Carence martiale des maladies chroniques

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Le fer est un élément paradoxal

- **Indispensable à la vie**
- Permet le transport d'O2
  - *Hémoglobine,*
  - *Myoglobine*

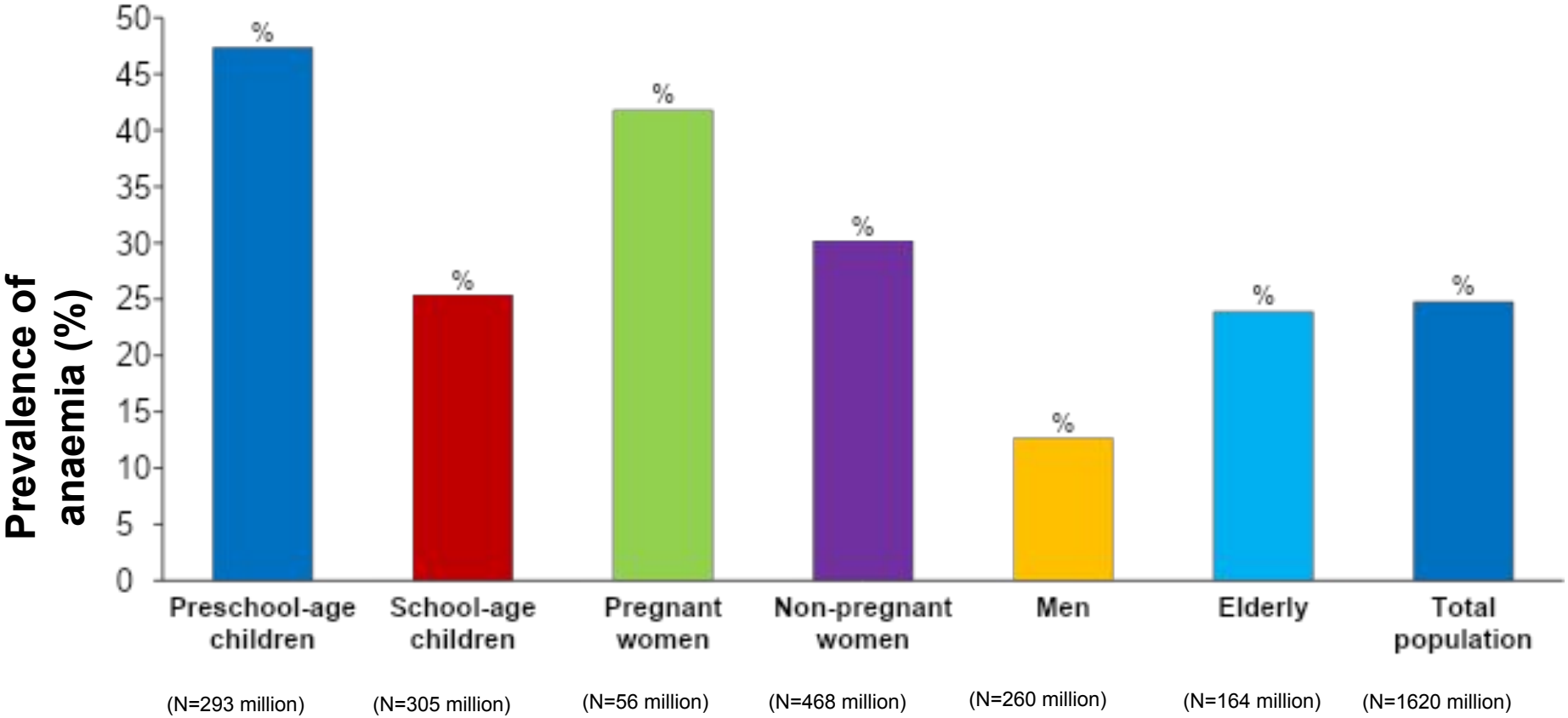
- **Potentiellement toxique**
- Peut générer un stress oxydant

$$Fe^{2+} + H_2O_2 \square Fe^{3+} + {}^{\cdot}OH + OH^-$$

- Cofacteur de nbses réactions enzymatiques,
- Constituant indispensable des protéines « héminiques », dont les cytochromes

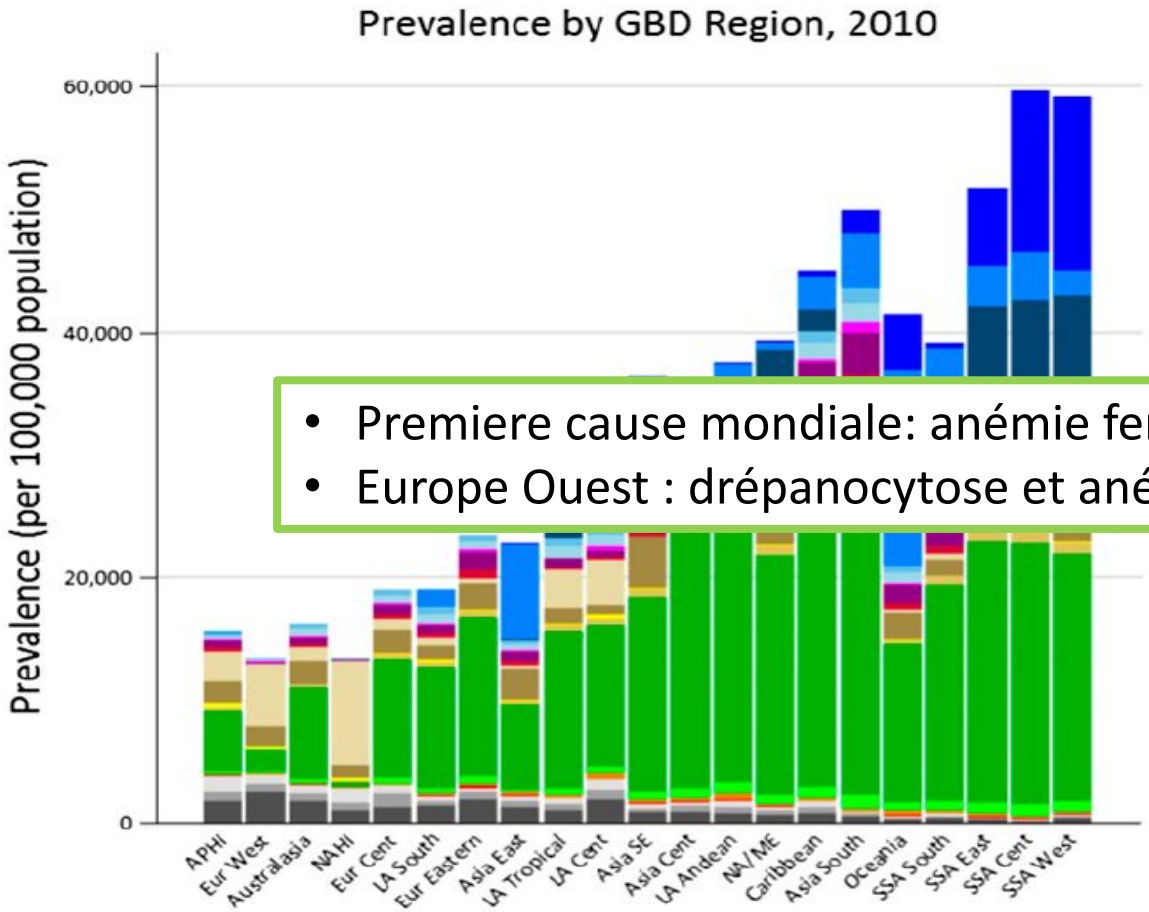
- « Toxicité » utile pour les défenses de l'organisme (PN…)

