

20 ANNI DI EMATOLOGIA A TREVISO

TREVISO | 18-20 NOVEMBRE 2021
Auditorium Fondazione Cassamarca

Quando un'emopatia nasconde una malattia digestiva

Domenico Girelli



Disclosures of Domenico Girelli

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Sanofi-Genzyme						x	
Vifor Pharma	x					x	



Topics

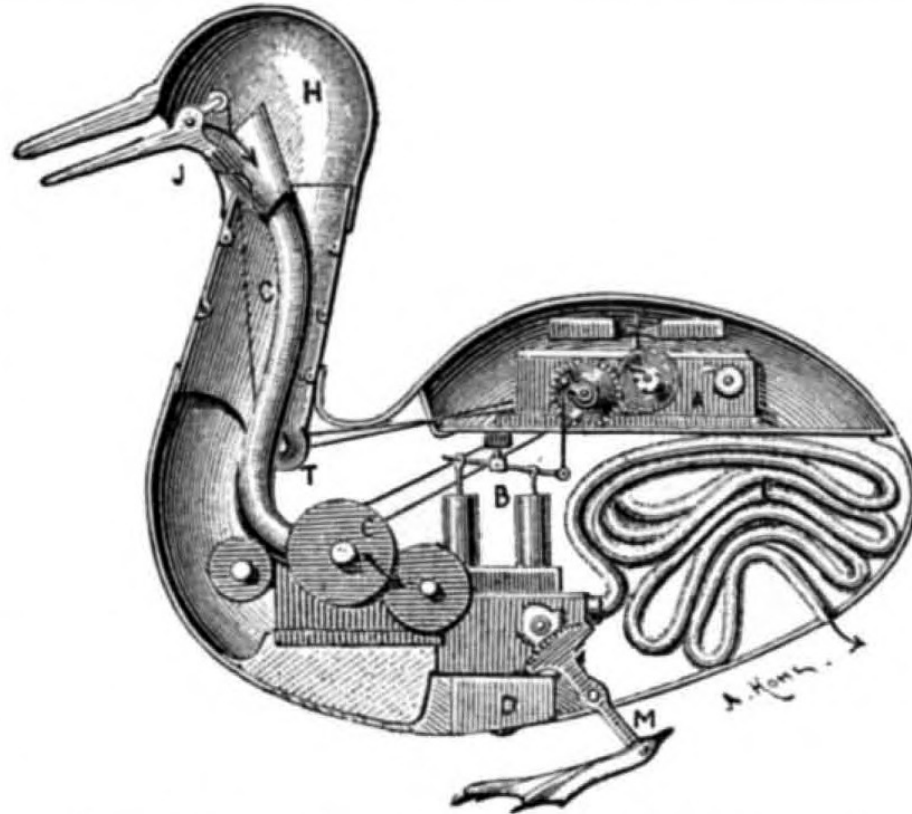
1. Cross-talk intestino/midollo emopoietico (fisiopatologia)

2. Focus: anemia sideropenica da mm. gastrointestinali

3. Indagini diagnostiche e cenni di trattamento



Riduzionismo



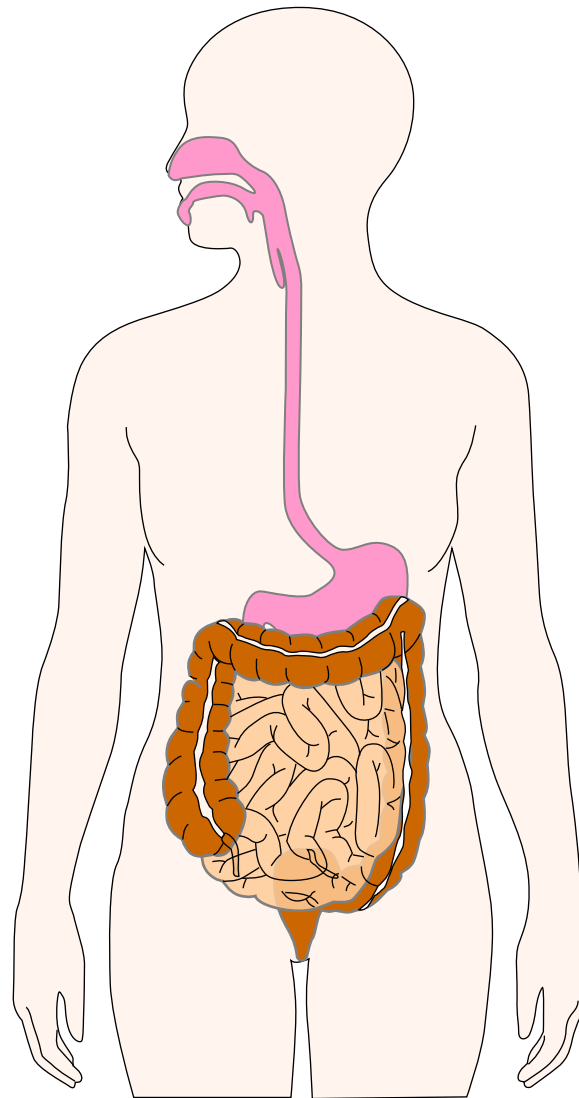
De homine (Renè Descartes, 1662)

INTERIOR OF VAUCANSON'S AUTOMATIC DUCK.

A, clockwork; *B*, pump; *C*, mill for grinding grain; *F*, intestinal tube;
J, bill; *H*, head; *M*, feet.



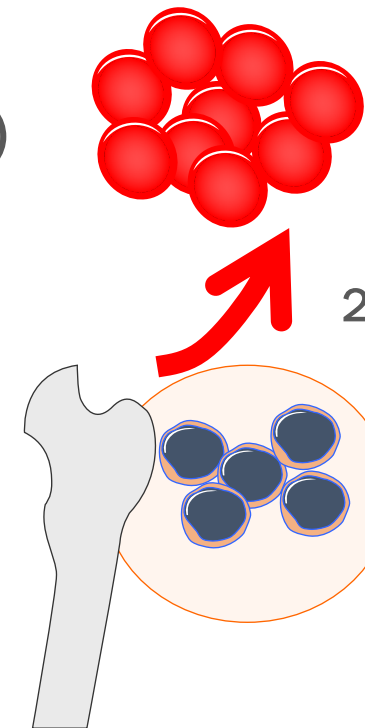
GI-BM Cross Talks



Microbiome products
Nutrients (Fe, B12, ...)



Erythroid regulators
of Fe absorption

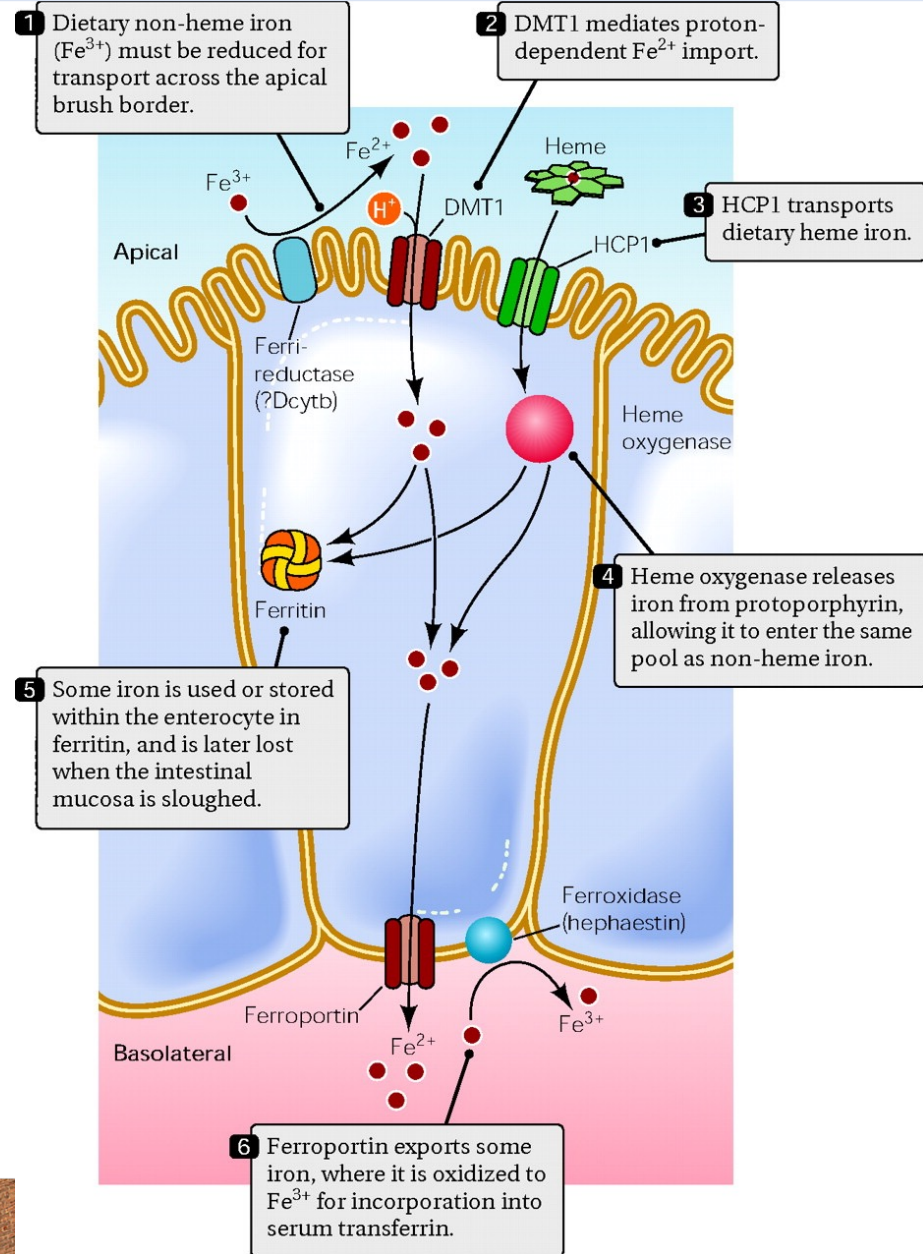


200 billion new RBCs/day
(2.4 million/sec)

Erythroid precursors
in Bone Marrow



Assorbimento ferro dietetico



Does the type of iron matter?

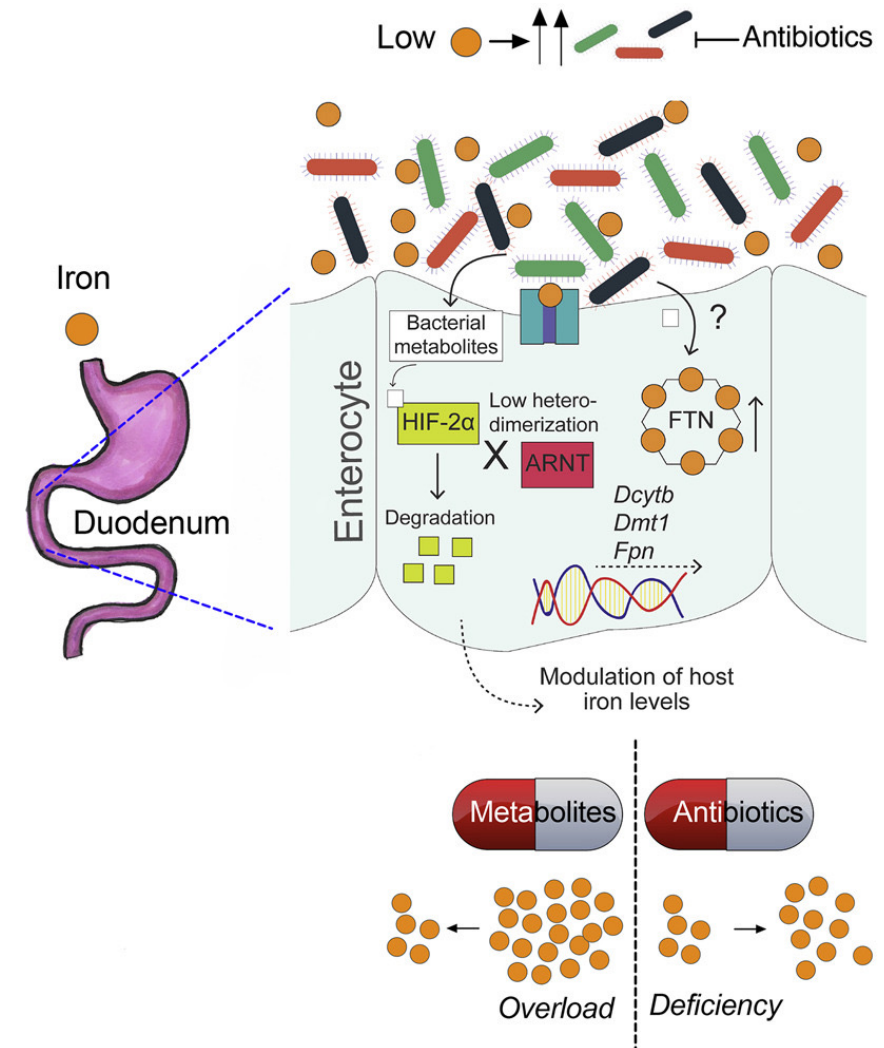
15% to 40% of heme iron is absorbed

1% to 15% of nonheme iron is absorbed.



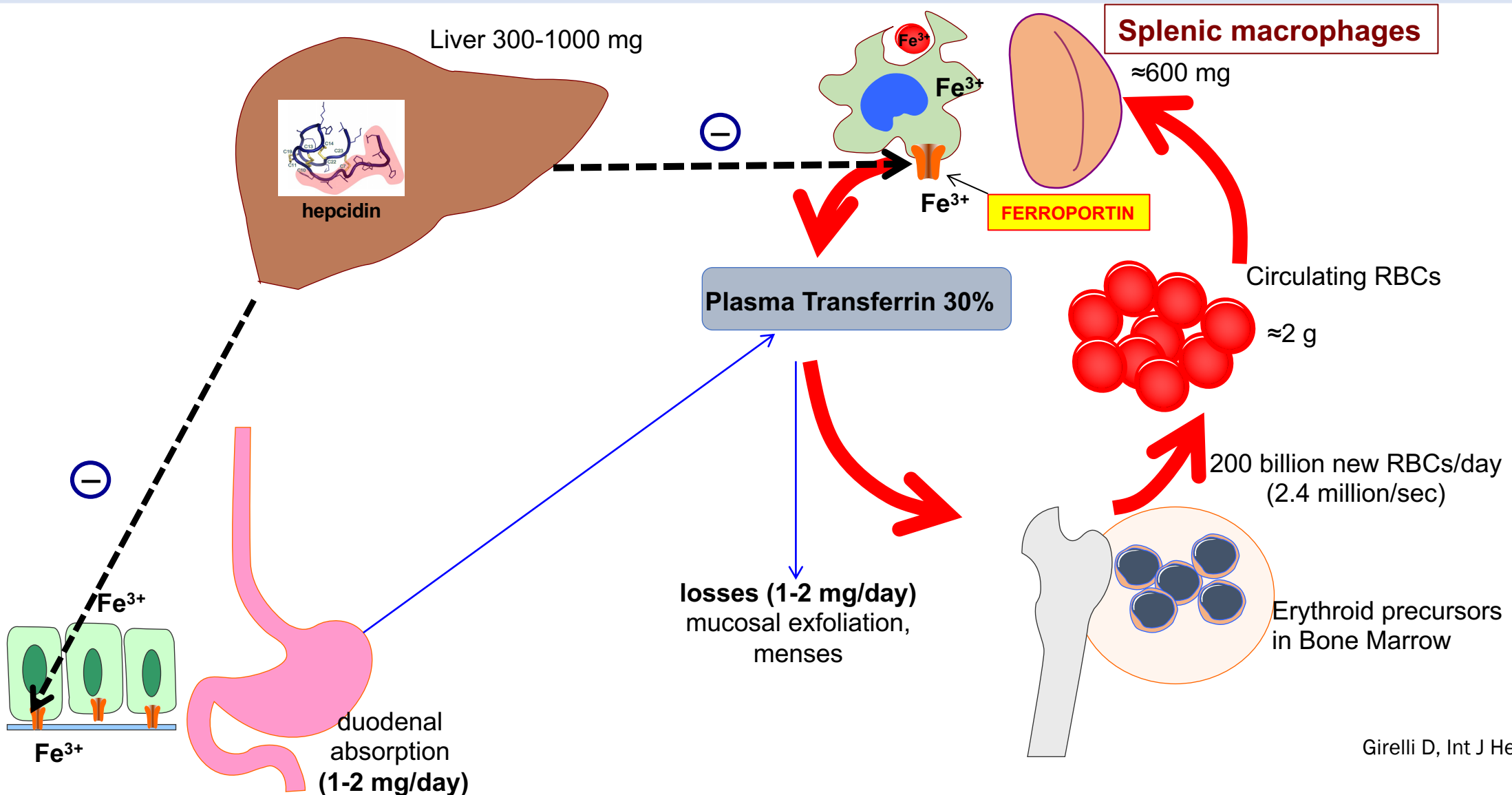
Gut microbial metabolites regulate host iron

1. Inhibitors of HIF-2 α disrupt the HIF-2 α -ARNT interaction \rightarrow HIF-2 α degradation \rightarrow transcriptional downregulation of Fe transporters.
 2. A different subset of metabolites upregulates ferritin (FTN) expression.
- 1 + 2 = decreased Fe absorption.



