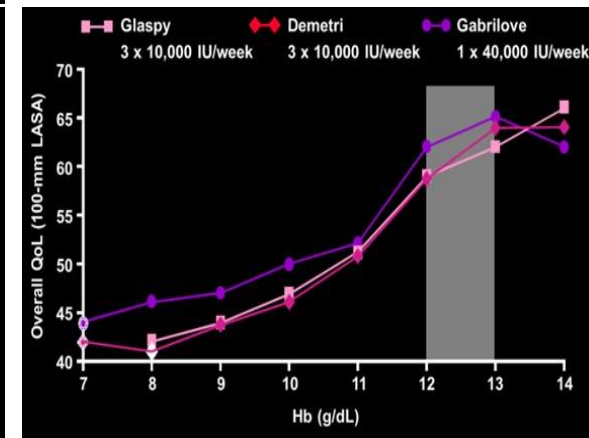
Vaupel et al, Oncologist 2008



Österborg et al. JCO 2002



Hedenus et al. BJH 2003



Glaspy, Demetri, Gabrilove JCO



EPO THERAPY IN CANCER : RESISTANCE 1/3 PATIENTS

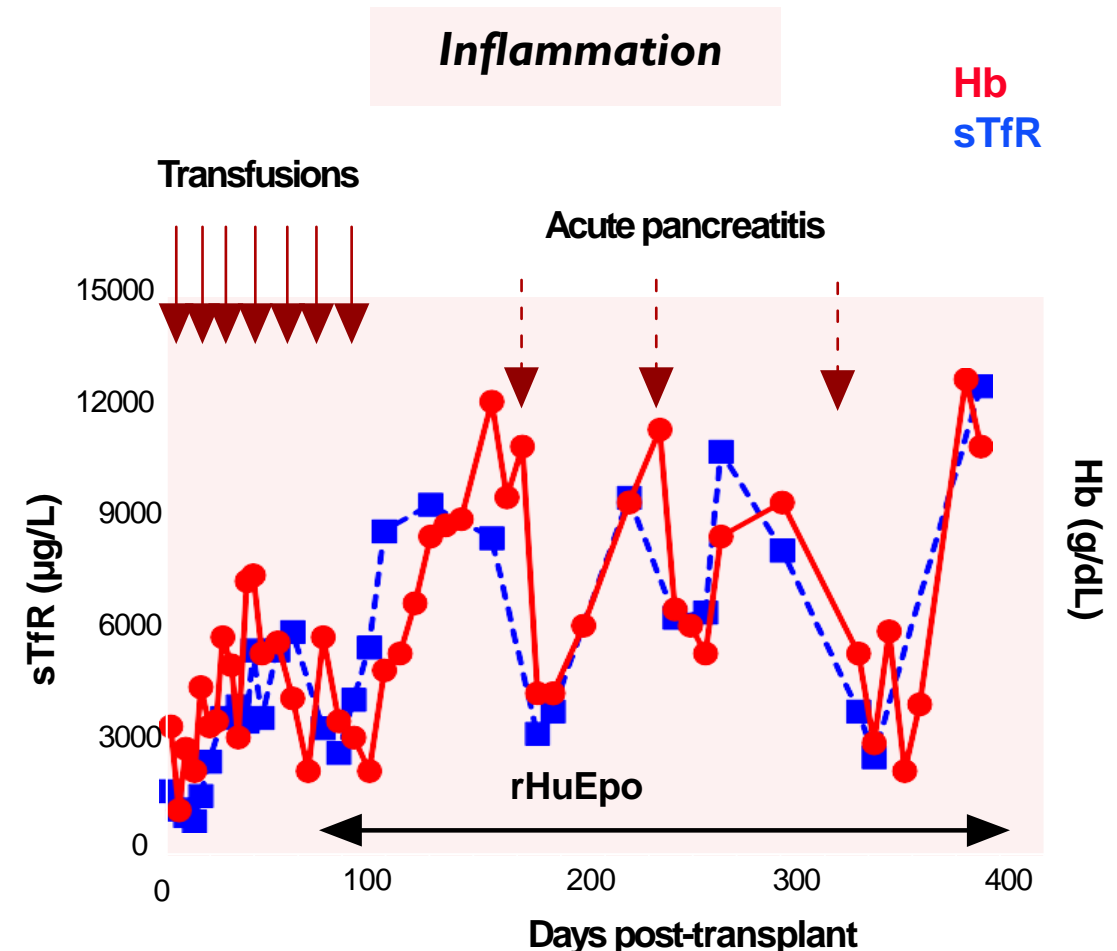
(Functional) iron deficiency

Inflammation (*incl.* infections, surgery...)