Global anaemia prevalence

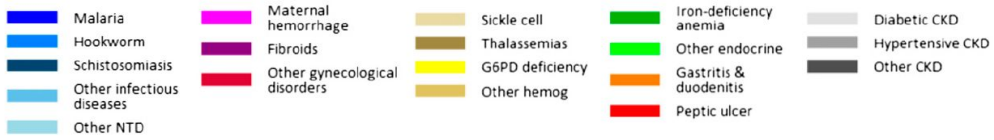


de Benoist B et al., eds. Worldwide prevalence of anaemia 1993-2005. WHO Global Database on Anaemia Geneva, World Health Organization, 2008.

Anémie, prévalences par étiologie et région



- Premiere cause mondiale: anémie ferriprive
- Europe Ouest : drépanocytose et anémie mal. chron.



Kassebaum N, Blood 2014

La carence martiale: définition et conséquences ?

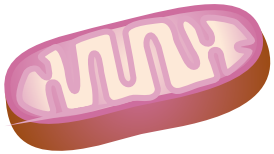
- Iron deficiency is a health-related condition in which iron availability is insufficient to meet body needs

- Iron deficiency can be present with or without anaemia

Importance of iron for functioning and survival across all levels of complexity of living structures

Iron is critical for optimal functioning and survival

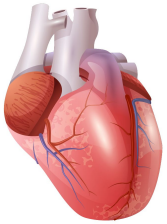
ID results in:



- Mitochondrial dysfunction
- Deranged activity of enzymes
- Abnormal transport and structural proteins
- Apoptosis

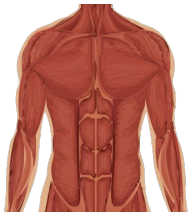
Cells

Tissues



- Tissue remodelling
- Impaired organ efficacy

Organs



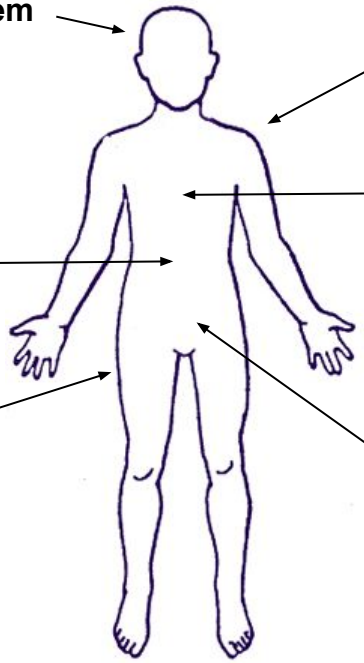
- Impaired exercise capacity
- Reduced work efficacy
- Impaired cognitive performance and behaviour
- Increased morbidity and mortality

Body

Population

Adapted from Jankowska EA *et al. Eur Heart J* 2013;34:816–26

Clinical consequences of anaemia and iron deficiency anaemia (very frequent 40-60%)



Central nervous system
- **Fatigue**
- **Headache**
- Depression
- Impaired cognitive function

Immune system
- Impaired T-cell and macrophage function

Cardio-respiratory system
- Exertion dyspnoea
- Tachycardia, palpitations
- Hypertrophy
- Risk of cardiac failure

Gastrointestinal system
- Anorexia
- Nausea

Vascular system
- Low skin temperature
- **Pallor of skin**

Genital tract
- Menstruation problems
- Loss of libido

Frewin, R, et al. BMJ 1997; 314:1333-1336; Beard, JL, et al. 2001 J Nutr. 131, 568S-579S; Yahuda SM., D.I. (Humana Press, 2010); Fourn L, et al. Sante Publique 2004;16:123-32; Bager P. Dan Med J 2014;61:B4824; Bergsjo P, et al. Trop Med Int Health 2008;13:272-7.