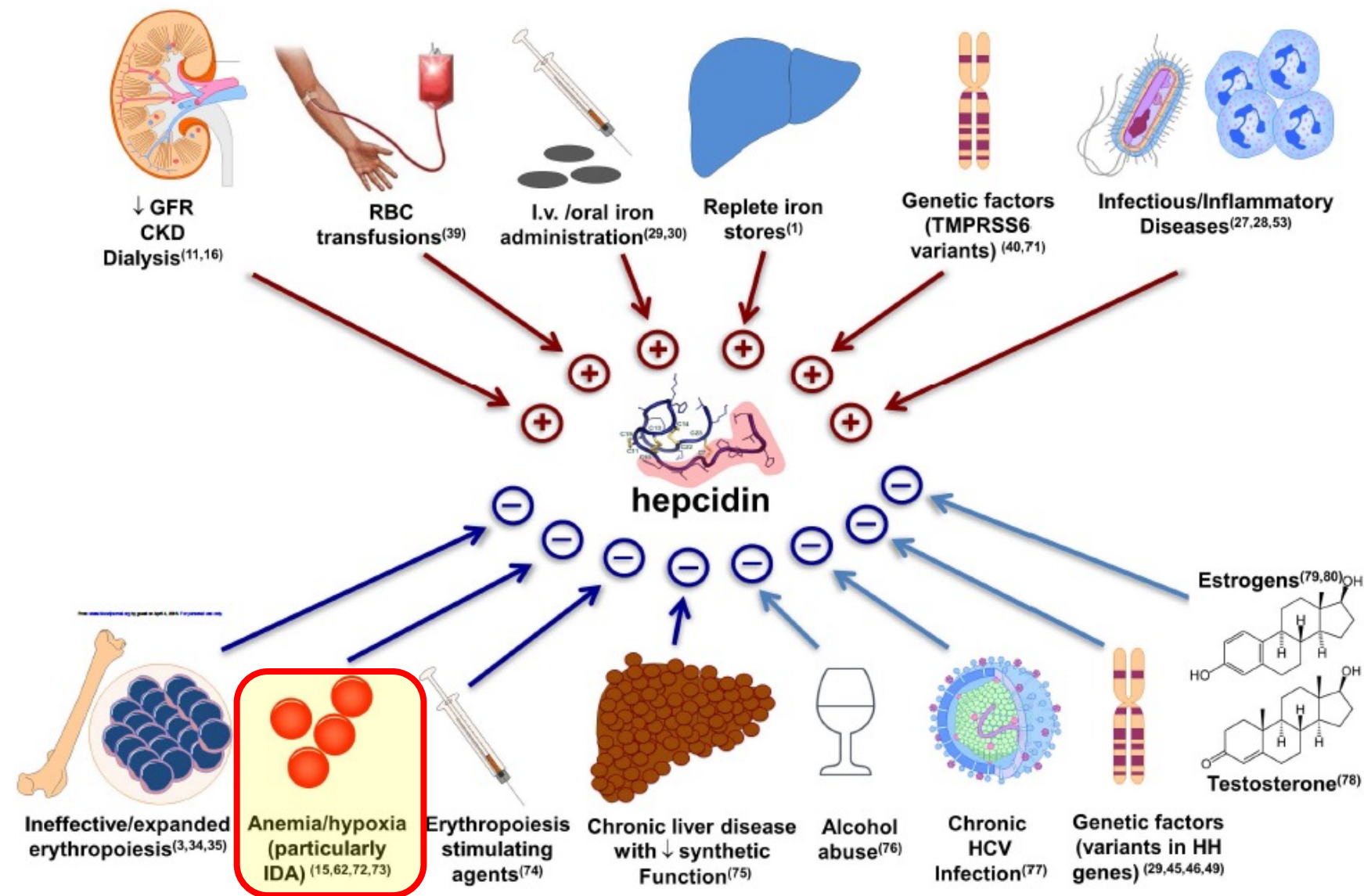
Das NK, Cell Metab 2021

Systemic “ecological” iron homeostasis



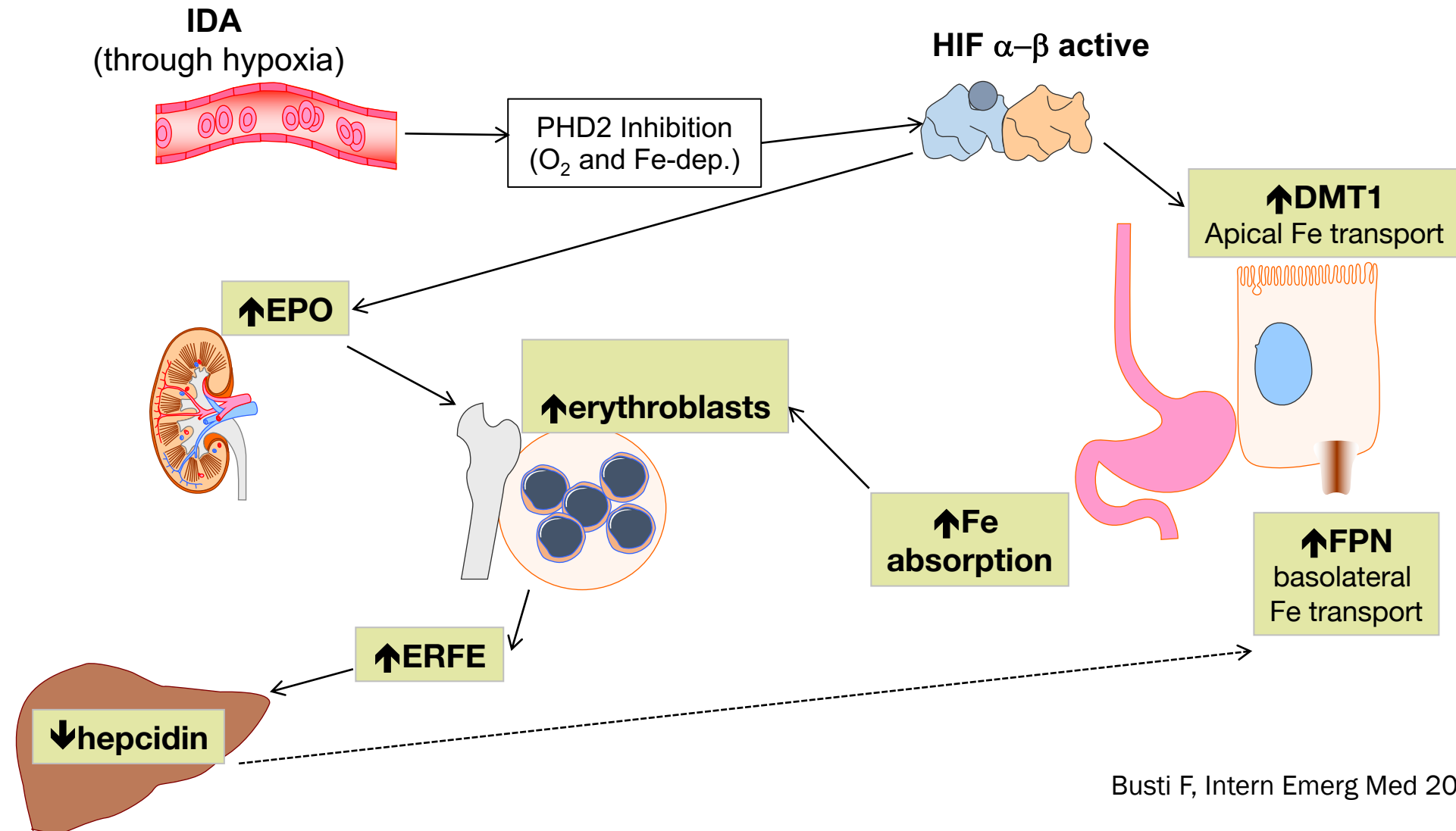
Girelli D, Int J Hematol 2018 (adapted)

Clinical conditions influencing s-hepcidin levels



Girelli D, Blood 2016

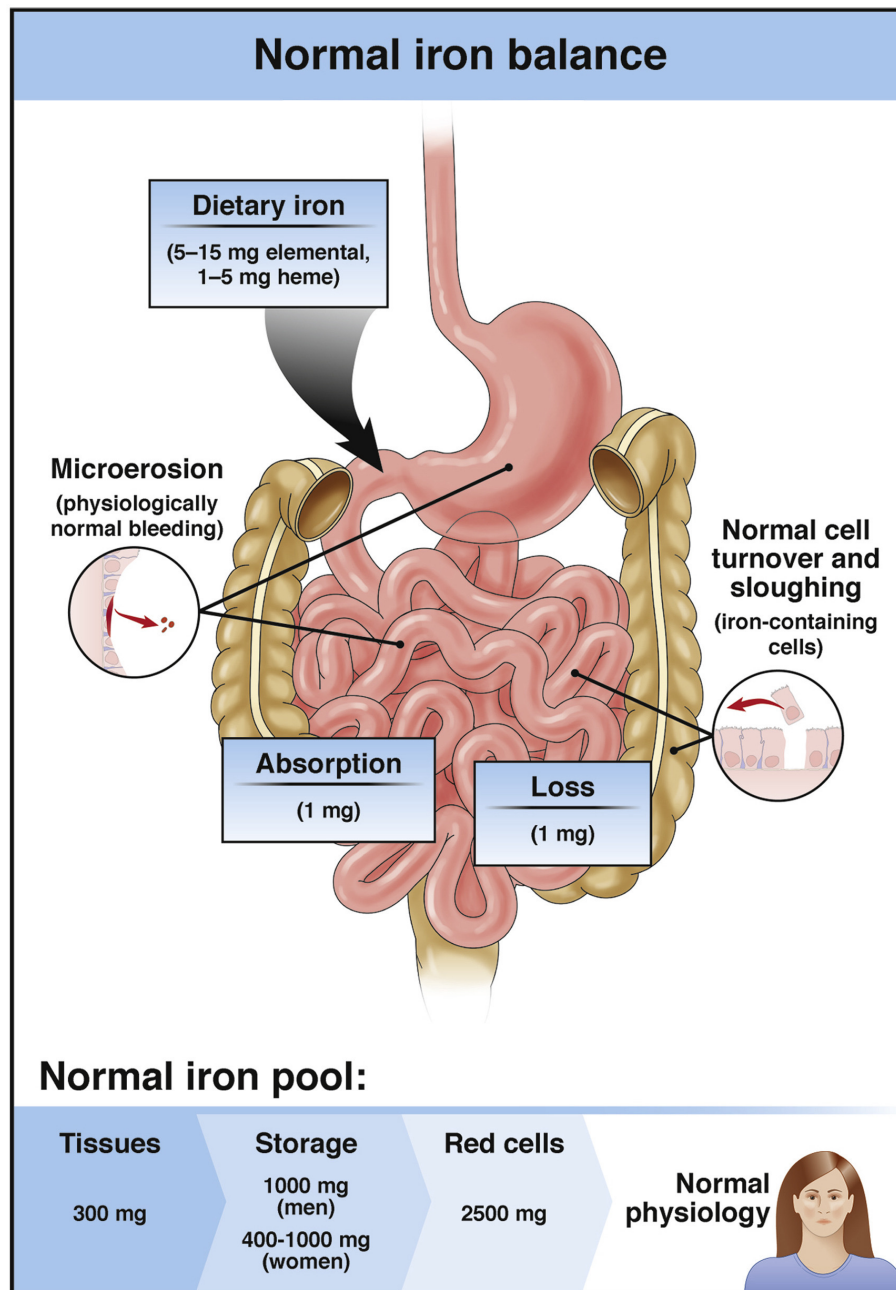
Hepcidin suppression in IDA



Busti F, Intern Emerg Med 2020 (adapted)

AGA Technical Review on Gastrointestinal Evaluation of Iron Deficiency Anemia

Rockey DC, Gastroenterology 2020



GI lesions causing IDA

Inflammatory

- Reflux esophagitis
- Cameron lesions
- Erosive gastritis
- Gastric ulcer
- Duodenal ulcer
- SB or colon ulcer
- Celiac sprue
- Whipple's disease
- Meckel's diverticulum
- Idiopathic ulcers
- Crohn's disease
- Ulcerative colitis

Vascular

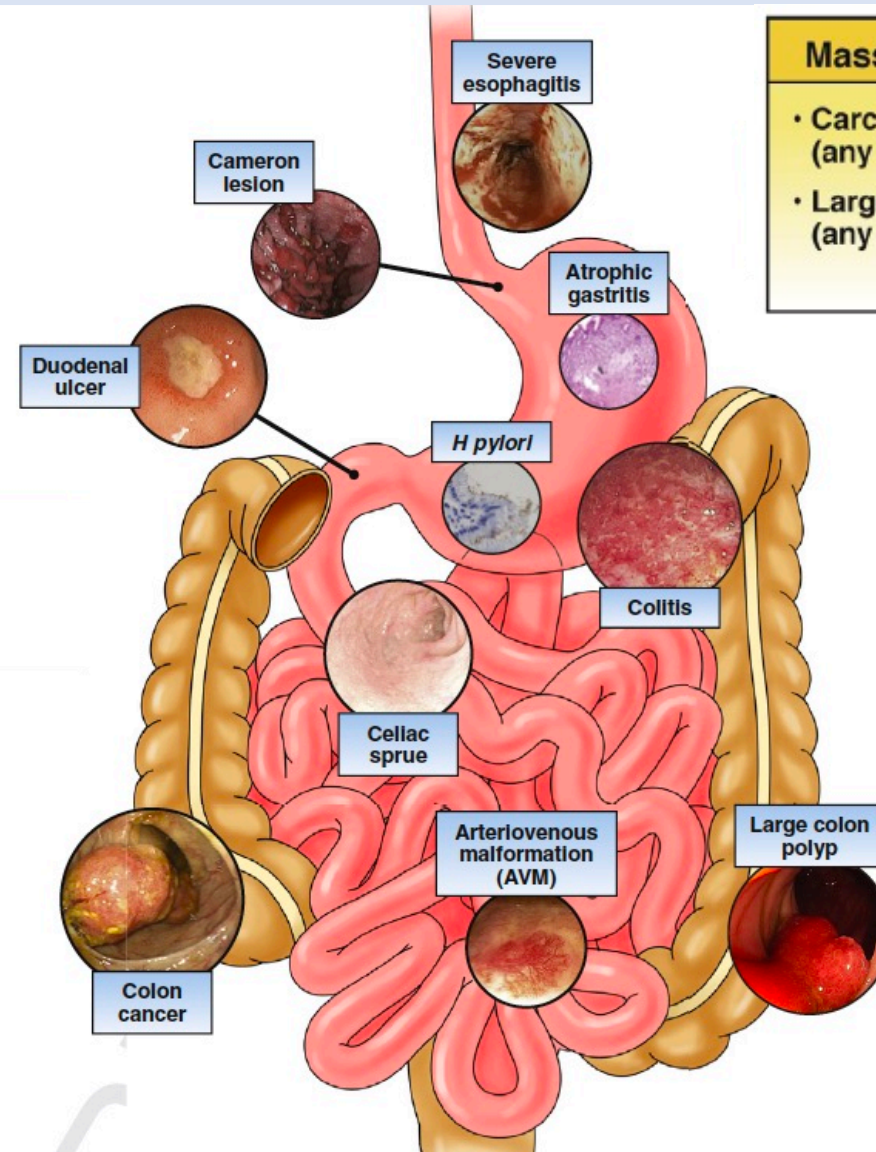
- Vascular ectasia(s)
- Portal hypertensive lesions
- Watermelon stomach
- Hemangiomas
- Blue rubber bleb nevus syndrome

Infectious and miscellaneous

- Hookworm
- Hemoptysis
- Epistaxis
- Strongyloidiasis
- Ascariasis
- Tuberculous enterocolitis
- Amebiasis
- Long-distance running
- Factitious

Mass lesions

- Carcinoma (any site)
- Large polyps (any site)



Rockey DC, Gastroenterology 2020



AGA 2020 “recommendations”