Intensive chemotherapy, impaired hematopoiesis

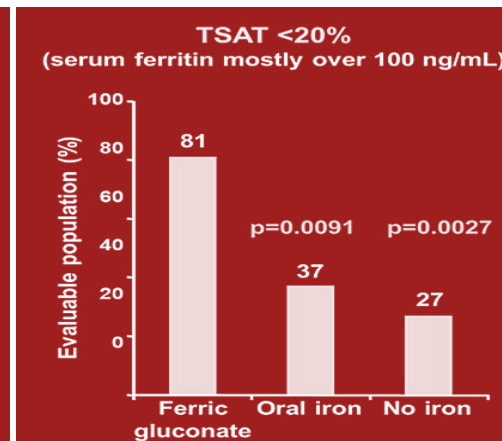
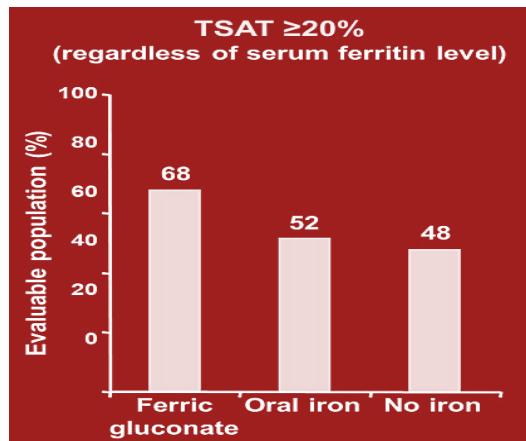
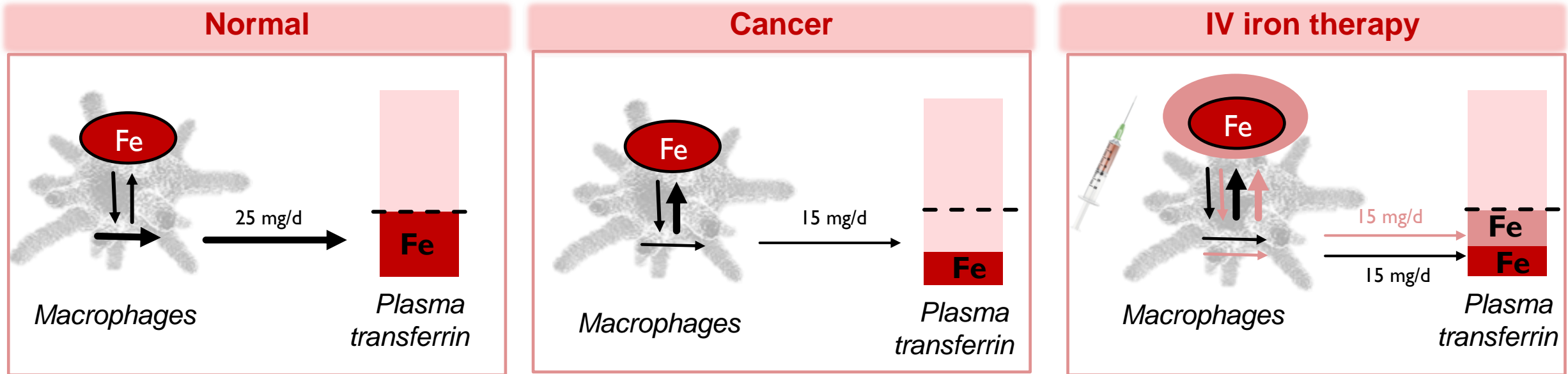
Other causes of anemia :

- Bleeding
- Hemolysis
- Marrow fibrosis, major marrow involvement
- Anti-Epo antibodies
- Folate/B12 deficiency