Most common causes of iron deficiency/iron deficiency anaemia

Blood loss

- Heavy or prolonged menstrual bleeding
- Heavy uterine bleeding
- Delivery
- GI tract disorders/bleeding
- Surgery
- Blood donation
- Haemodialysis

Decreased iron intake

- Poor diet
- Vegetarian diet
- Disease-related anorexia (cancer)
- Eating disorder

Decreased iron absorption and utilization / release

- Inflammatory bowel disease
- Chronic inflammatory or malignant diseases
- Interaction food / drugs
- Malabsorption

Increased iron demand

- Infancy, adolescence
- Pregnancy
- Endurance sport

1. Zimmerman MB, et al. Lancet 2007;370:511-20; 2. Barton JC, et al. BMC Blood Disorders 2010;10:9; 3. Aapro M, et al. Ann Oncol 2012;23:1954-62; 4. Marret H, et al. Eur J Obst Gyn Reprod Biol 2010;152:133-7; 5. Milman N. Ann Hematol 2006;85:559-65; 6. Crichton R. UNI-MED Verlag AG, 2008; 7. Stein J, et al. Nat Rev Gastroenterol Hepatol 2010;7:599-610.

Common causes of absolute and functional iron deficiency, and main biomarkers

Absolute iron deficiency

- Chronic blood loss
- Decreased iron intake
- Increased iron demand

- **Low TSAT**
- **Low serum ferritin**
- **High sTfR**

Functional iron deficiency

- Inadequate iron release
- Simultaneously increased iron need (e.g. due to ESAs)

- **Low TSAT**
- **Normal / high serum ferritin**
- **Normal sTfR**

TSAT, Transferrin saturation; sTfR, soluble transferrin receptor.

Weiss G, et al. N Engl J Med 2005;352:1011-23.

La carence martiale: comment la diagnostiquer ?