	Patient Population	Treatment Recommendations	Strength of Recommendation	Quality of Evidence	Comments
1	Patients with anemia	The AGA recommends using a cut-off of 45 ng/mL over 15 ng/mL when using ferritin to diagnose iron deficiency	Strong	High	
2	Asymptomatic postmenopausal women and men with iron deficiency anemia	The AGA recommends bidirectional endoscopy over no endoscopy	Strong	Moderate	
3	Asymptomatic premenopausal women with iron deficiency anemia	The AGA suggests bidirectional endoscopy over iron replacement therapy only	Conditional	Moderate	<i>Patients who place a high-value on avoiding the small risk of endoscopy, particularly those who are young and might have other plausible reasons for IDA, and a low-value on the very small risk of missing a GI malignancy would reasonably select an initial course of iron replacement therapy and no initial bidirectional endoscopy.</i>
4	Asymptomatic patients with iron deficiency anemia and possible or suspected <i>Helicobacter pylori</i>	The AGA suggests non-invasive testing for <i>Helicobacter pylori</i> , followed by treatment if positive, over no testing	Conditional	Low	
5	Asymptomatic patients with iron deficiency anemia and possible or suspected atrophic gastritis	The AGA suggests against the use of routine gastric biopsies to diagnose atrophic body gastritis	Conditional	Very low	
6	Asymptomatic patients with iron deficiency anemia and suspected celiac disease	The AGA suggests initial serologic testing, followed by small bowel biopsy only if positive, over routine small bowel biopsies	Conditional	Very low	<i>Celiac disease is a well-recognized cause of iron deficiency anemia, even in asymptomatic patients, and therefore it must be considered in the differential diagnosis of iron deficiency anemia.</i>
7	Uncomplicated asymptomatic patients with iron deficiency anemia and negative bidirectional endoscopy	The AGA suggests a trial of initial iron supplementation over the routine use of video capsule endoscopy	Conditional	Very low	<i>Caution needs to be applied in patients with comorbid conditions where the identification of small bowel pathology will change medical management such as the use of anticoagulation and/or antiplatelet therapy.</i>

Rockey DC, Gastroenterology 2020

Decisional levels for Iron Deficiency

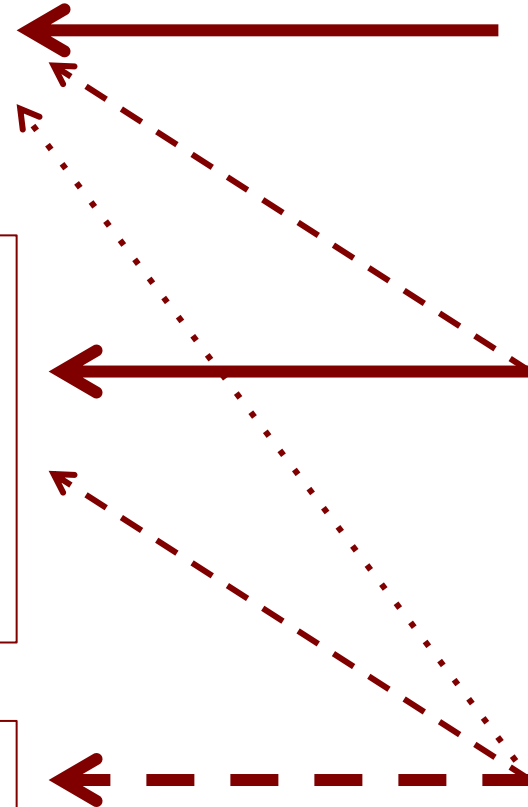
	Meaning	Proposed threshold
Ferritin	Protein released by macrophages; index of iron stores except in inflammation	≤30 µg/dL (≤100 or up to 300 if TSAT<20% in inflammation)
TSAT	Index of iron available for erythropoiesis and other tissues	<20%
MCV	Erythrocyte mean volume	<80 fl
%HYPO	Early index of iron-restricted erythropoiesis especially after ESAs	>6%
CHr (Hb ret)	Reflects recent changes of Hb synthesis	Vary across different studies
sTfR	Index of iron avidity of erythroid precursors	Vary across different methods and studies
sTfR/log ferritin	sTfR normalized to ferritin levels	>2
Hepcidin	Physiologic regulator of systemic iron homeostasis	n.y.a.
Zpp:H	Reflects iron/zinc competition in the last step of heme synthesis	Vary across different age populations

Anemia sideropenica da sospetta m. GI: quali indagini?

Endoscopia
1 EGDS/colonscopia
2 (video capsula)

Esami non invasivi
1 SOF
2 sierologia m. celiaco
3 ricerca HP
4 APCA/anti-FI
5 ...

Trial con Fe per os +
osservazione



Maschi adulti
Femmine post-menopausa

Femmine in età fertile
(sproporzione verso entità del
ciclo/multiple gravidanze)

Altre categorie
Anziani/grandi
anziani/multimorbidi/fragili
Bambini/adolescenti

Fecal occult blood test (FOBT) for evaluation of IDA



Effectiveness well validated for use in colon cancer screening.

Poor sensitivity (0.58, 95% CI 0.53–0.63) and specificity (0.84, (95% CI 0.75–0.89) in IDA (both guaiac-based and immunochemical testing).

“It is unlikely that a result of an FOBT would substantially influence the decision as to whether to perform endoscopy or not.”

→ NOT RECOMMENDED

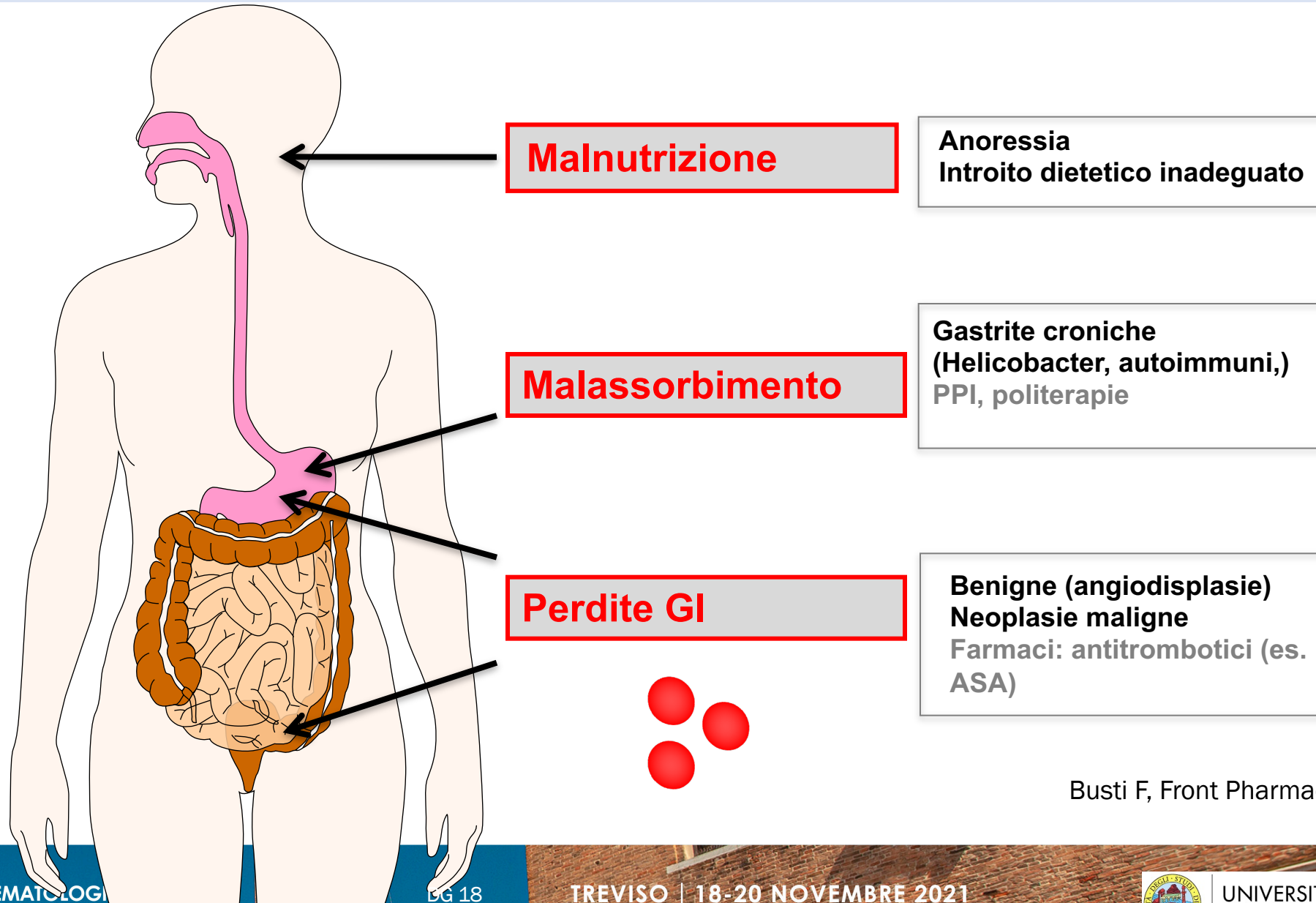
Rockey DC, Gastroenterology 2020

Non invasive tools for evaluation of IDA

	<i>H pylori</i>	Autoimmune gastritis	Celiac disease
Screening	<i>H pylori</i> IgG antibodies or fecal antigen	Serum gastrin Anti-parietal Abs Anti-intrinsic factor Abs	Tissue transglutaminase IgA Abs
Advanced	Urease breath test Gastroscopy and biopsies (optional)	Gastroscopy and biopsies (recommended)	Duodenal biopsy, HLA screening for DQ2 or DQ8 genotypes
Response to specific treatment	<i>H pylori</i> eradication	N.A.	Gluten-free diet

Hershko C, Blood 2014

Sideropenia nell'anziano



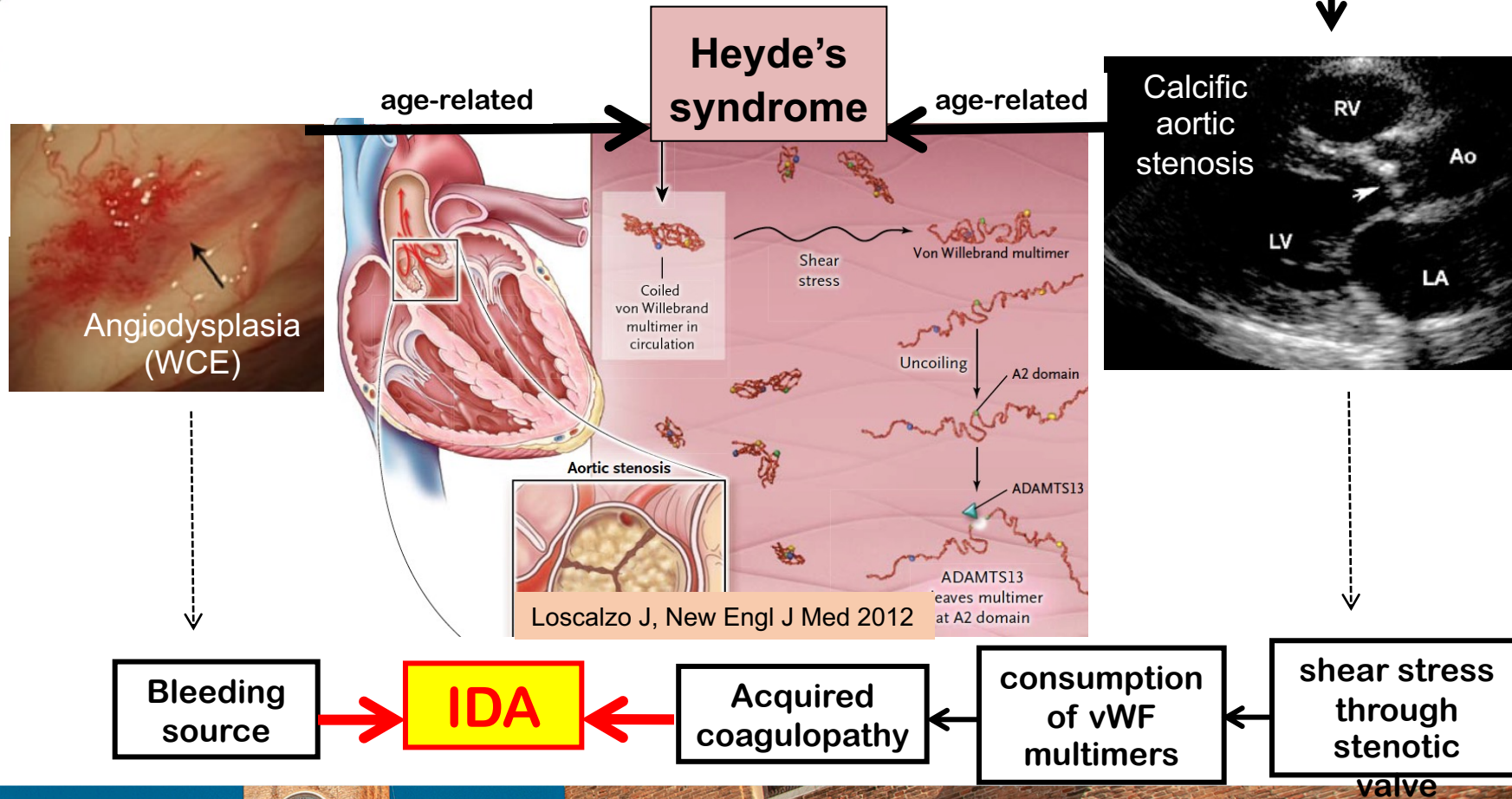
Busti F, Front Pharmacol 2014 (adapted)

Sideropenia complessa nell'anziano

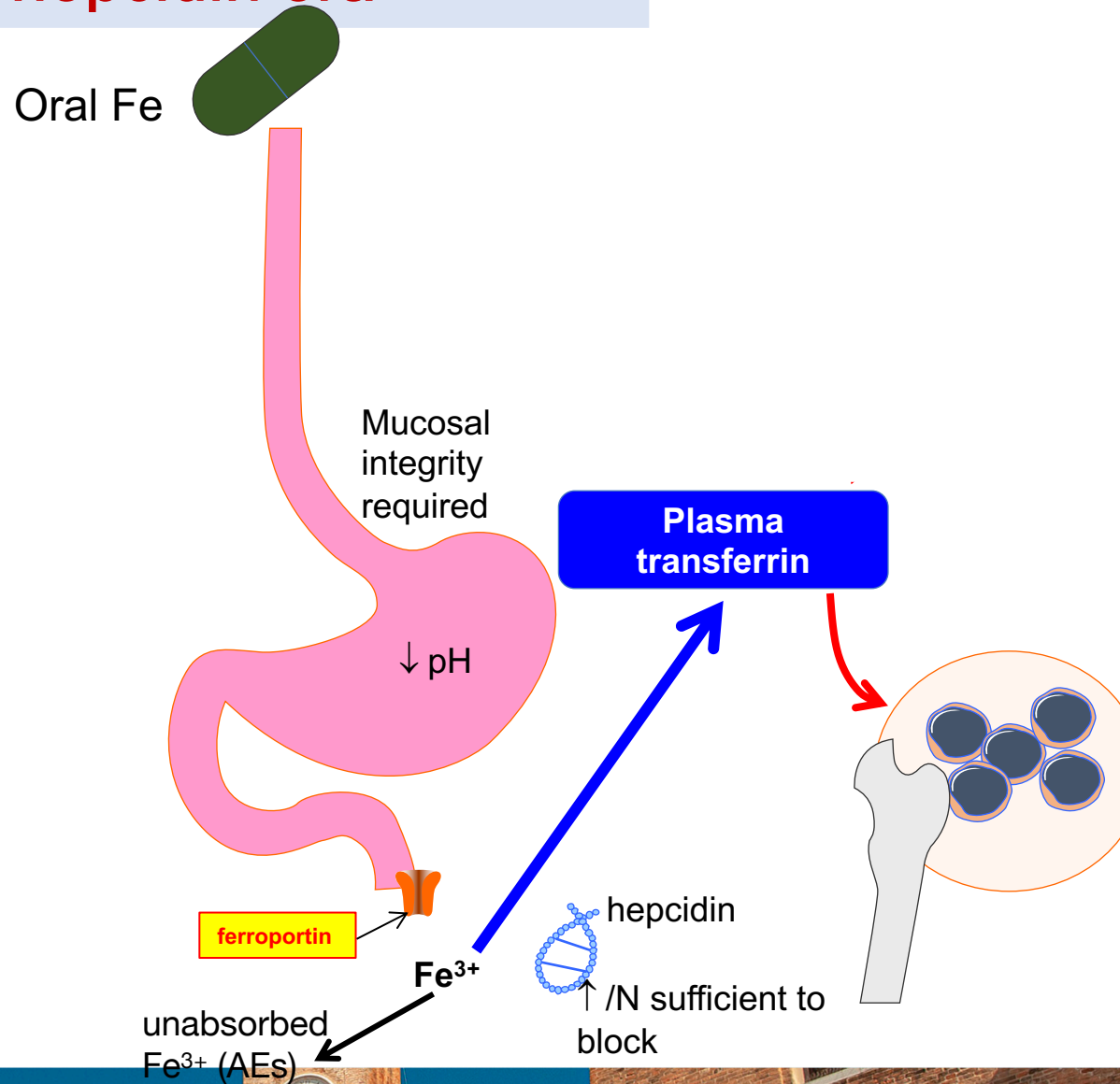


F 70y, referring for "unexplained" IDA
 FOB intermittently +
 EGDS and colonoscopy neg.