EPO THERAPY IN CANCER : OVERCOMING HEPCIDIN BLOCK WITH IV IRON



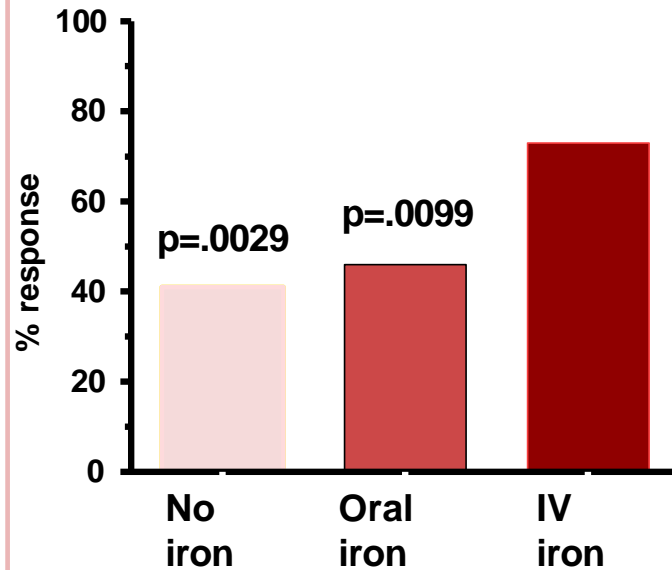
Fillet et al, Blood 74:844, 1989
Aapro et al, Ann.Oncol 23:1954, 2012
Henry et al, Oncologist 12:231, 2007



EPO THERAPY IN CANCER : IV IRON

**More Responses
+ 30%**

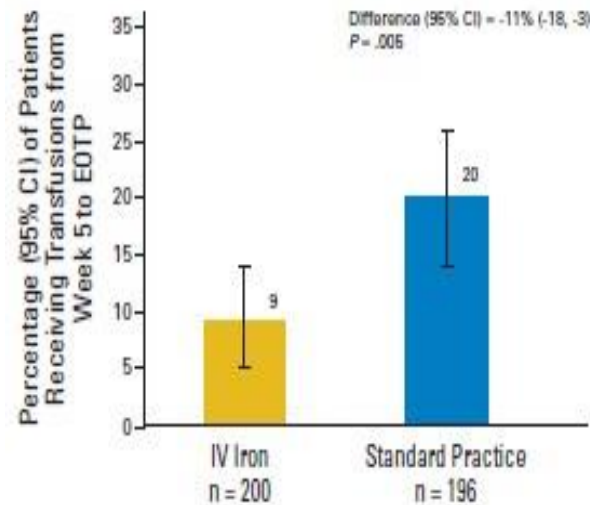
All patients : rHuEPO



Henry et al, Oncologist
12:231-242, 2007

**Fewer Transfusions
- 23%**

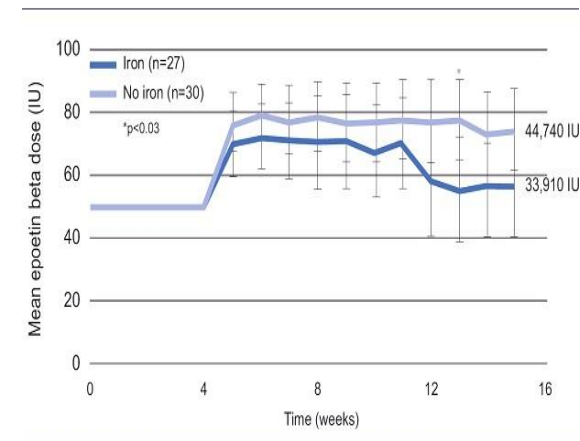
All patients : DA



Bastit et al, JCO
26:1611, 2008

**Less Epo use
- 24%**

All patients : DA



Hedenus et al, Leukemia
21:627, 2007

**Cost savings
- 13%**

All patients : DA

Drug costs

- Epo without iron 3,346 €
- Epo with iron 2,811 €
- + 91 € (iron)
- Savings = 444 €