Iron biomarkers according to the compartment

Cellular Iron

- Hb
- MCV, MCH
- Retics
- HypoRBC%
- ReticHb content
- Low Hb density%
- ZPP

Storage Iron

- Serum ferritin
- Bone marrow stain

Transport Iron

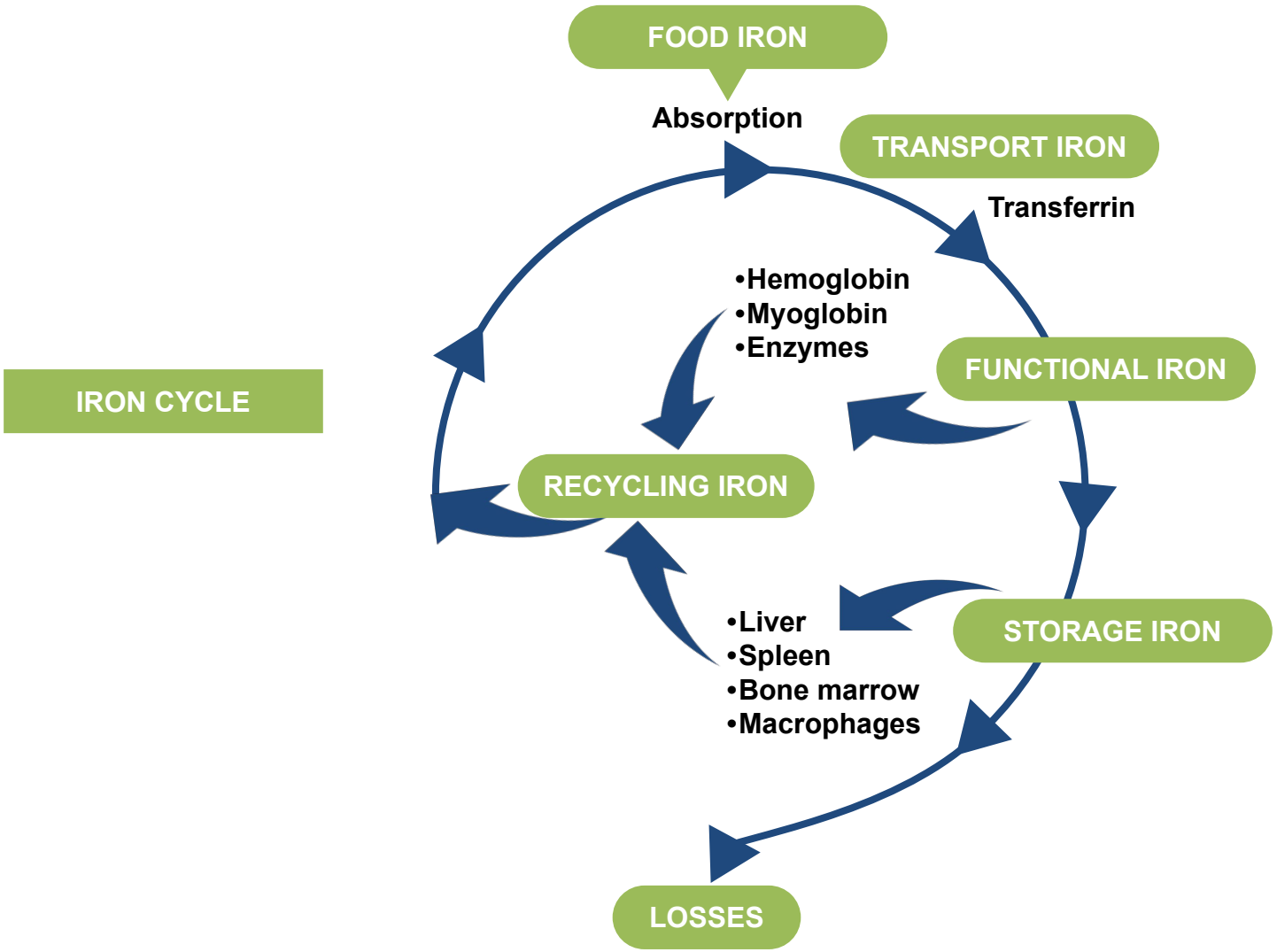
- Tf, Tf sat,
- sTfR, sTfR/ferritin

Other tests

- Epo, Hepcidin
- ESR, CRP

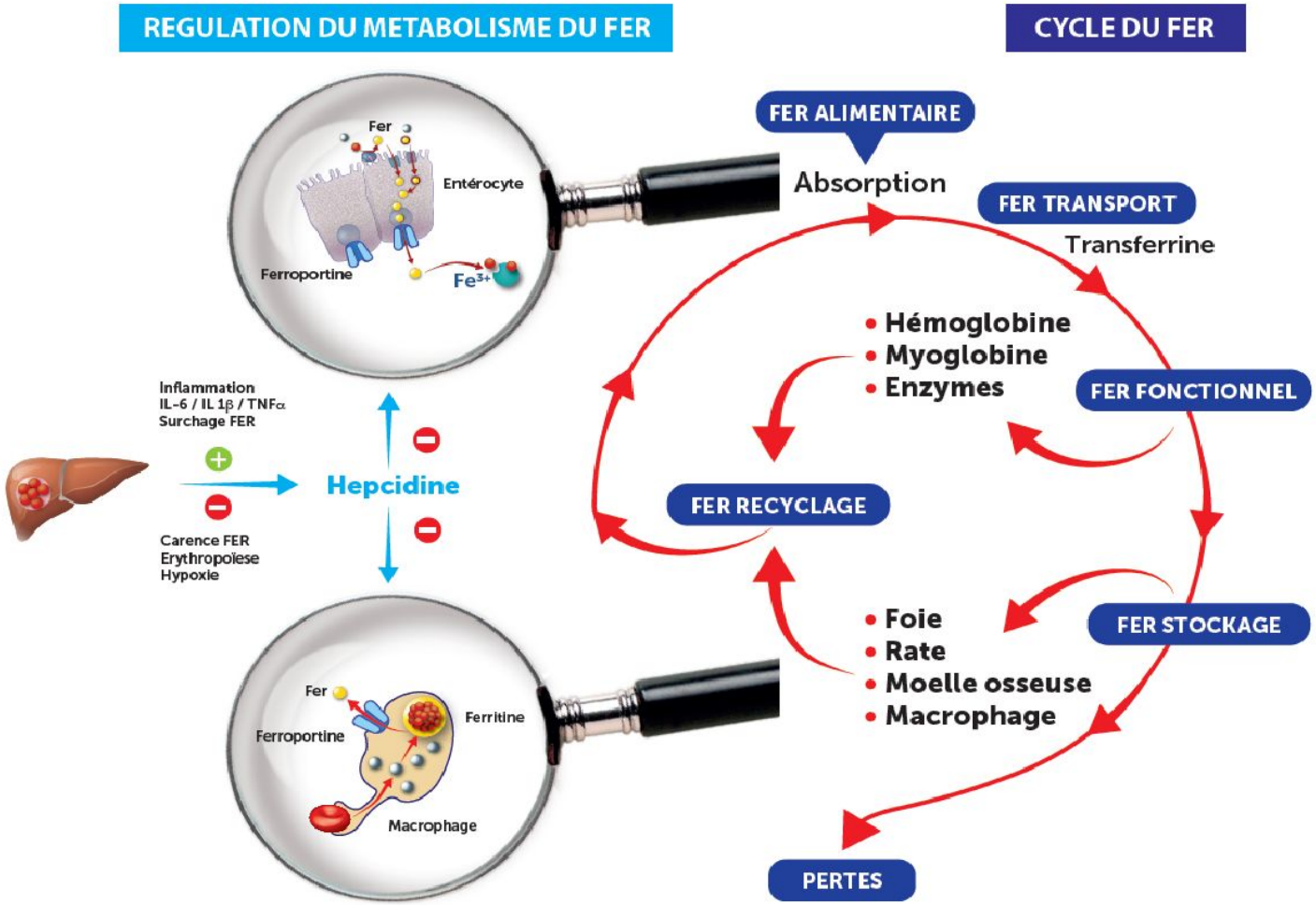
Hb, haemoglobin; MCV, mean corpuscular volume; MCH, mean corpuscular haemoglobin; Epo, erythropoietin;
ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; Tf sat, transferrin saturation; ZPP, zinc erythrocyte protoporphyrin.

Régulation du métabolisme du fer: un circuit fermé



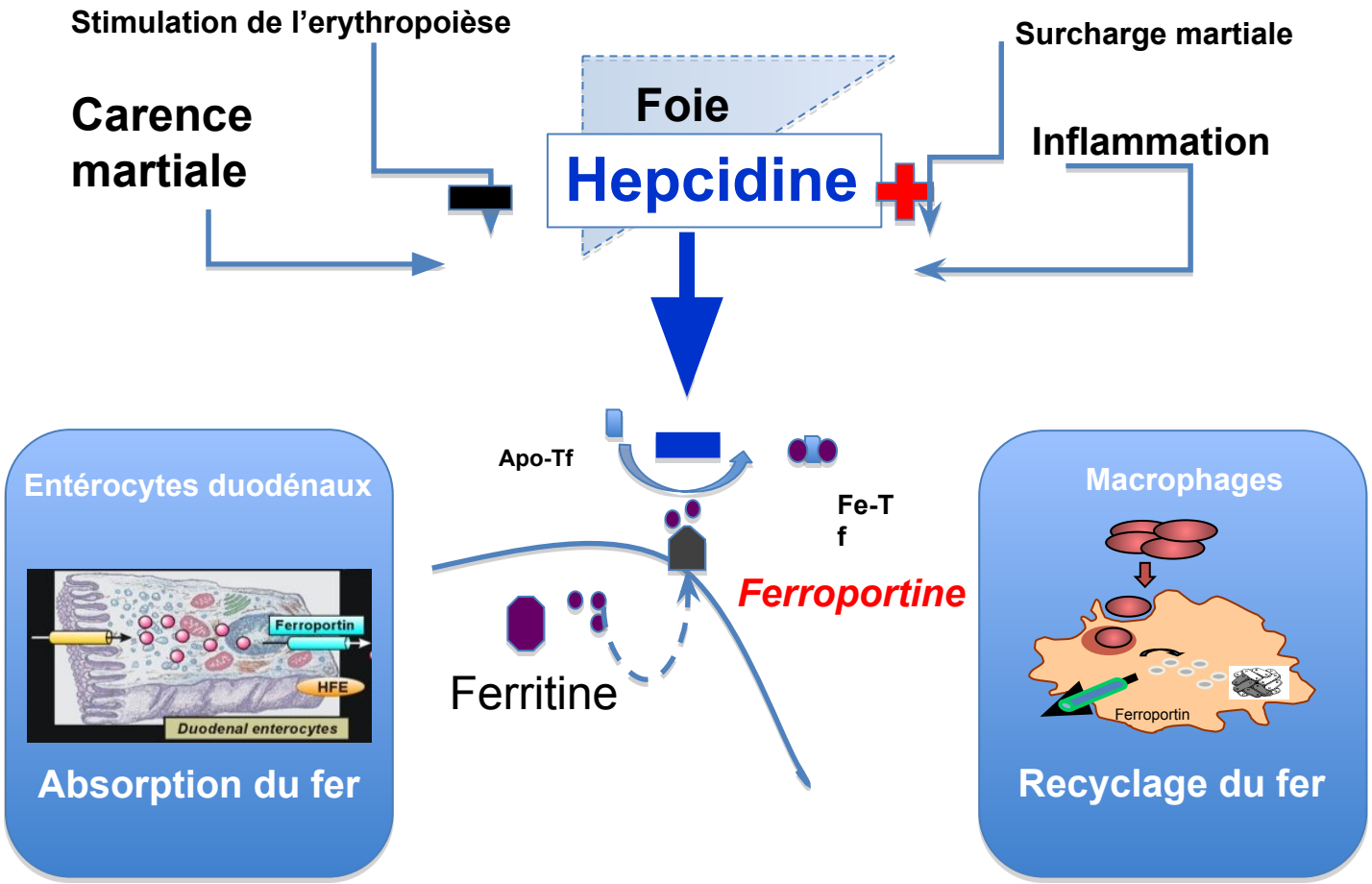
Cacoub P, Rev Med Interne, 2018.