PE: 3-4/6
 systolic heart murmur



Different pharmacokinetic between oral and IV iron, revisited in the hepcidin era



Girelli D, Int J Hematol 2018



European
Reference
Network



Gruppo Interdisciplinare delle Malattie del Ferro di Verona

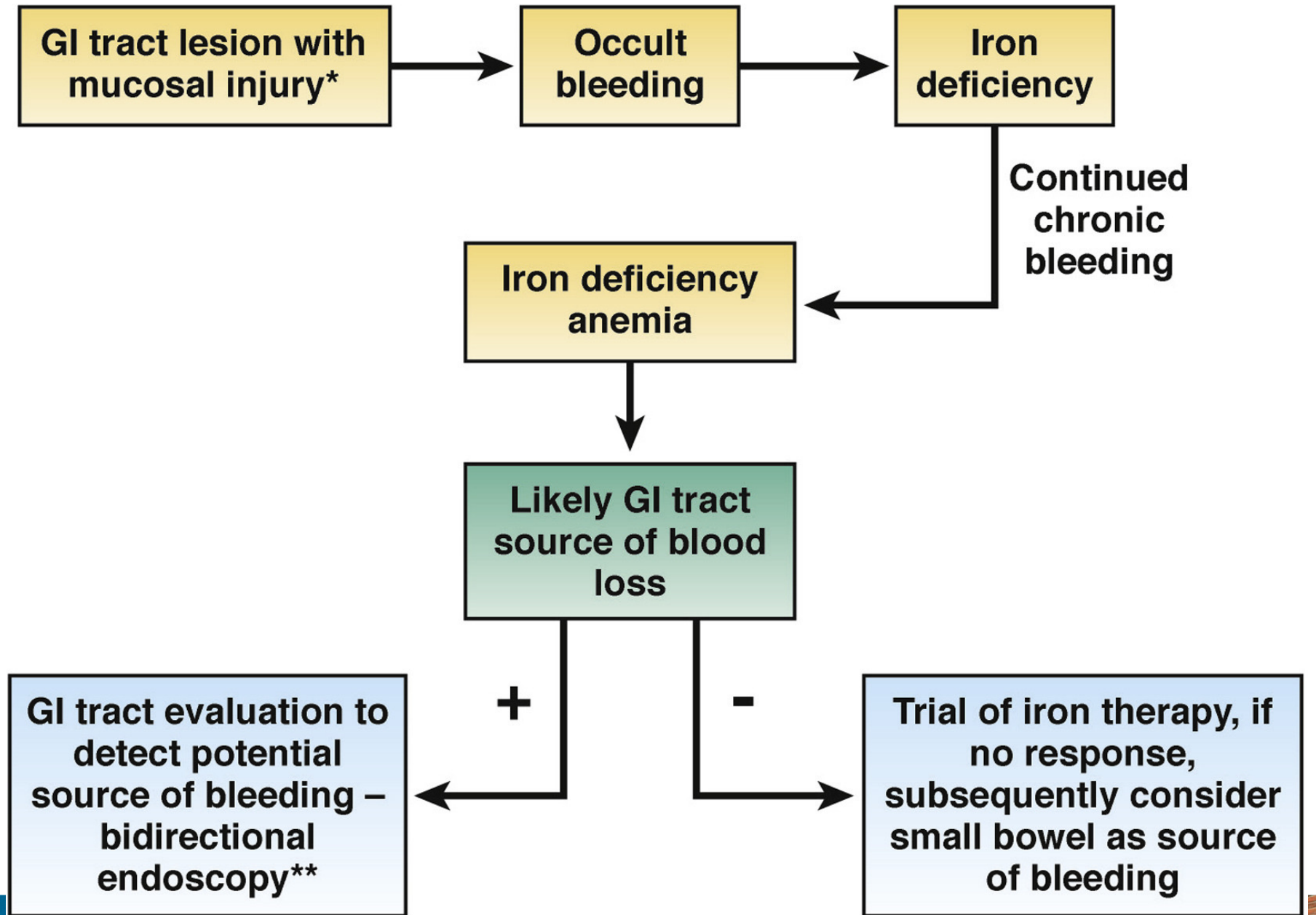


Sideropenia nell'anziano



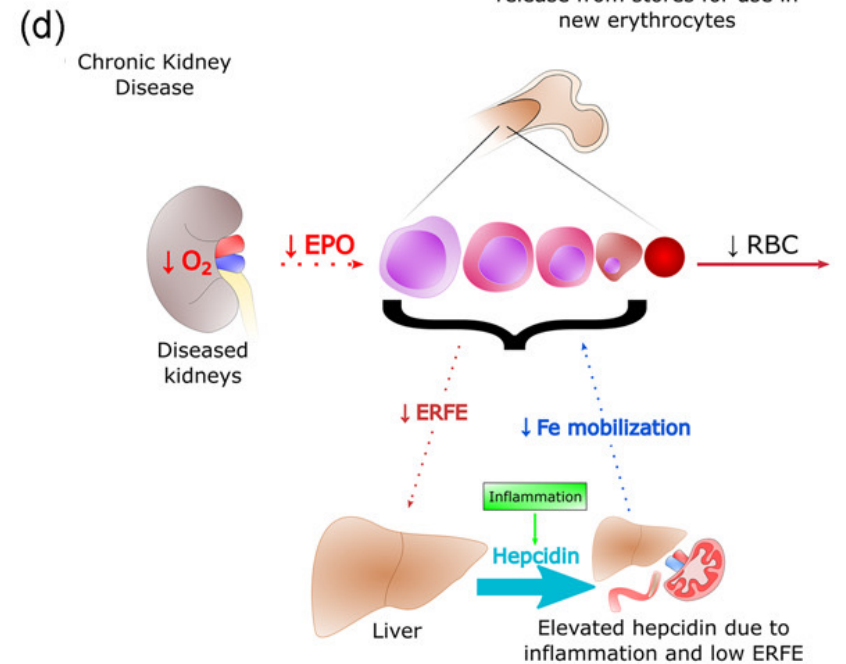
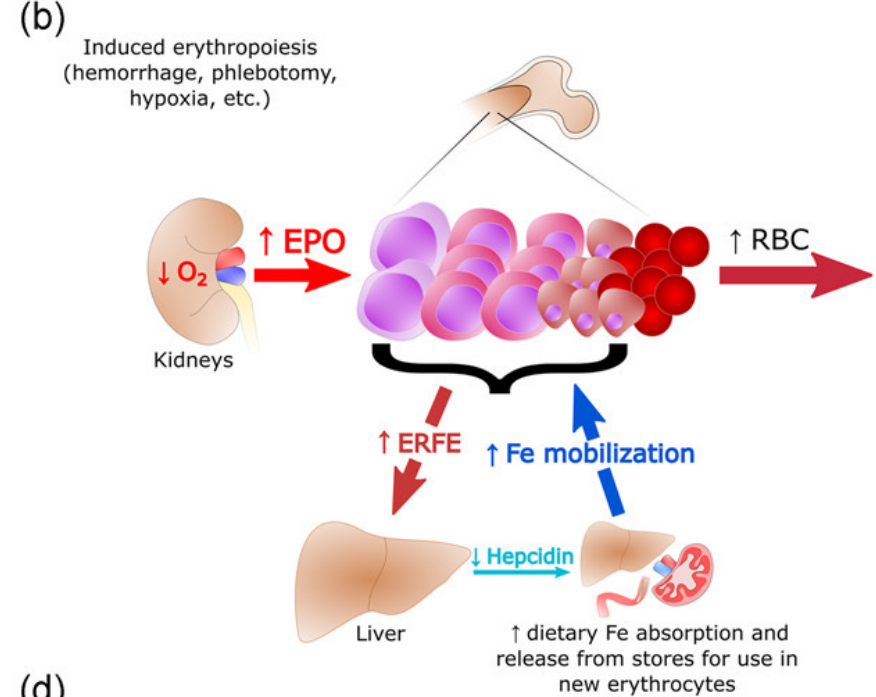
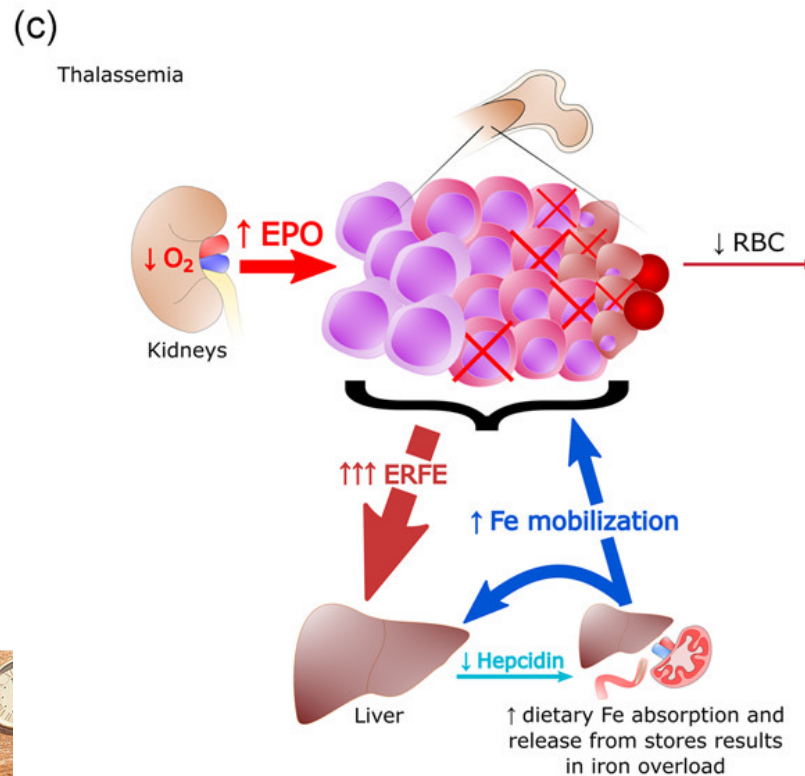
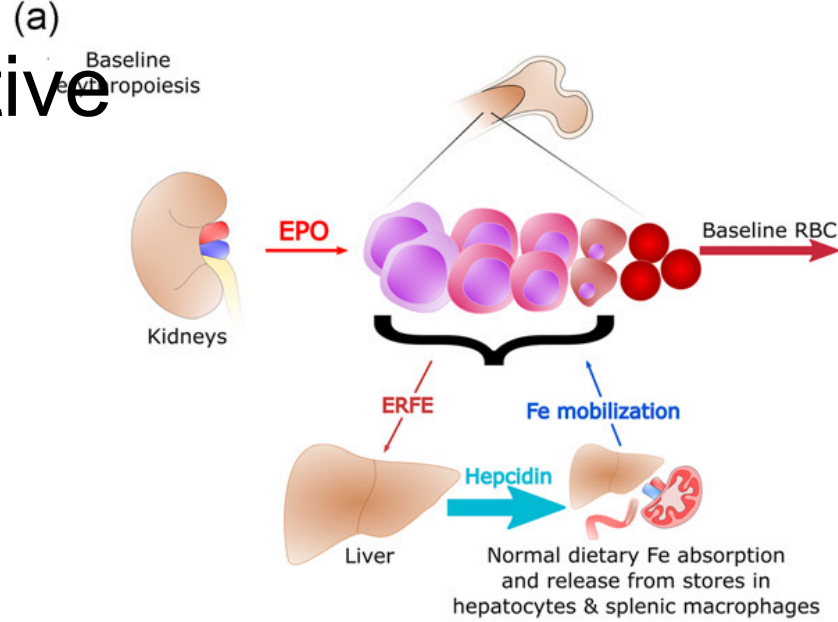
AGA Technical Review
on Gastrointestinal
Evaluation of Iron
Deficiency Anemia

Rockey DC,
Gastroenterology 2020

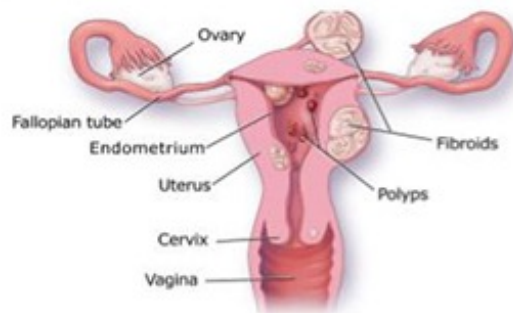


Effective and ineffective erythropoiesis

- (a) Baseline erythropoiesis generates red blood cells to replace old and damaged cells. Physiological levels of erythroferrone (ERFE) and hepcidin at baseline provide sufficient iron for steady-state production of erythrocytes.
- (b) When the kidneys sense cellular hypoxia, they secrete erythropoietin (EPO), which stimulates erythropoiesis and the production of ERFE. As ERFE suppresses hepcidin, iron is mobilized from stores for use by the expanded population of maturing red blood cells.
- (c) In β -thalassemia, most erythroblasts do not generate mature erythrocytes, causing anemia and tissue hypoxia. This results in high levels of EPO and ERFE, chronically low hepcidin, and iron overload.
- (d) In chronic kidney disease, low EPO production, low clearance of hepcidin by the kidney, and inflammation can lead to low iron availability in the erythroid system



WHAT IS MENORRHAGIA OR HEAVY PERIODS?



MENORRHAGIA

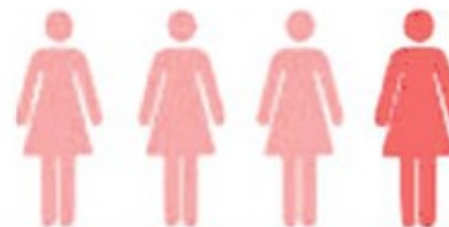
This condition is associated with heavy or extended menstrual bleeding. Women suffering from menorrhagia experience severe blood loss, pain and cramping. These can restrict normal life.

WHO DOES IT AFFECT?

1 in 5 WOMEN

AGED 30-55 YEARS

perceive their menstrual bleeding to be abnormal.



Only 5% of women seek evaluation or treatment

SYMPTOMS IS MENORRHAGIA

If you need:

- more than one pad per hour for multiple hours to soak flow
- to use double sanitary protection to control the blood flow
- to change pads frequently during the night

If your blood flow:

- lasts longer than seven days
- includes large blood clots
- causes fatigue, weakness or shortness of breath



IDA and ID in IBD



Malnutrition
(severe forms)

Malabsorption
(proximal localizations in Crohn's disease)

GI blood losses
(from ulcerated lesions)

in IBD, ferritin levels up to 100 $\mu\text{g/L}$ in the presence of inflammation may still reflect absolute iron deficiency.

Ascertainment of iron status in such cases is problematic, although other markers of iron metabolism can be used.