Beguin et al, AJH
88:990, 2013



EPO THERAPY IN CANCER : ESMO GUIDELINES IN 2018

Indication

- On chemotherapy
- On radiotherapy or no anti-cancer treatment

Objectives

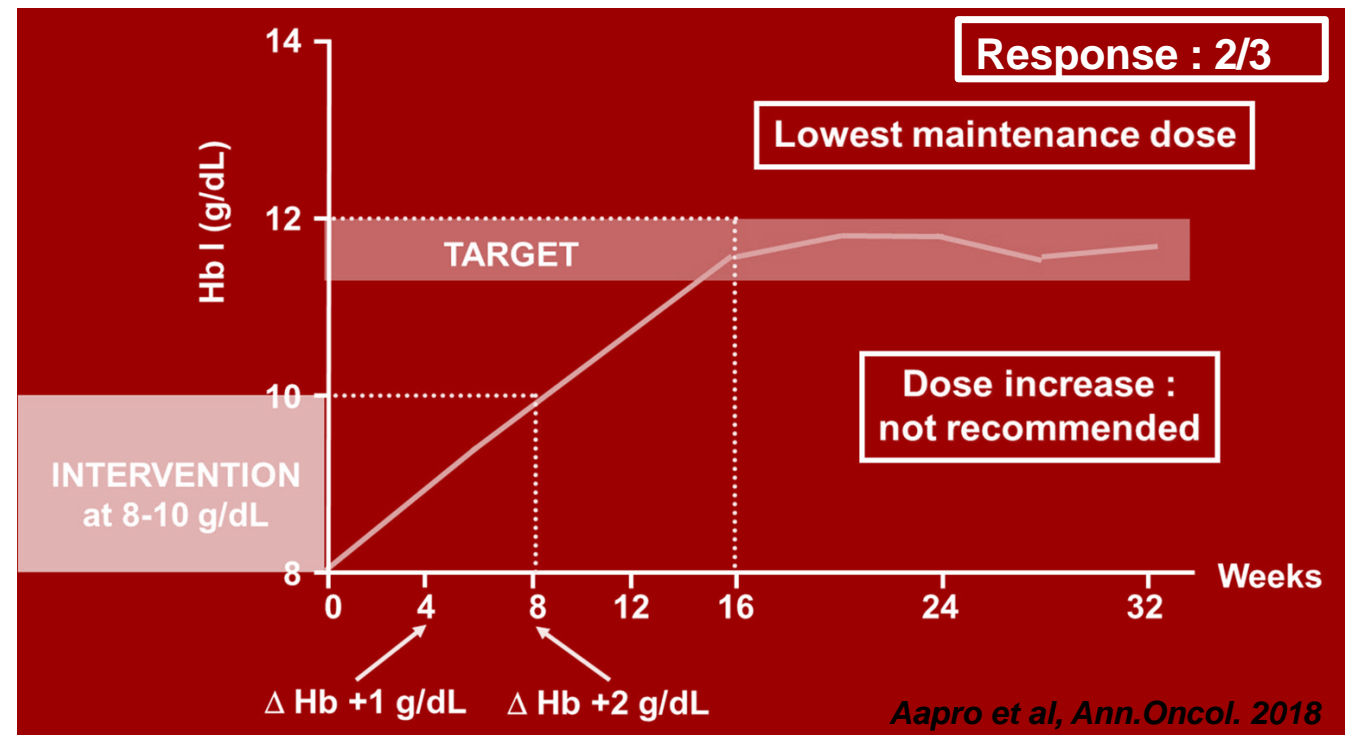
- ↓ transfusions
- ↑ QOL

Risks

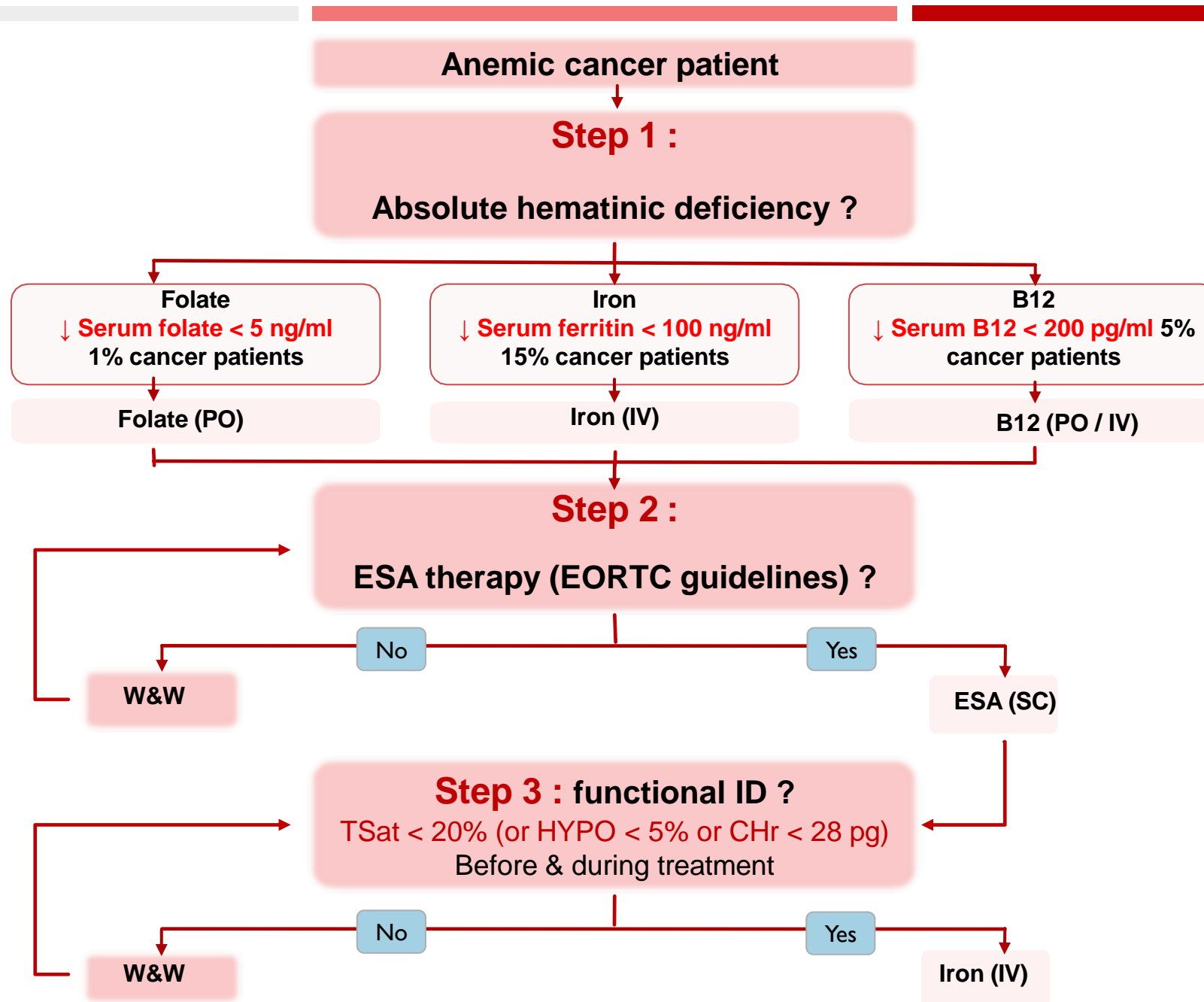
- TE event if Hb > 13
- Hypertension

Dose : SC

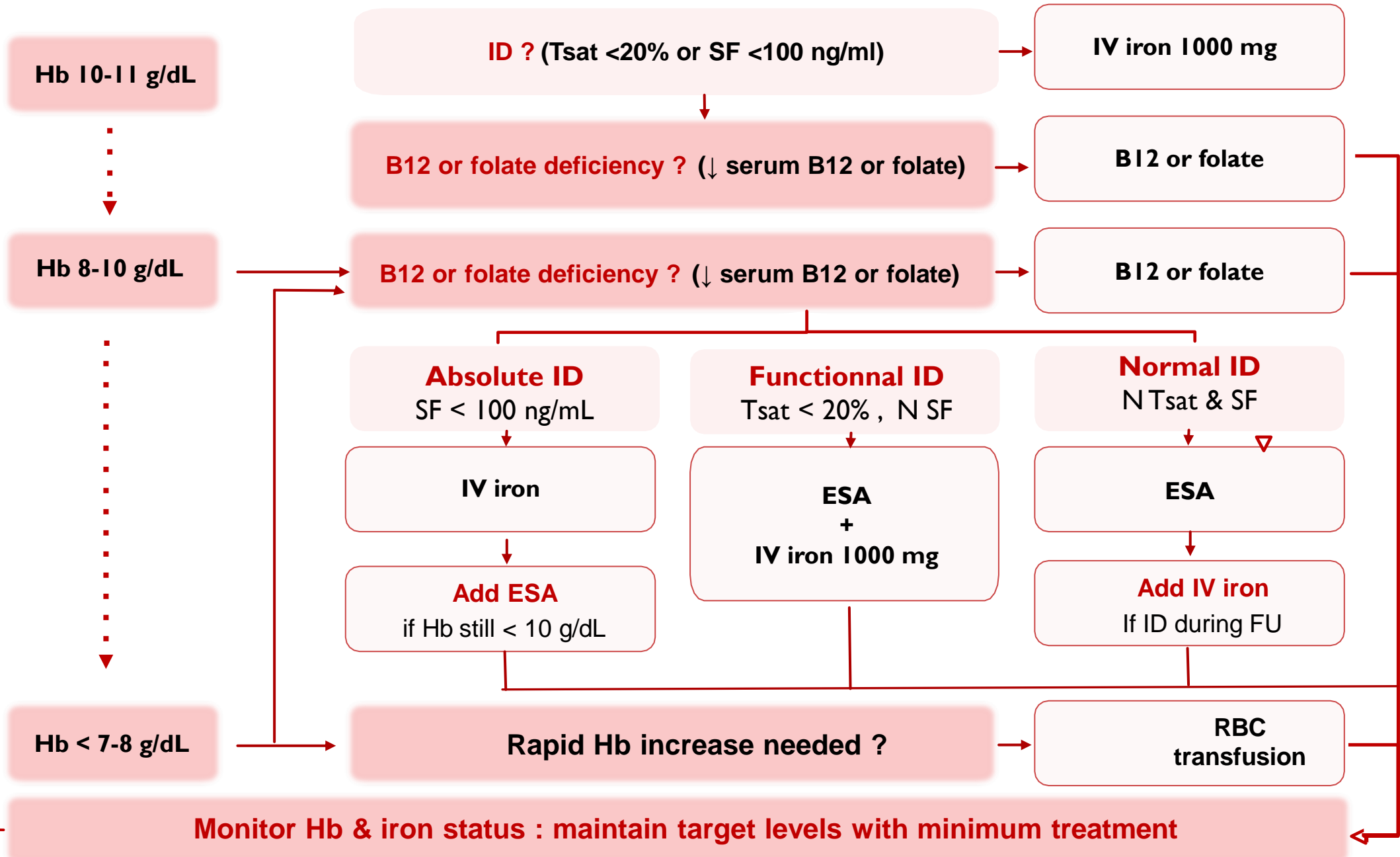
- rHuEPO (Neorecormon[®], Eprex[®])
30-40,000 U/wk (500 U/kg/wk)
- Darbepoetin (Aranesp[®])
150 µg/1 wk (2.25 µg/kg/1 wk)
300 µg/2 wks (4.5 µg/kg/2 wks) *
500 µg/3 wks (6.75 µg/kg/3 wks)



Conclusion



Assess Hb & iron status (Tsat & ferritin)
At baseline & before each chemo cycle



Hb 10-11 g/dL

Hb 8-10 g/dL

Hb < 7-8 g/dL

ID ? (Tsat <20% or SF <100 ng/ml)

IV iron 1000 mg

B12 or folate deficiency ? (↓ serum B12 or folate)

B12 or folate

B12 or folate deficiency ? (↓ serum B12 or folate)

B12 or folate

Absolute ID
SF < 100 ng/mL

IV iron

Add ESA
if Hb still < 10 g/dL

Functional ID
Tsat < 20% , N SF

**ESA +
IV iron 1000 mg**

Normal ID
N Tsat & SF

ESA

Add IV iron
If ID during FU

Rapid Hb increase needed ?

**RBC
transfusion**

Monitor Hb & iron status : maintain target levels with minimum treatment

A microscopic view of red blood cells (erythrocytes) in a blood vessel. The cells are shown as biconcave discs, with some in sharp focus and others blurred in the background. The overall color palette is dominated by various shades of red and orange, with a dark background. The text 'THANK YOU!' is overlaid in the center in a bold, black, sans-serif font.

THANK YOU !