Régulation du métabolisme du fer



Cacoub P. Rev Med Interne , 2018

L'hepcidine contrôle le métabolisme du fer via la ferroportine



Body iron distribution and biomarkers

Storage

= Ferritin

- Liver
- Spleen
- Bone marrow
- Blood (macrophages)
- Muscles

Transport

= Transferrin

- Blood / plasma

Functional

= Haemoglobin

- Blood / plasma

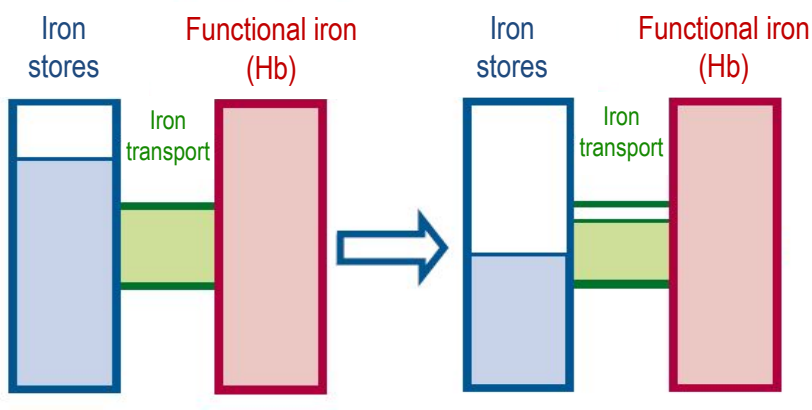
Myoglobin

- Muscles

Total body iron: 3–4 grams (30–45 mg iron/kg)

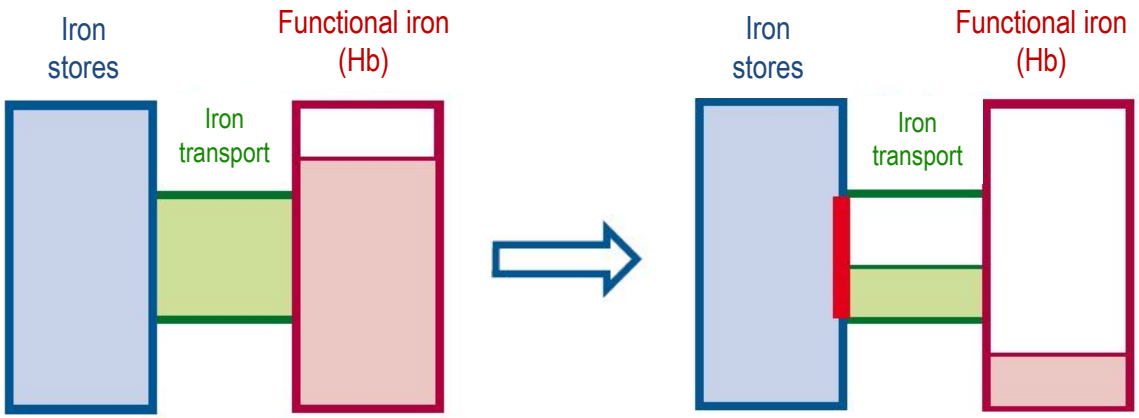
R. R. Crichton: UNI-MED, Iron Therapy with Special Emphasis on Intravenous Administration, 4th edition, 2008;
Iron Metabolism: Biological and molecular Aspects. A. Wagner. Le rôle du laboratoire dans l'exploration du métabolisme du fer. ACOMEN 2000, vol. 6, n°1.