Diagnostic biomarkers of iron deficiency

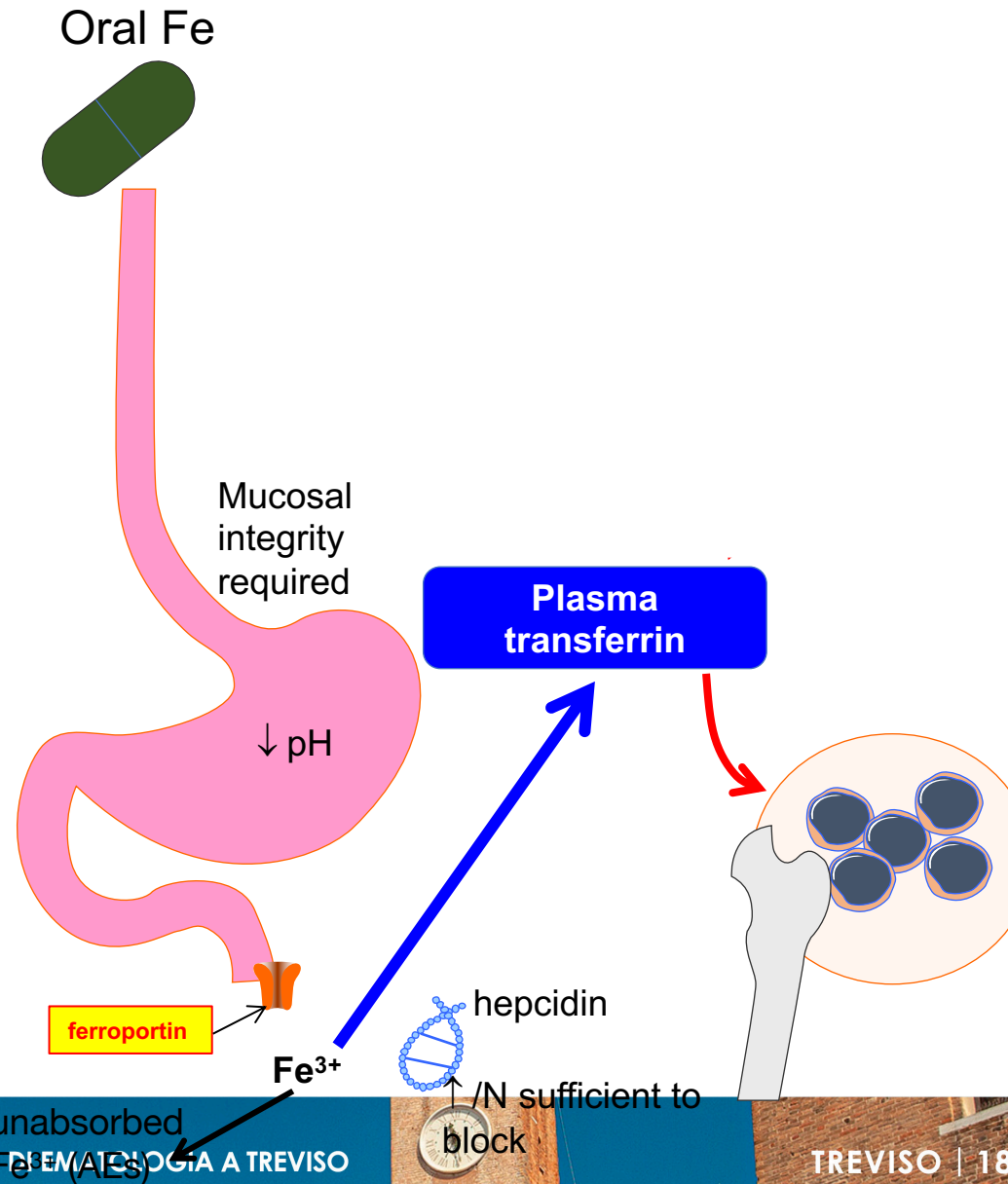
Table 3
Diagnostic biomarkers of iron deficiency.

	Meaning	Proposed threshold	Pros	Cons	References
Ferritin	Protein released by stores; index of iron stores except in inflammation	≤ 30 µg/dL (≤ 100 or up to 300 if TSAT < 20% in inflammation)	Widely available, cheap, diagnostic as single test in absence of comorbidities	Heavily influenced by inflammation	(Garcia-Casal et al., 2018; Cappellini et al., 2017; Ginzburg, 2019)
TSAT	Index of iron available for erythropoiesis and other tissues	< 20%	Widely available, cheap, useful also in the presence of inflammation	May be influenced by transferrin fluctuations	Cacoub et al. (2019)
MCV	Erythrocyte mean volume	< 80 fl	Classical index, almost invariably present in young patients with IDA	Useless in the elderly with comorbidity	Girelli et al. (2018)
%HYPO	Early index of iron-restricted erythropoiesis especially after ESAs	> 6%	Available with routine CBC with modern counters. Fast turnaround	Need of a specific request to the laboratory.	Archer and Brugnara (2015)
CHR	Reflects recent changes of Hb synthesis	Vary across different studies	Available with routine CBC with modern counters. Fast turnaround. Early detection of iron therapy efficacy	Need of a specific request to the laboratory. Further studies required	(Archer and Brugnara, 2015; Ogawa et al., 2020)
sTfR	Index of iron avidity of erythroid precursors	Vary across different methods and studies	Unaffected by inflammation Potentially useful to detect ID in AI	Lack of standardization	Ginzburg (2019)
sTfR/log ferritin	sTfR normalized to ferritin levels	> 2	Useful for detecting ID in the context of AI	Lack of standardization (sTfR).	Ginzburg (2019)
Hepcidin	Physiologic regulator of systemic iron homeostasis	N.A.	Diagnostic in special conditions (e.g. IRIDA)	Available only at referral centers. International harmonization in progress.	Girelli et al. (2016)
Zpp:H	Reflects iron/zinc competition in the last step of heme synthesis	Vary across different age populations	Easy to use, valuable screening tool to exclude IDA	Marker of iron restricted erythropoiesis; cannot distinguish between absolute and functional ID	Ginzburg (2019)

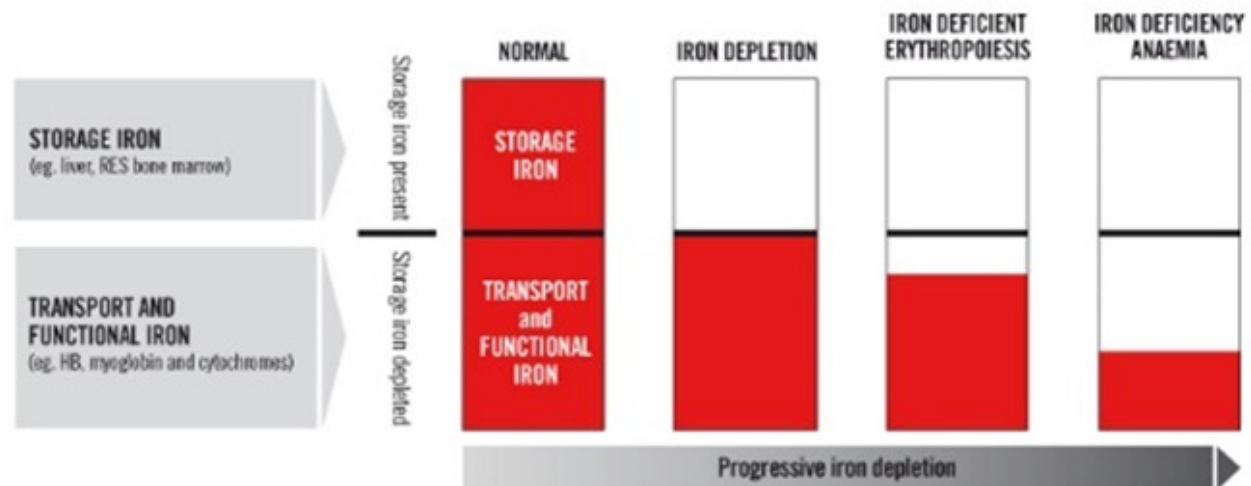
TSAT: transferrin saturation; %HYPO: percent of hypochromic red cells; CBC: complete blood count; CHR: reticulocyte hemoglobin content; sTfR: soluble Transferrin Receptor; sTfR/log ferritin: ratio of sTfR to log ferritin; Zpp/H: ratio of erythrocyte Zinc Protoporphyrin to heme; N.A.: not available.



Different pharmacokinetic between oral and IV iron, revisited in the hepcidin era



SPECTRUM OF IRON DEFICIENCY



Example of laboratory profile

Serum ferritin (µg/L)	60	<15	<15	<15
Transferrin saturation (%)	35	35	<15	<15
Haemoglobin (g/L) – female	>120	>120	>120	<120
Haemoglobin (g/L) – male	>130	>130	>130	<130

Modified with permission from Sarah Curick PhD, Centers for Disease Control and Prevention, 2008.

transfusion.com.au

 Australian Red Cross
BLOOD SERVICE

Know Your Ferritin Numbers!



Ideal level: 30-100ng/mL

Reserve tank: < 30

Empty tank: < 15

www.theironclinic.co.uk



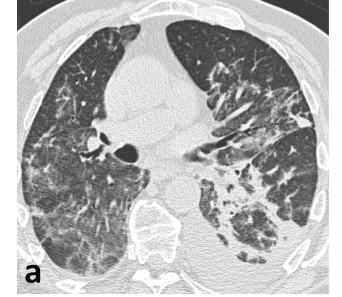


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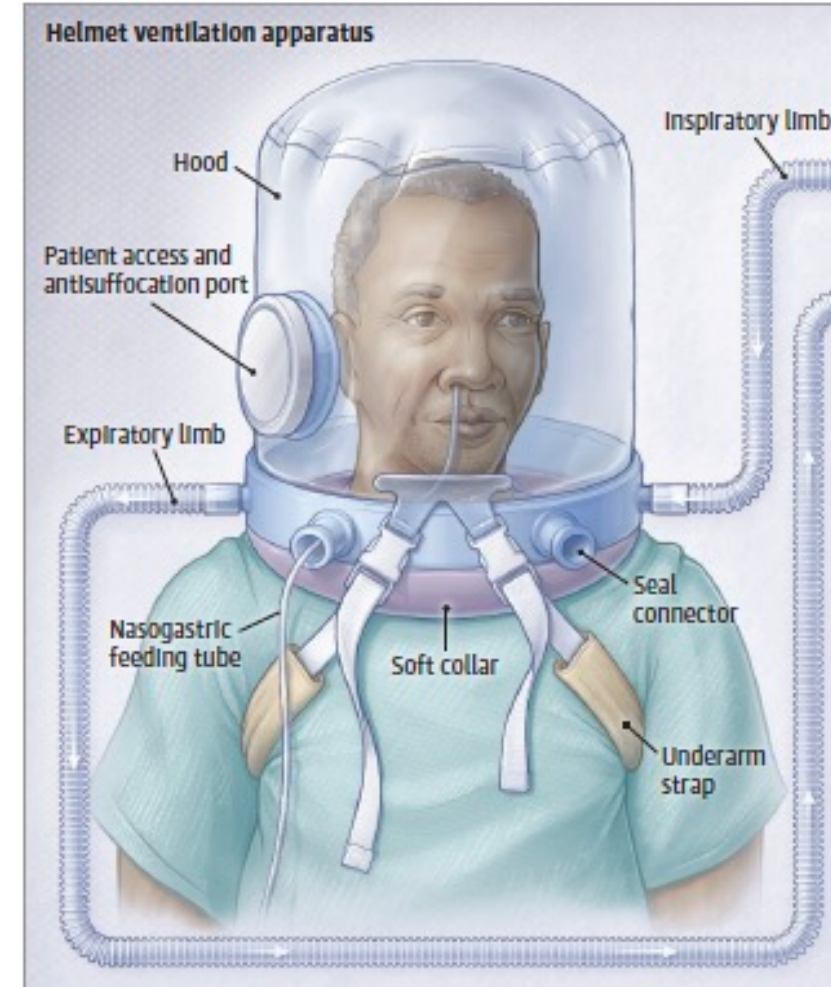
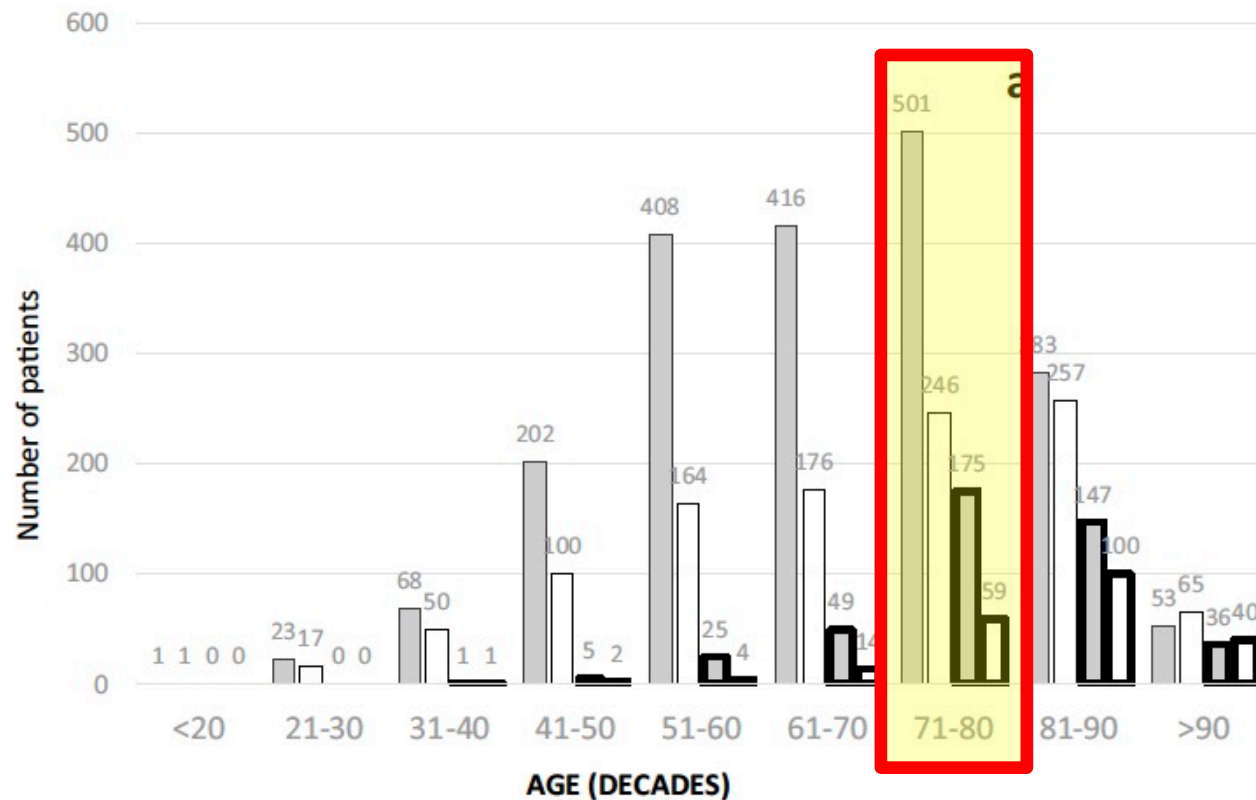
Caso clinico COVID-19 grave: conseguenze dell' «immuno-paralisi»

M 73 a., in PS per febbre, tosse, dispnea.
APR: T2DM, IPA, FA, BPAC, PCLBCL localizzato.
PS: polmonite bilaterale, P/F 98
→ Med. Int. Alta I.



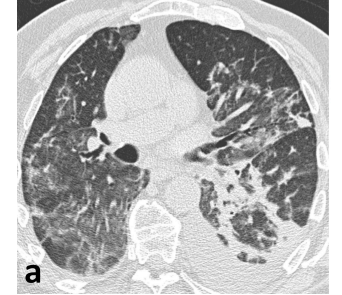
REGISTRO COLLABORATIVO «SIMI-COVID»

Clinical factors associated with death in 3044 COVID-19 patients managed in internal medicine wards in Italy: results from the SIMI-COVID-19 study of the Italian Society of Internal Medicine (SIMI)



Caso clinico COVID-19 grave: conseguenze dell' «immuno-paralisi»

M 73 a., in PS per febbre, tosse, dispnea.
APR: T2DM, IPA, FA, BPAC, PCLBCL localizzato.
PS: polmonite bilaterale, P/F 98
→ Med. Int. Alta I.



PCR 263 mg/L, GB 16,610/mm³ (N 15,940/mm³; L 260/mm³), ferritina 487 µg/L, D-dimero 719 µg/L, fibrinogeno 8.91 g/L. Hb, PLTs, AST, ALT, Cr. normali. L. T CD4+ 100/mm³.

NIV (CPAP) → miglioramento graduale fino a svezzamento (giorno 14).

giorno 18: dolore epigastrico, melena, ipotensione, tachicardia; ↓ Hb 14.5 → 10.6 g/dL.

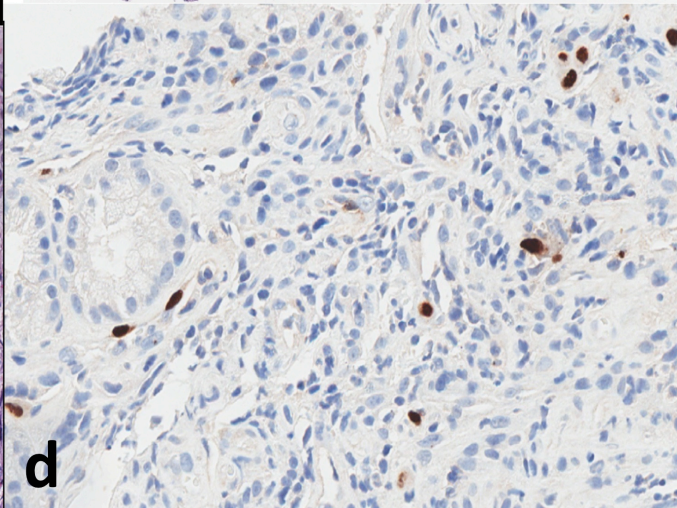
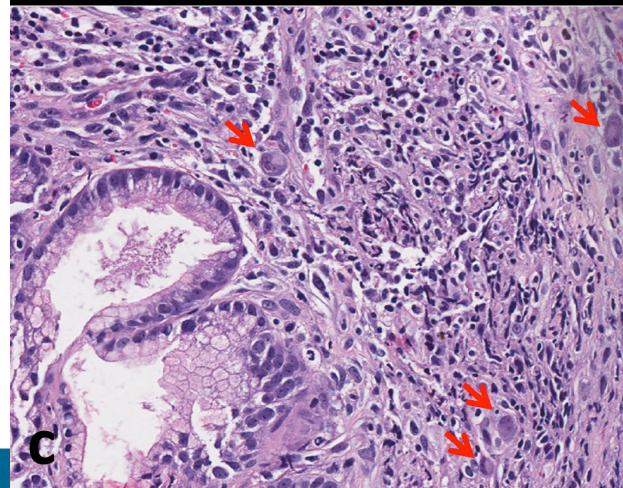
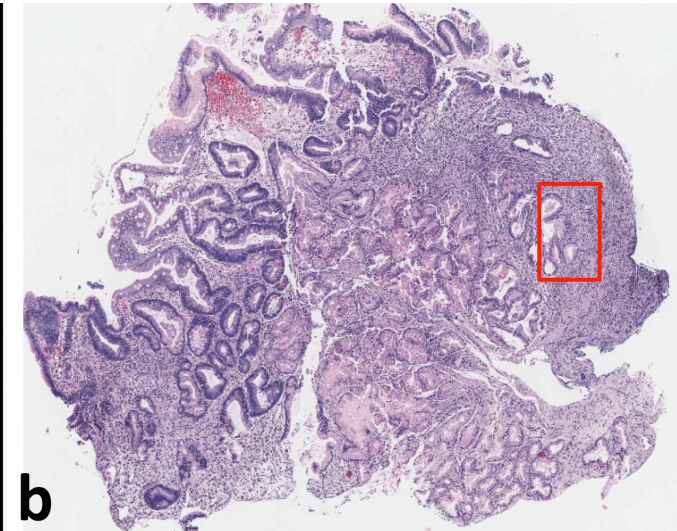
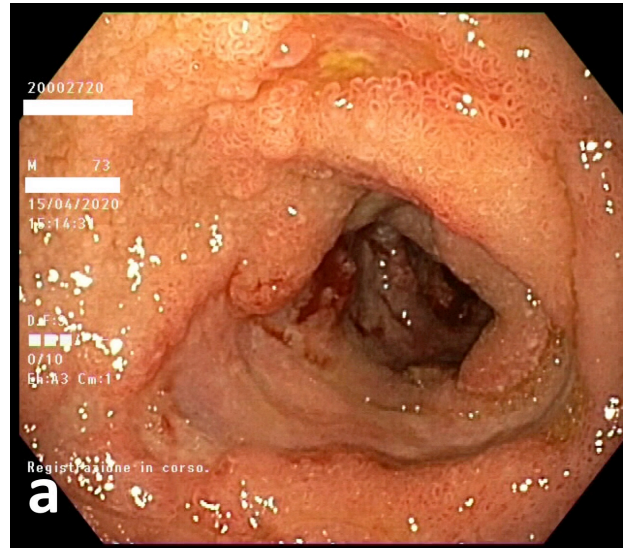
Stabilizzazione emodinamica (riempimento volemico + 2 U GRC) → EGDS.



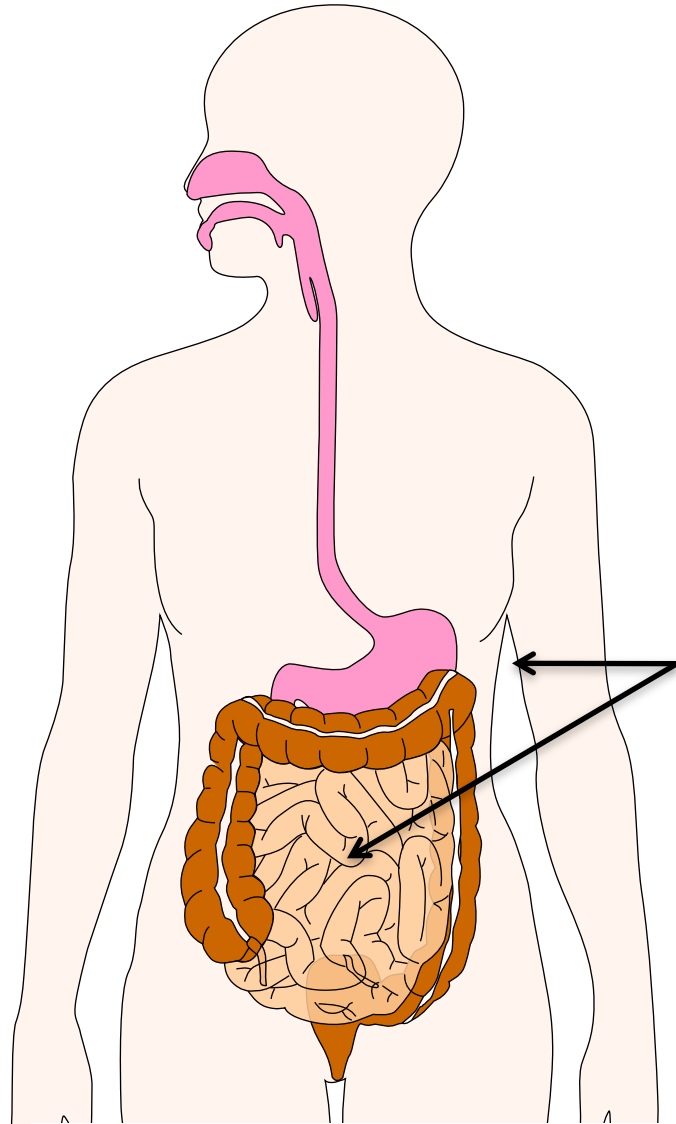
Caso clinico COVID-19 grave: conseguenze dell' «immuno-paralisi»

Ulcere duodenali multiple con pattern pseudo-ischemico → infezione da **Cytomegalovirus** confermata da es. Istologico e immunoistochimico.

→ Ganciclovir per 2 sett. → evoluzione favorevole (CMV-DNA 6080→1320 IU/mL, ripresa alimentazione e dimissione).



Acquired IRIDA (iron malabsorption with ↓ hepcidin)



Malabsorption

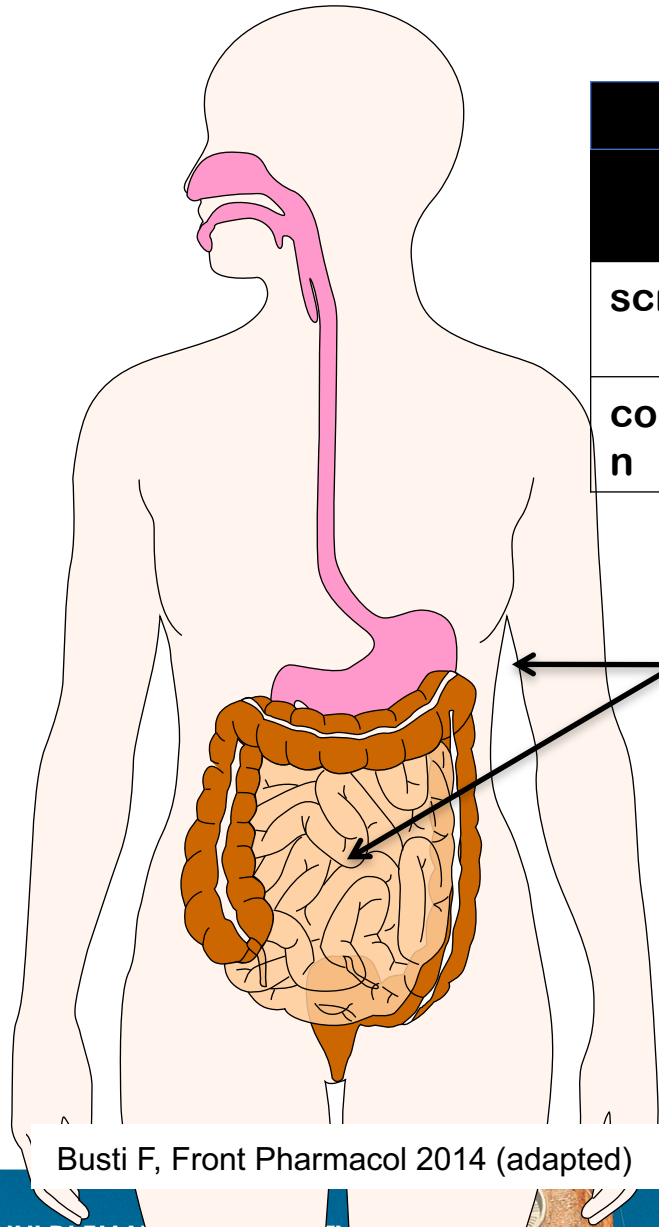
- ✓ Chronic gastritis (i.e. autoimmune, HP-associated)
- ✓ Celiac Disease
- ✓ (PPI)



refractory
IDA

Busti F, Front Pharmacol 2014 (adapted)

Acquired IRIDA (iron malabsorption with ↓ hepcidin)



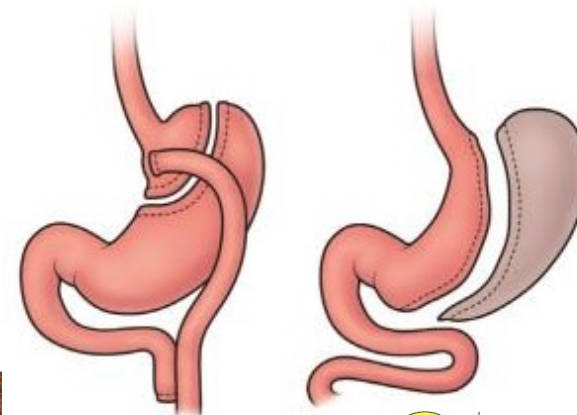
Diagnostic workup for unexplained or refractory IDA			
	H pylori	Autoimmune gastritis	Celiac disease
screening	Hp Ab or fecal Ag	APCA	TTG IgA (+ total IgA)
confirmation	(EGDS biopsy)	EGDS biopsy	EGDS biopsy

Hershko C, Blood 2014

Malabsorption

- ✓ Chronic gastritis (i.e. autoimmune, HP-associated)
- ✓ Celiac Disease
- ✓ (PPI)

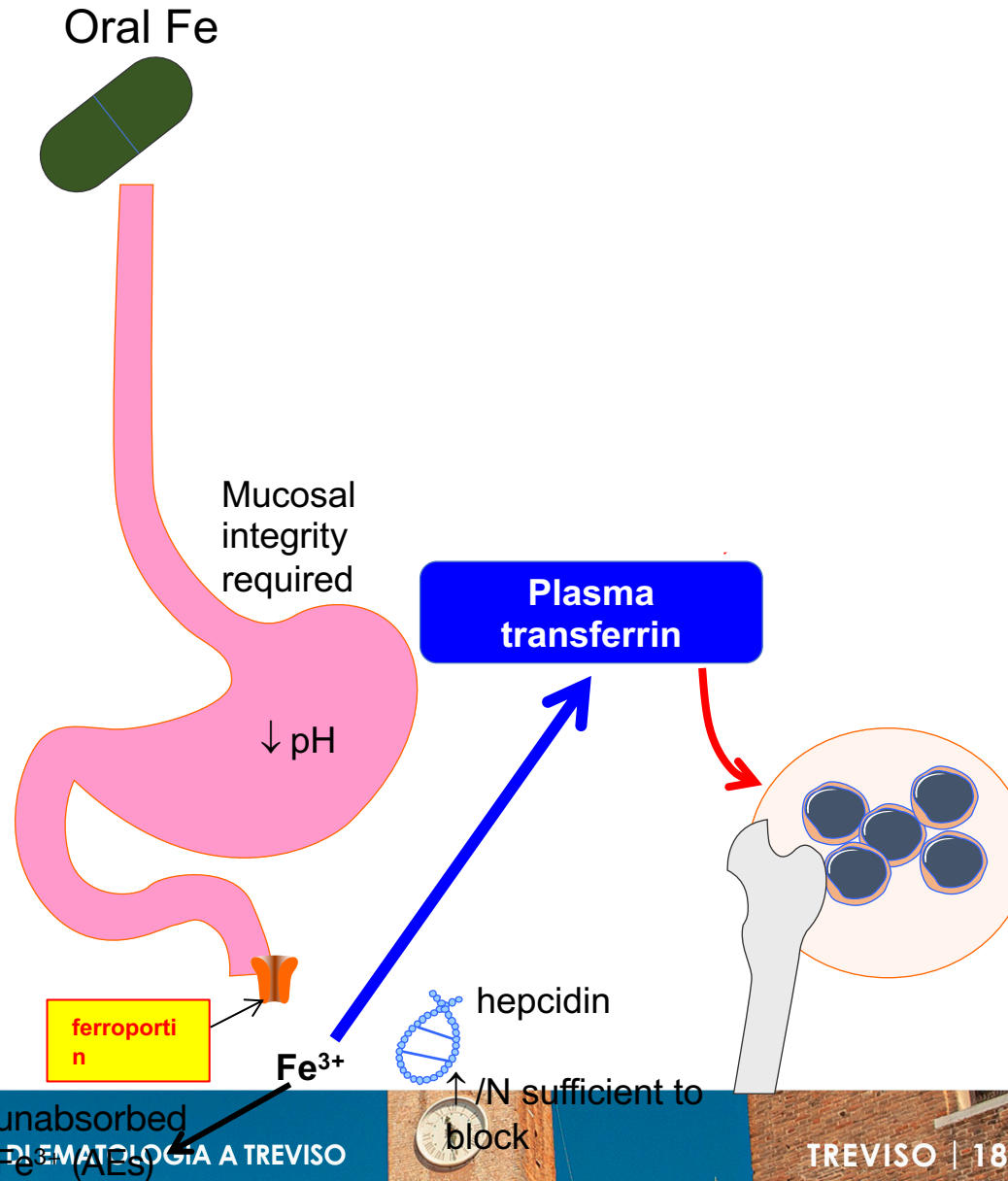
BARIATRIC SURGERY
 Roux-en-Y Gastric Bypass (RYGB) Vertical Sleeve Gastrectomy (VSG)



refractory IDA

Busti F, Front Pharmacol 2014 (adapted)

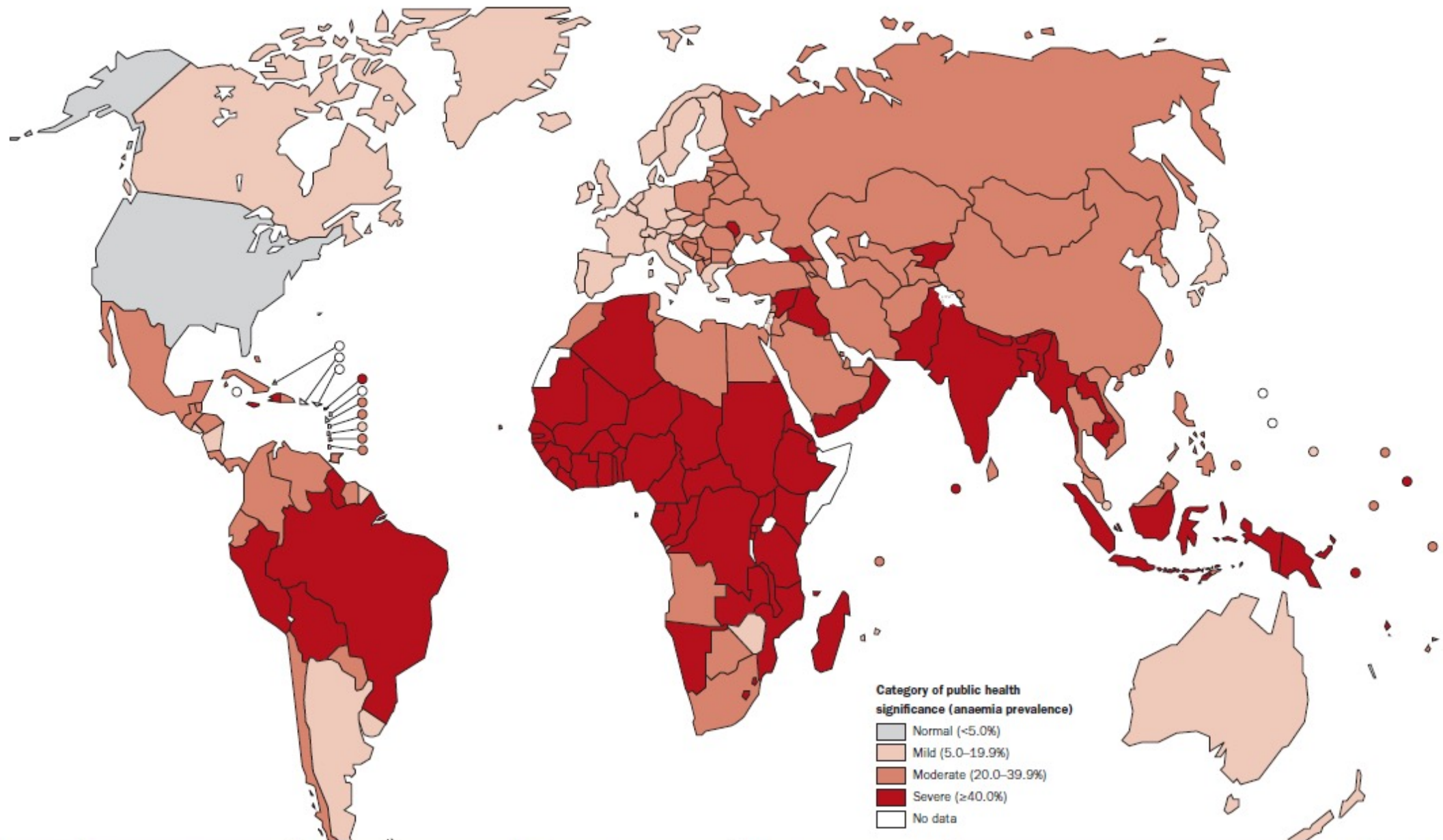
Different pharmacokinetic between oral and IV iron, revisited in the hepcidin era