Absolute iron deficiency: Decreased levels of iron stores lead to reduced iron availability for normal erythropoiesis



- ↘ **Ferritin**
- ↘ **TSAT**

Functional iron deficiency: Inadequate iron available for normal erythropoiesis, although iron storage is adequate



- **Ferritin: normal, or high**
- **↘↘ TSAT**

Traitements par fer: utilisation des biomarqueurs en vraie vie (EGB 2006-2013) en France

Biomarqueur	Bilan avant traitement		Bilan après traitement		Bilan avant ET après traitement	
	n	(%)	n	(%)	n	(%)
CST	1677	(1,0)	863	(0,5)		
Ferritine	56081	(33,8)	24952	(15,0)		
CST ou ferritine	57510	(34,6)	25654	(15,5)	12161	(7,3)

Tous traitements par fer – Echantillon total, n=166 015 épisodes; CST, coefficient de saturation de la transferrine
EGB, échantillon généraliste des bénéficiaires de l'assurance maladie

Cacoub P et al. Scientific Rep 2020

Causes of functional ID/iron sequestration

- Chronic kidney disease (CKD)[1,2,3]
- Chronic heart failure (CHF)[2]
- Inflammatory bowel disease (IBD): Crohn's disease (CD)/ulcerative colitis (UC)[2,3]
- Autoimmune diseases eg rheumatoid arthritis (RA)[1,3]
- Other chronic viral, fungal, bacterial or parasitic infections[1,3]
- Cancers (haematological malignancies and solid tumours)[1,3]
- Obesitiy[1,2]

In GI diseases, inflammation may progress to erosions and ulcers, which can lead to perforations and bleeding causing absolute ID[4]

Absolute and functional ID are not exclusive conditions but can be present at the same time

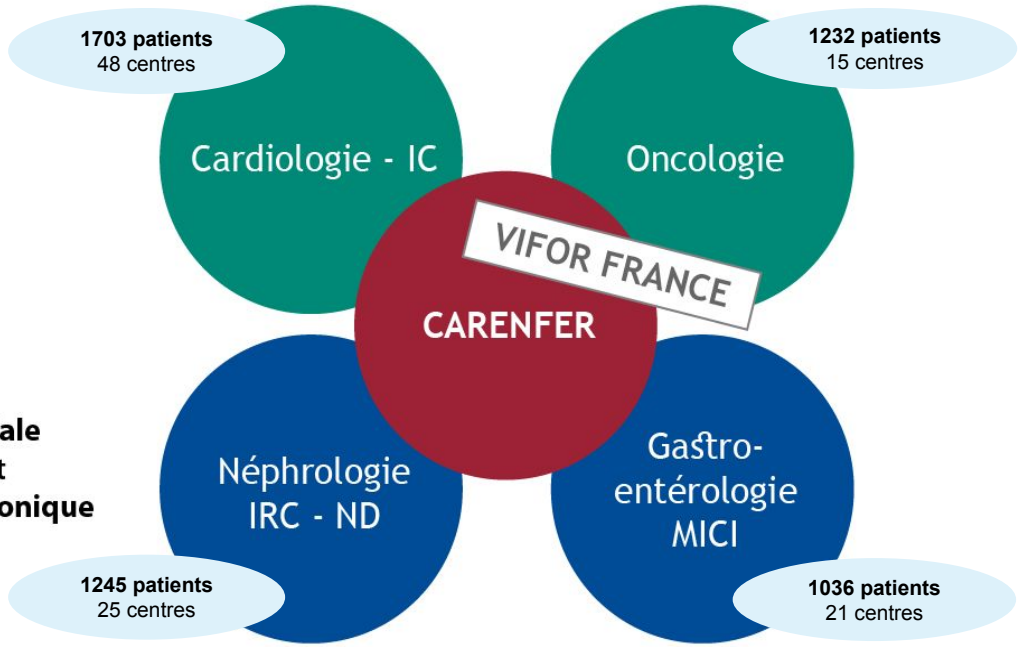
1. Fraenkel PG. *Med Clin North Am* 2017;101(2):285–96; 2. Camaschella C. *Hematology* 2015;2015:8-13.
3. Madu *et al. Med Princ Pract* 2017;26(1):1–9; 4. König *et al. Clin Transl Gastroenterol* 2016;7(10):e196

Prévalence de la carence martiale au cours des maladies chroniques en France 2019-2020,

Programme CARENFER n= 5216 patients

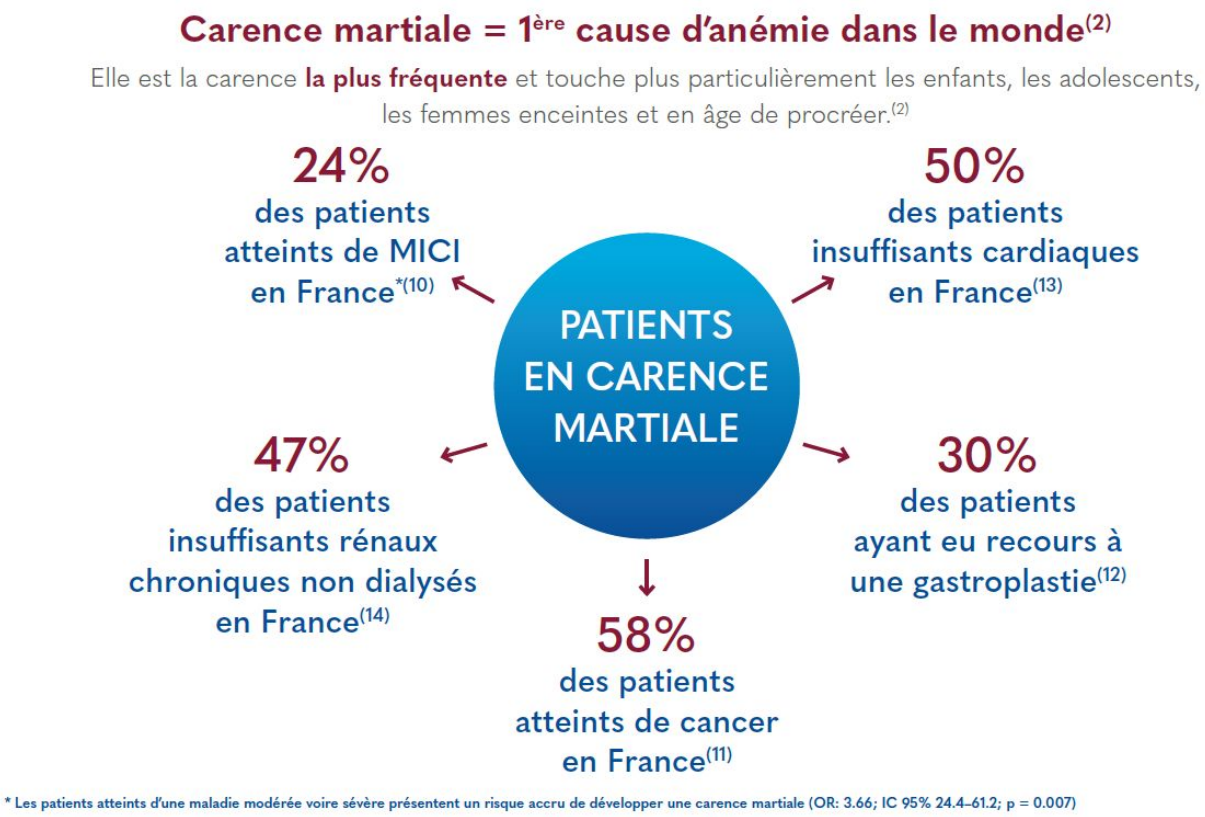
4 études de même design réalisées en 2019 et 2020

OBJECTIF :
Prévalence de la carence martiale
chez des patients présentant
une **pathologie inflammatoire chronique**



Cacoub P et al, J Intern Med 2022; Luporsi E et al, BMJ Support Palliat Care 2021; Cohen-Solal A et al, ESC Heart Fail. 2022; Peyrin-Biroulet L et al, Dig Dis Sci. 2022; Choukroun G et al, Nephrol Ther. 2022;

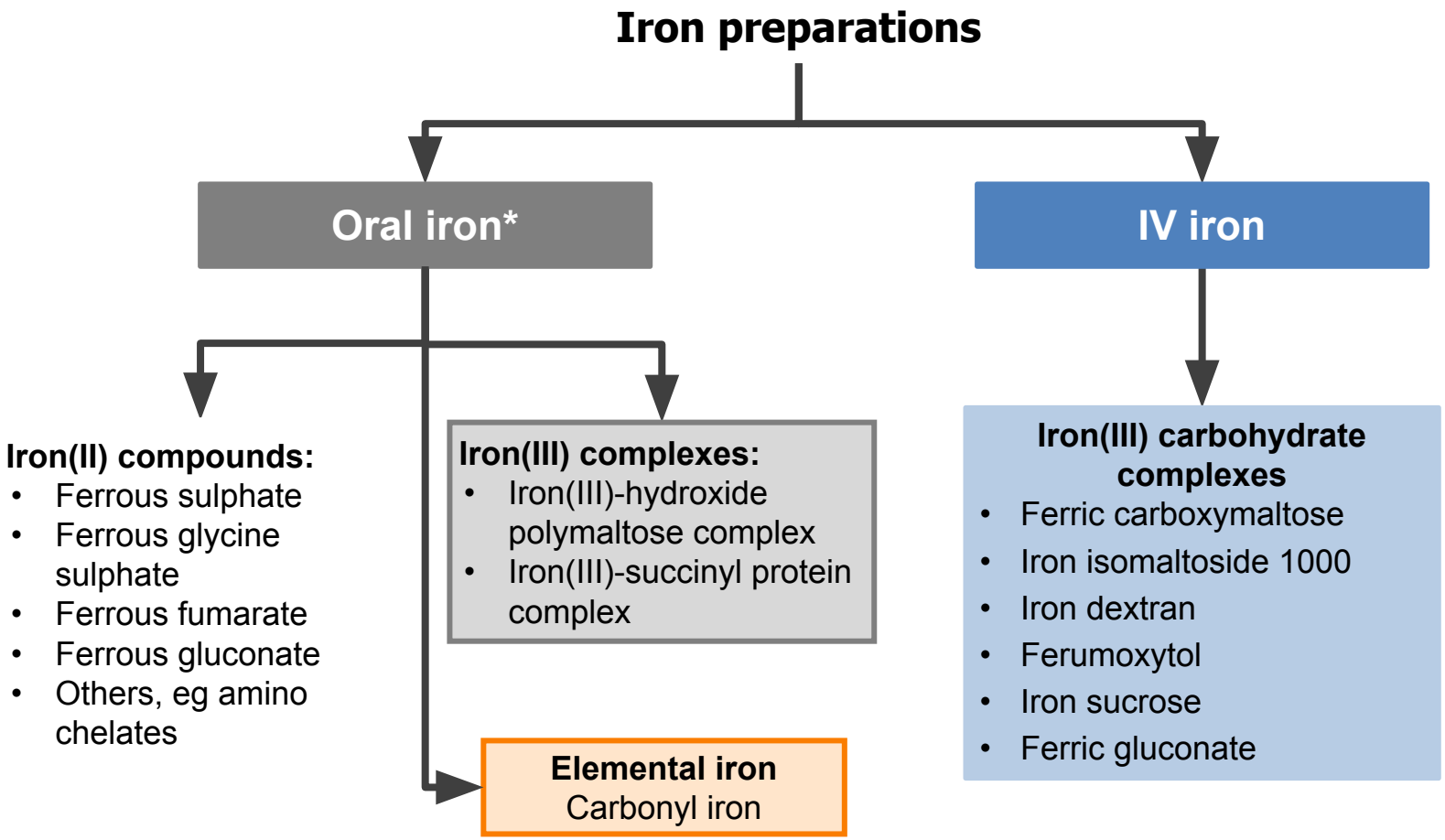
Prévalence de la carence martiale au cours des maladies chroniques en France 2019-2020, *CARENFER*



Cacoub P et al, J Intern Med 2022; Luporsi E et al, BMJ Support Palliat Care 2021; Cohen-Solal A et al, ESC Heart Fail. 2022; Peyrin-Biroulet L et al, Dig Dis Sci. 2022; Choukroun G et al, Nephrol Ther. 2022;

La carence martiale: comment la traiter ?