Girelli D, Int J Hematol 2018

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Figure 3.1a Anaemia as a public health problem by country: Preschool-age children



Diagnostic workup for acquired IRIDA

	<i>H pylori</i>	Autoimmune gastritis	Celiac disease
Screening	<i>H pylori</i> IgG antibodies or fecal antigen	Serum gastrin Anti-parietal Abs Anti-intrinsic factor Abs	Tissue transglutaminase IgA Abs
Advanced	Urease breath test Gastroscopy and biopsies (optional)	Gastroscopy and biopsies (recommended)	Duodenal biopsy, HLA screening for DQ2 or DQ8 genotypes
Response to specific treatment	<i>H pylori</i> eradication	N.A.	Gluten-free diet

Hershko & Camaschella, Blood 2014

IDA in elderly: a case paradigm

- S.A. aged 70
- Unexplained IDA since 2006
- FOB intermittently +
- EGDS -
- Colon endoscopy -
- Virtual colonoscopy -
- Multiple transfusions (last yr)



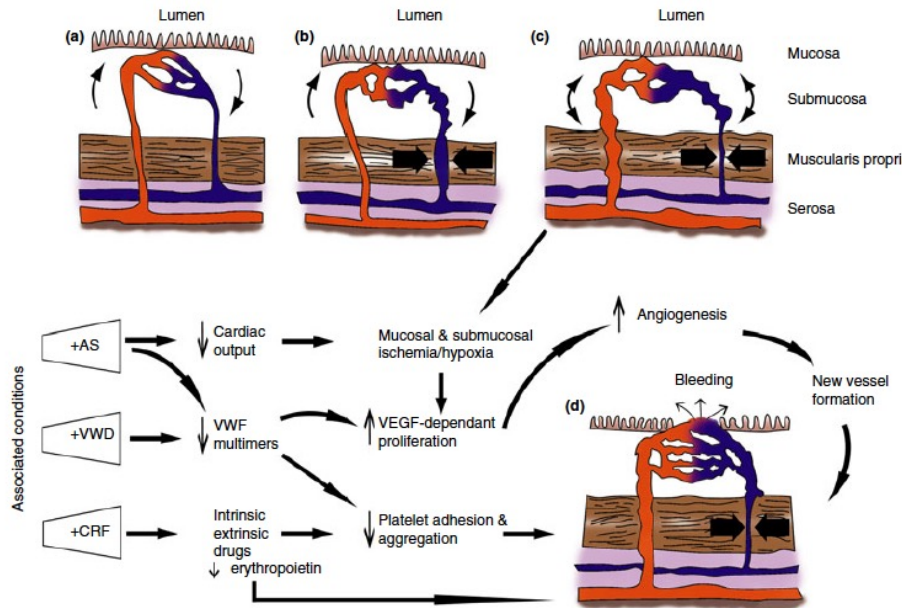
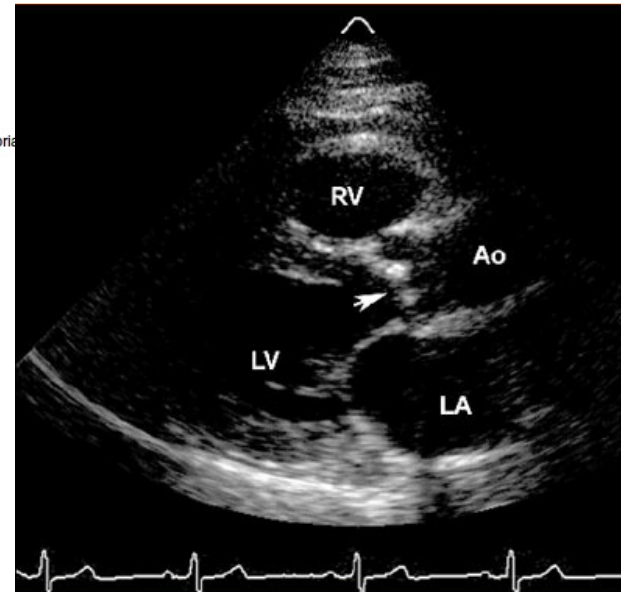
Angiodysplasia in the ascending colon (WCE)



Heyde's syndrome (1958)



Calcific aortic stenosis

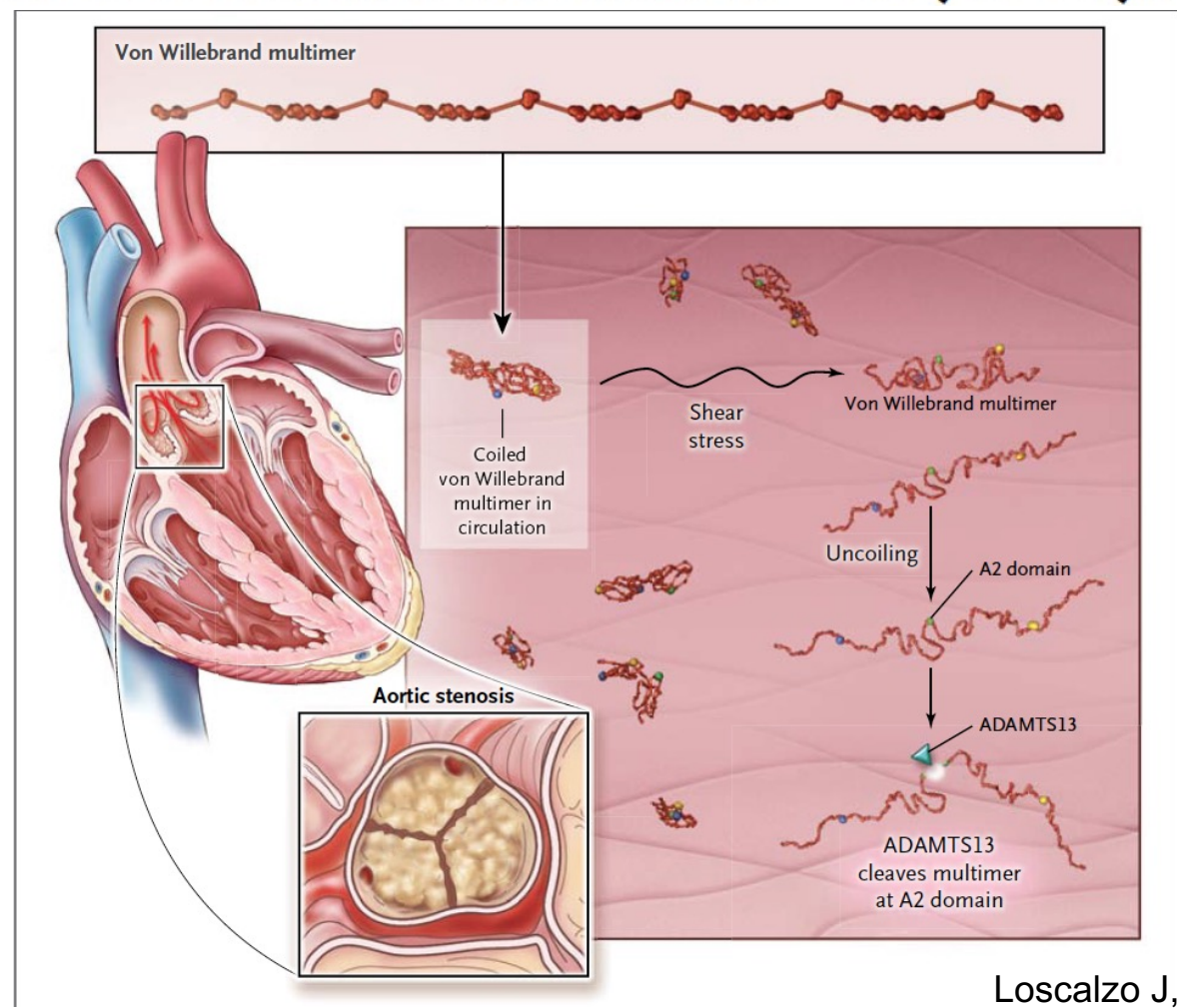


Sami SS, Aliment Pharmacol Ther 2014

Acquired von Willebrand's disease in Heyde's Syndrome

CLINICAL IMPLICATIONS OF BASIC RESEARCH

From Clinical Observation to Mechanism — Heyde's Syndrome



Loscalzo J, New Engl J Med 2012

20 ANNI DI EMATOLOGIA A TREVISO

Treviso, Auditorium Fondazione Cassamarca

18-20 Novembre 2021

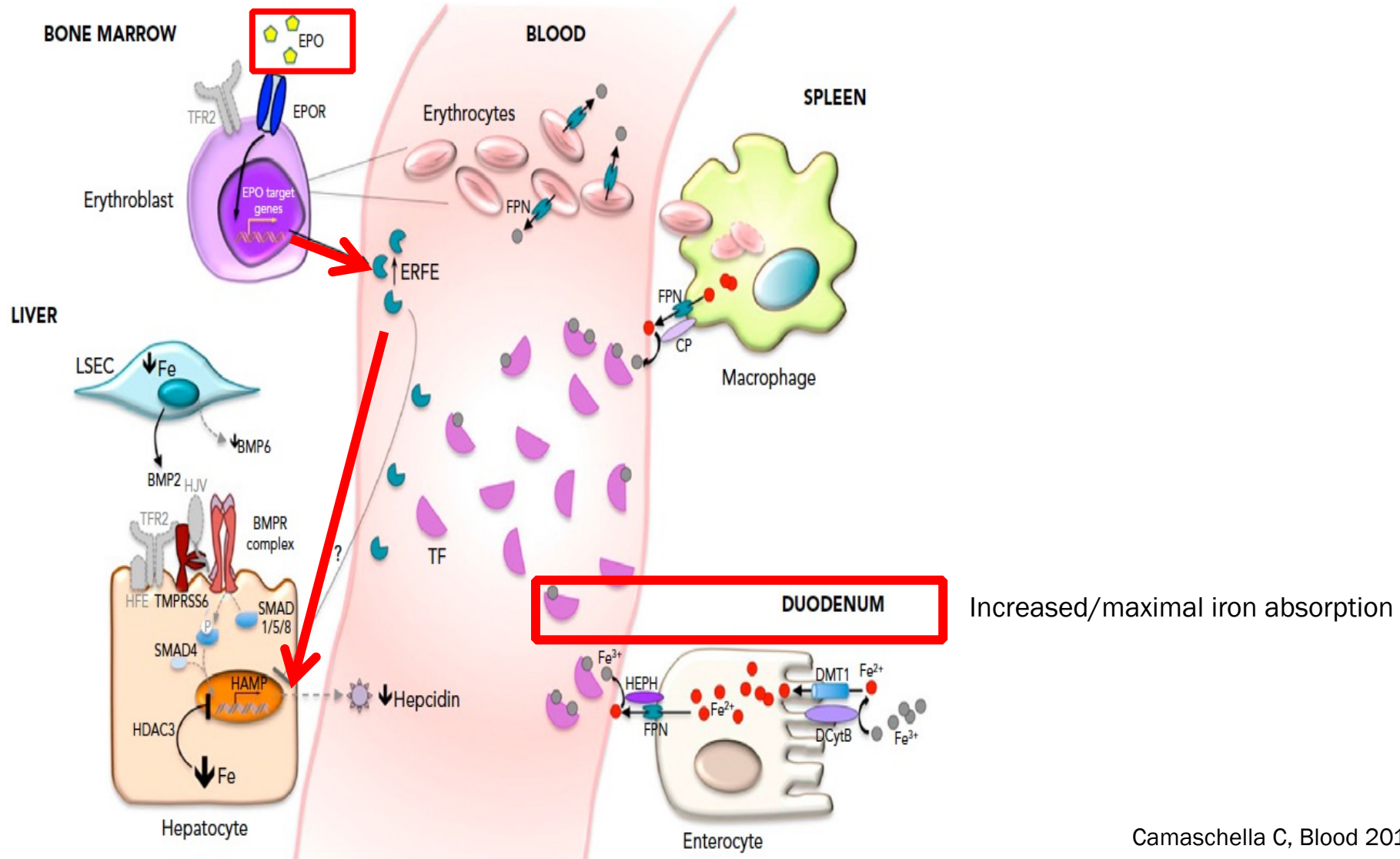
DICHIARAZIONE

Relatore: NOME COGNOME

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Altro

Hepcidin suppression in IDA



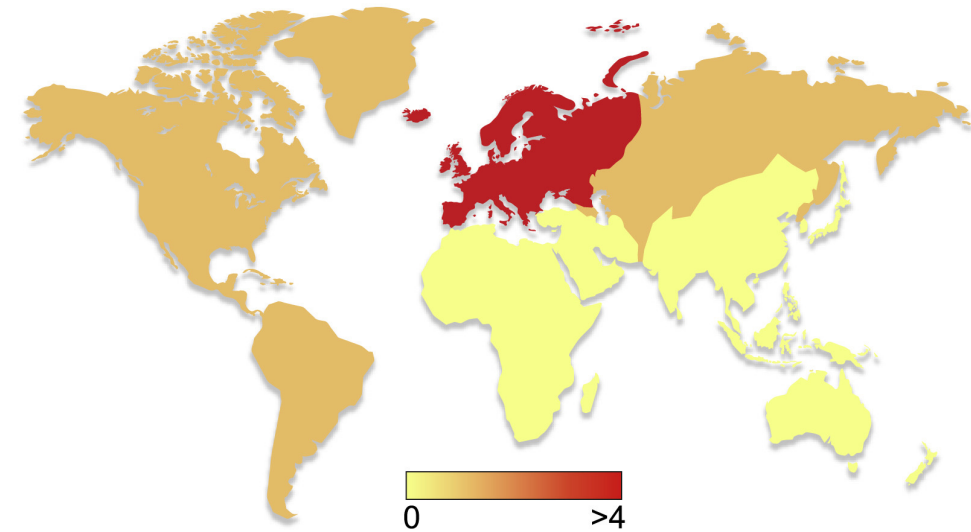
Camaschella C, Blood 2019

Iron imbalance as a global health concern

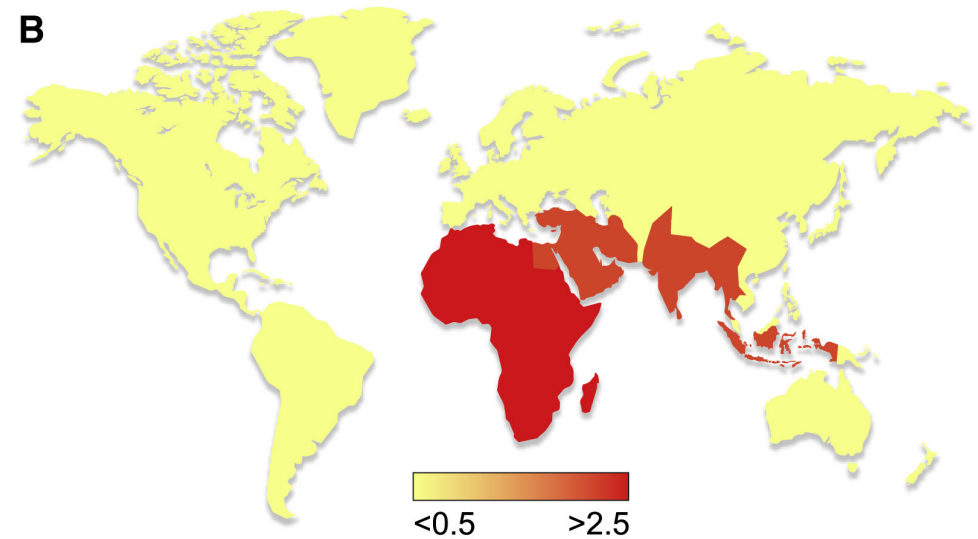
(A) Frequency of C282Y allele (linked to hemochromatosis) in origin populations.