Treatment of Iron deficiency



*With/without folic acid

IV, intravenous

1. Fehr J *et al. Praxis* 2009;98:1445–51; 2. Gordeuk VR *et al. Am J Clin Nutr* 1987;46:1029–34; 3. Aapro M *et al. Ann Oncol* 2012;23:1954–62;
4. Auerbach M *et al. Hematology Am Soc Hematol Educ Program* 2010;2010:338–47

Carence martiale absolue versus fonctionnelle: implications thérapeutiques

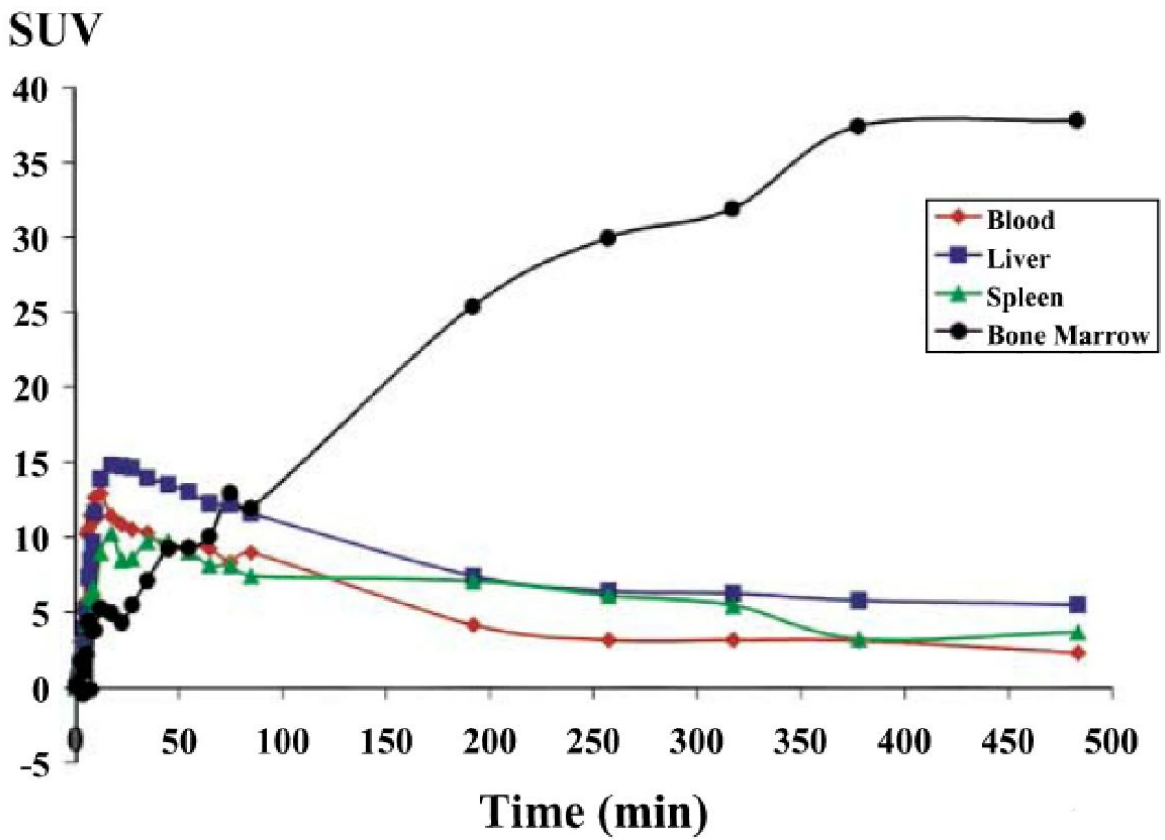
ABSOLUTE - inadequate body iron stores
- (ferritin < 100 µg/L)
- hepcidin levels low

Oral or i.v. iron

FUNCTIONAL - adequate total body iron stores
- (normal or high ferritin)
- hepcidin levels high
- failure to release Fe rapidly enough to satisfy demands of bone marrow

Only i.v. iron

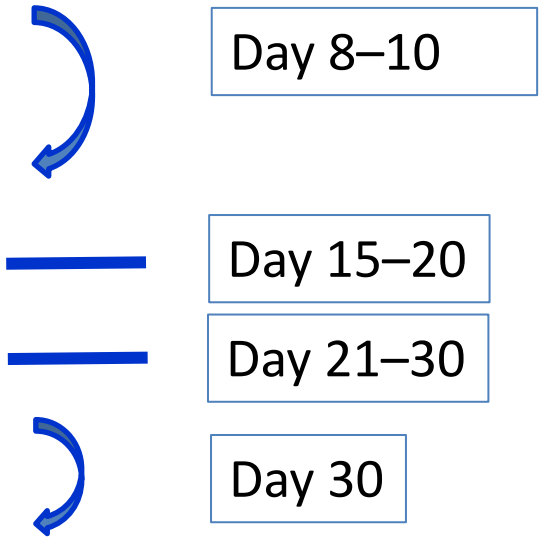
Où va le Fer après une injection i.v. ?
Distribution et accumulation dans la moelle osseuse



Beshara S. Br J Haematol, 2003, 120, 853–859

Quels biomarqueurs du Fer utiliser pour le suivi post-thérapeutique ?

- Tf sat (TSAT)
- sTfR
- sTfR/log10 ferritin
- Haemoglobin
- Ferritin
- MCV
- MCH



Carence martiale: conclusion

- La carence martiale est fréquente, avec ou sans anémie.
- **Faire le diagnostic** de carence martiale est simple: ferritine, saturation Trf.
- **La stratégie thérapeutique** de correction de la carence martiale adaptée au mécanisme: absolu vs. fonctionnel.
- Une augmentation modérée de l'hémoglobine et/ou du Fer "utilisable" entraine une réduction significative des symptomes.