(B) Percent (%) population experiencing severe anemia among children and women (WHO 2015)

A



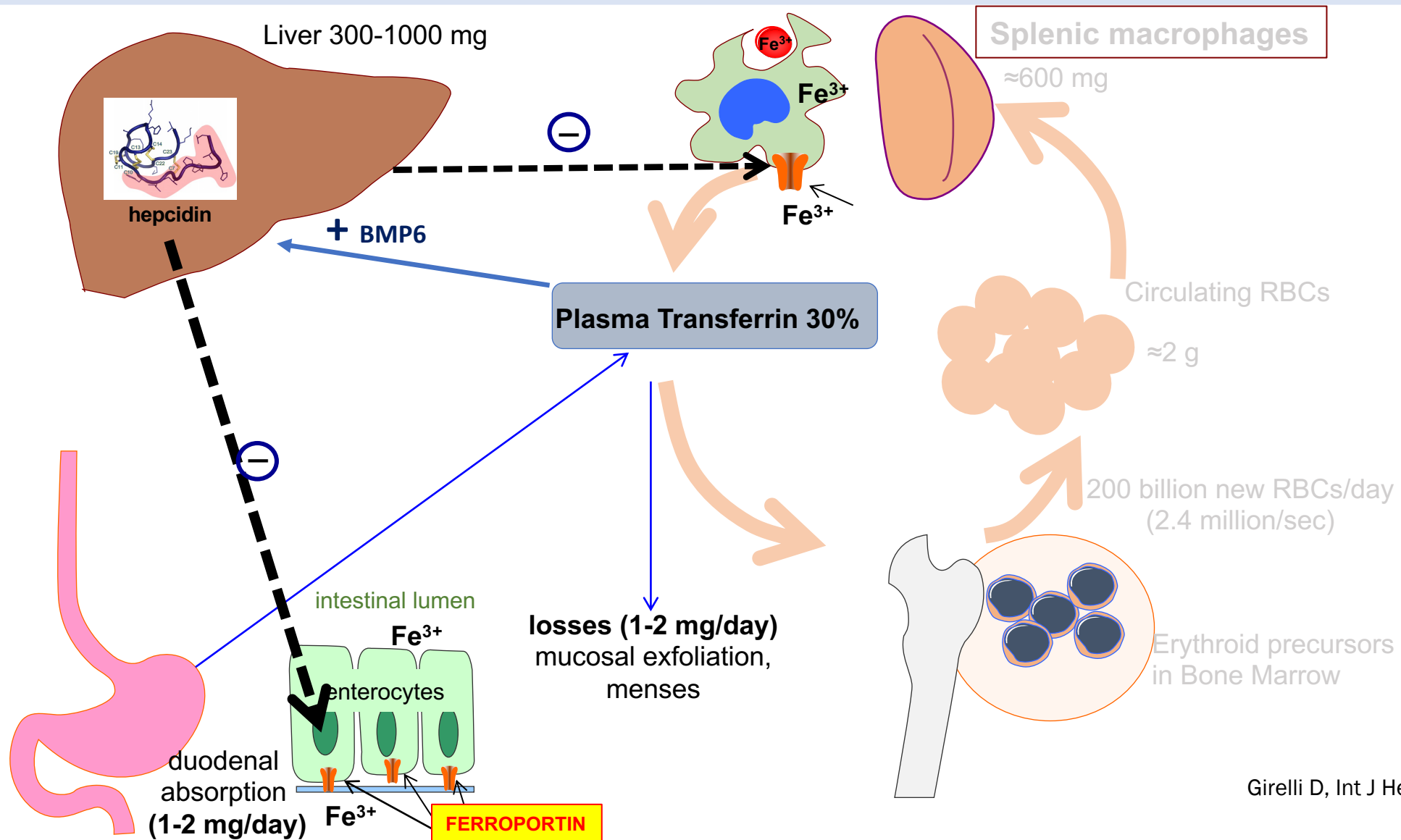
B



Das NK, Cell Metab 2021

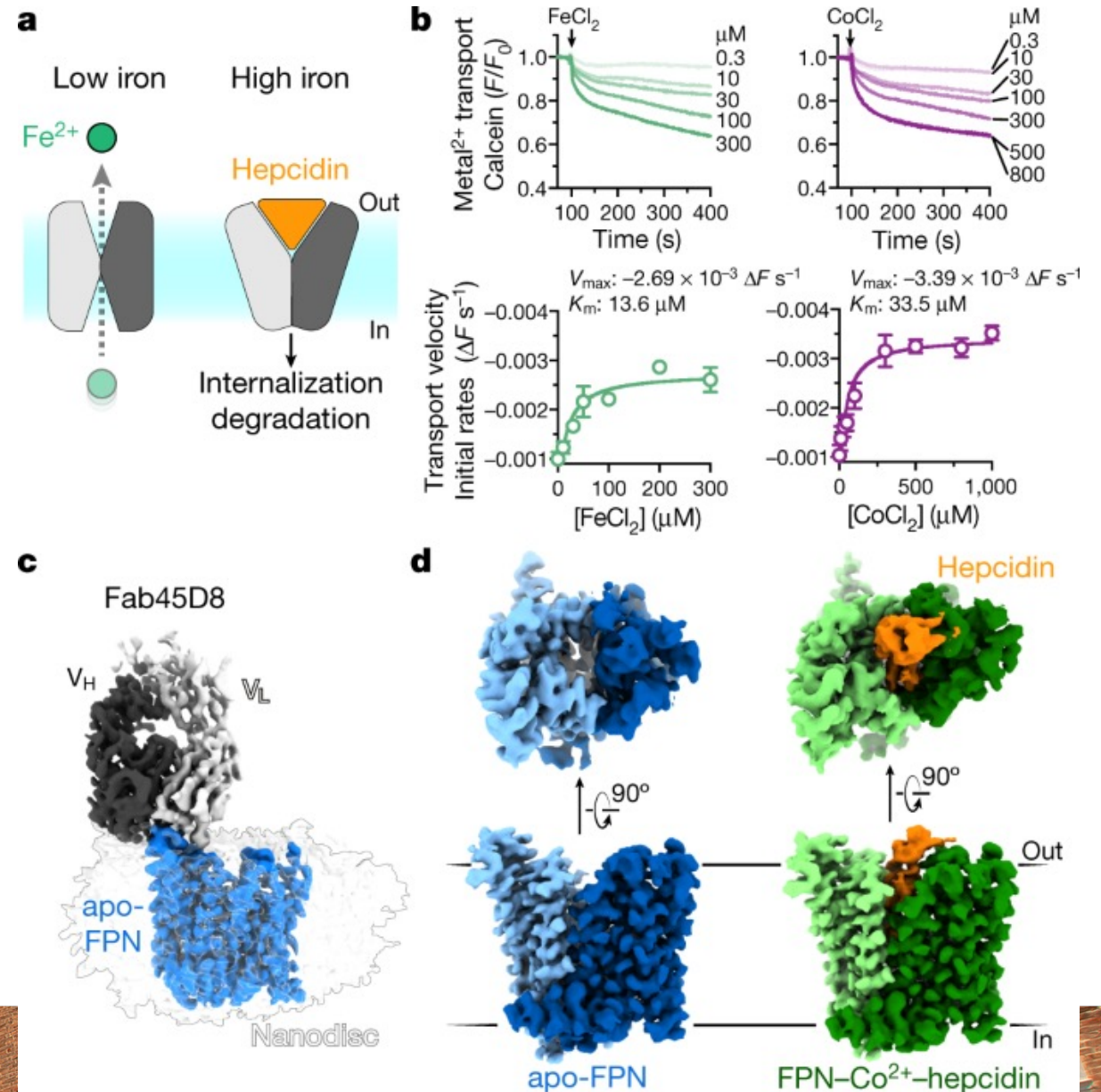


Systemic “ecological” iron homeostasis



Girelli D, Int J Hematol 2018 (adapted)

Hepcidin-ferroportin interaction



Billesbolle CB, Nature 2020



Topics



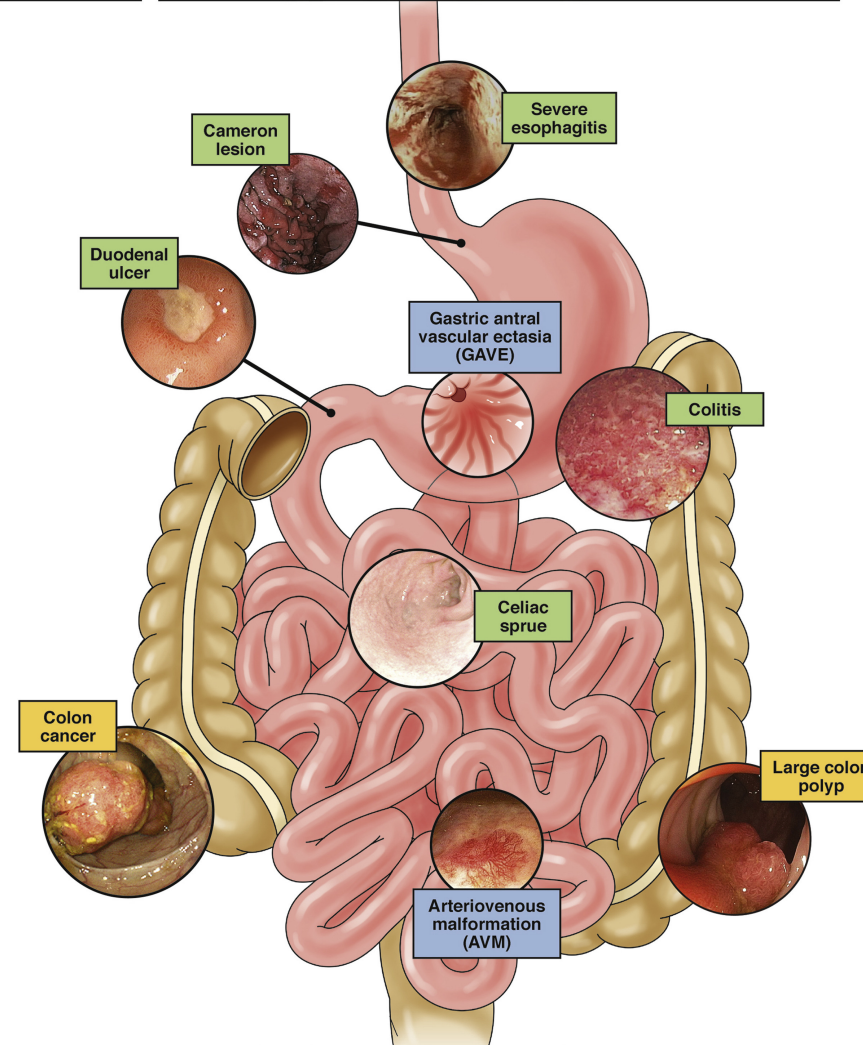
Topics



AGA Technical Review on Gastrointestinal Evaluation of Iron Deficiency Anemia

Rockey DC,
Gastroenterology 2020

Mass lesions	Inflammatory		
<ul style="list-style-type: none"> • Carcinoma (any site) • Large polyps (any site) 	<ul style="list-style-type: none"> • Reflux esophagitis • Cameron lesions • Erosive gastritis • Gastric ulcer 	<ul style="list-style-type: none"> • Duodenal ulcer • SB or colon ulcer • Celiac sprue • Whipple's disease 	<ul style="list-style-type: none"> • Meckel's diverticulum • Idiopathic ulcers • Crohn's disease • Ulcerative colitis

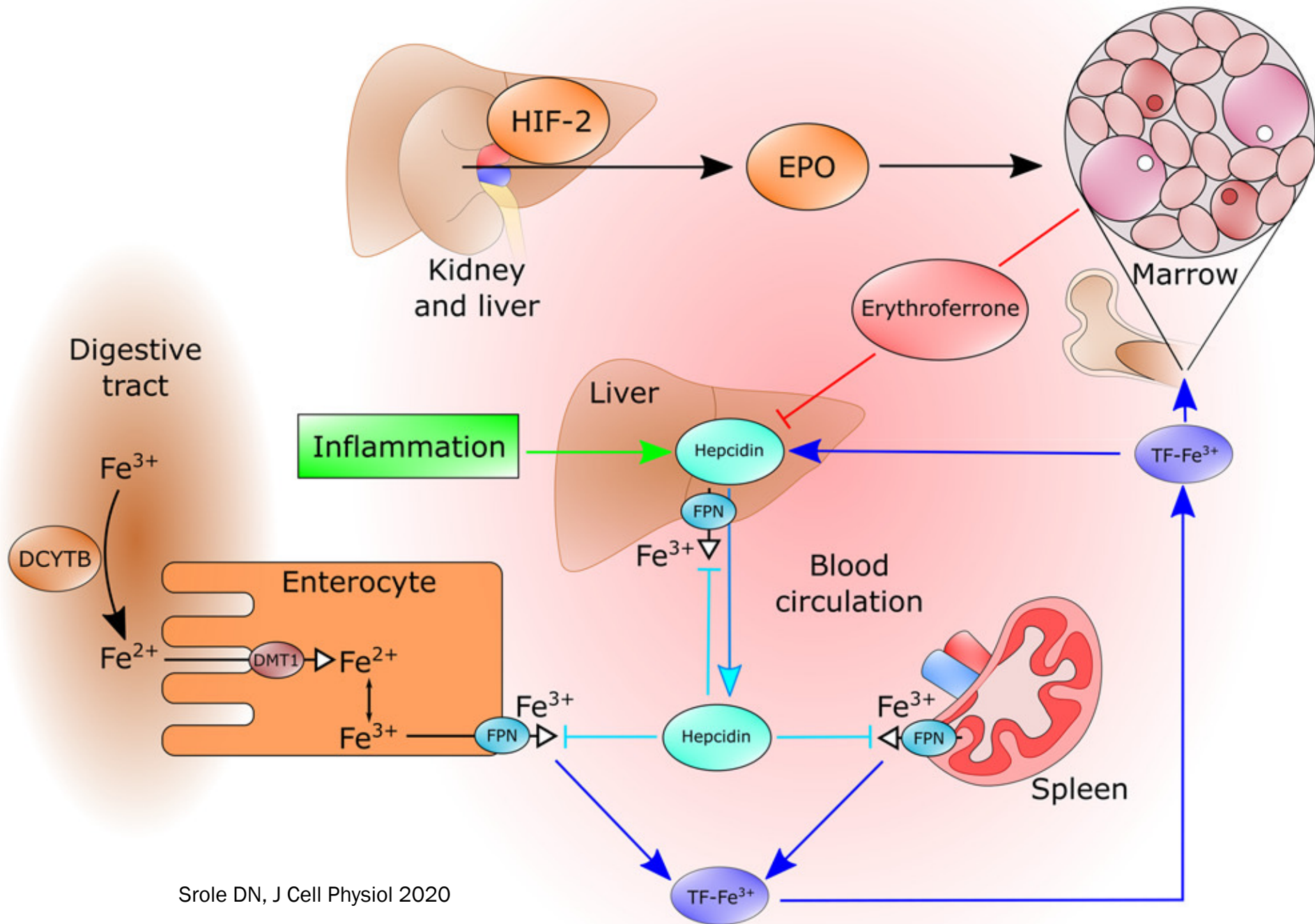


Vascular		Infectious and miscellaneous		
<ul style="list-style-type: none"> • Vascular ectasia(s) • Portal hypertensive lesions 	<ul style="list-style-type: none"> • Watermelon stomach • Hemangiomas • Blue rubber bleb nevus syndrome 	<ul style="list-style-type: none"> • Hookworm • Hemoptysis • Epistaxis 	<ul style="list-style-type: none"> • Strongyloidiasis • Ascariasis • Tuberculous enterocolitis 	<ul style="list-style-type: none"> • Amebiasis • Long-distance running • Factitious



ERFE–hepcidin–ferroportin axis

Interstitial fibroblasts in the kidney and hepatocytes in the liver respond to cellular hypoxia by HIF-2-induced transcription and production of EPO. EPO stimulates the expansion of erythroblasts as well as increases production of ERFE. ERFE inhibits the transcription of hepatic hepcidin, thereby stabilizing the cellular iron exporter ferroportin on the surfaces of hepatocytes and macrophages. Cellular iron stores are then mobilized into plasma to be used for hemoglobin synthesis by the expanded population of maturing erythrocytes.



Srole DN, J Cell Physiol 2020

Either Iron Deficiency or Iron Overload is detrimental

