Iron deficiency anemia: New developments in diagnosis and treatment

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Faculty disclosure

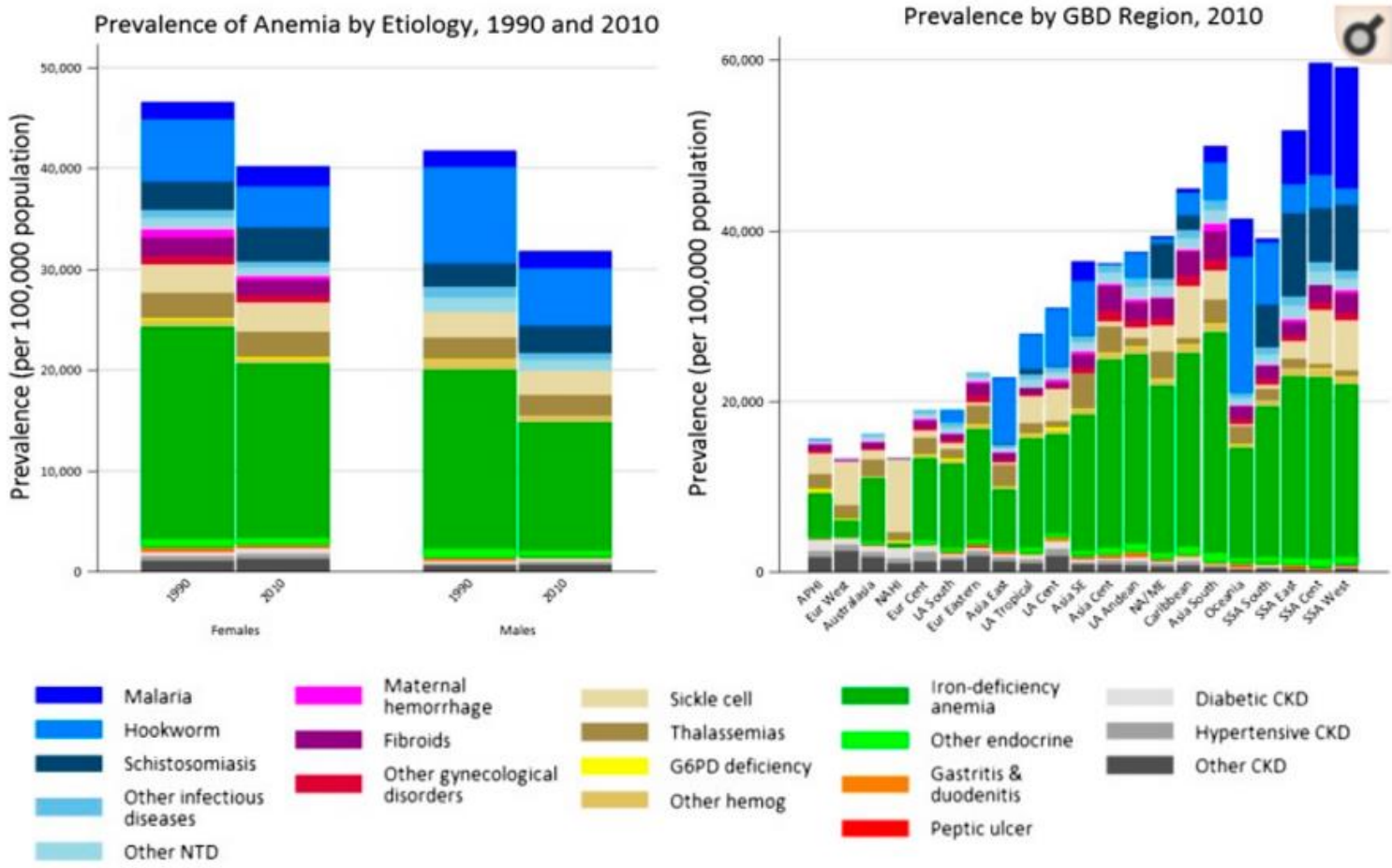
- Research funding from American Regent
- Off-label use of intravenous iron therapy in children will be discussed

Objectives

- Recognize causes and clinical presentations of iron deficiency anemia (IDA) by age group and sex
- Recall the conventional IDA diagnostic tests and treatment approaches
- Describe the limitations of past and current IDA management practices
- Use novel treatment strategies with oral and/or intravenous iron to improve outcomes of patients with IDA

PREVALENCE AND RISK FACTORS

IDA affects over 1 billion people globally



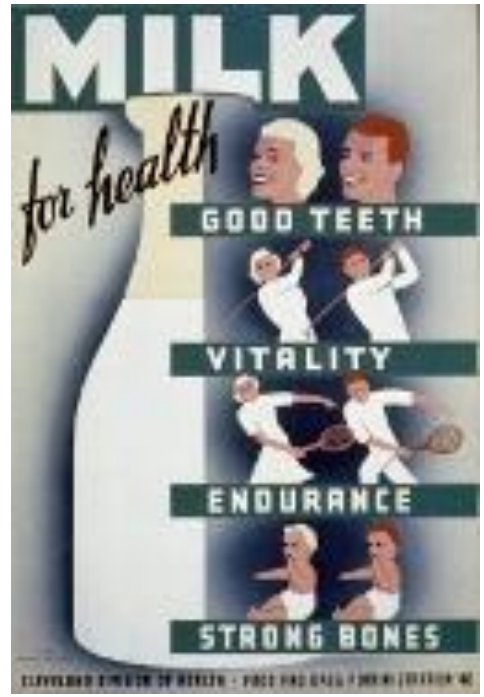
Kassebaum, et al. Blood. 2014.

Majority affected are women and children

- In US, iron deficiency, with/without anemia, affects:
  - 3-7% of young children
  - 9-16% of adolescent girls
  - 9-20% of adult women
- Disproportionately affects those from:
  - Low socioeconomic background
  - Racial/ethnic minority groups

The rise of IDA in young children in U.S.

- 1940s: Rates of breast-feeding decreased + federal-funding to advertise milk → cow milk anemia
- 1970s: Formulas iron-fortified & WIC program developed



WIC
WOMEN · INFANTS · CHILDREN

Iron deficiency: Neurocognitive outcomes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Institution: N/A

Article

Iron Deficiency Anemia and Iron Therapy Effects on Infant Developmental Test Performance

Betsy Lozoff, Gary M. Brittenham, Abraham W. Wolf, Donna K. McClish, Paul M. Kuhnert, Elias Jimenez, Rafael Jimenez, Luis A. Mora, Ivonne Gomez, Dina Krauskoph


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ORIGINAL ARTICLE

Long-Term Developmental Outcome of Infants with Iron Deficiency

- Costa Rican cohort treated with IM vs oral iron
- Developmental assessment: baseline, 1 week, 3 months
- Children with IDA did worse initially & only partially improved after correction of anemia

Lozoff B, et al. Pediatrics. 1987; NEJM. 1991

Iron deficiency: Non-hematologic effects

Iron's critical functions:

- DNA synthesis
- Energy metabolism
- Myelination
- Neurotransmitter metabolism
- Immune function
- Myoglobin structural component

Iron deficiency symptoms:

- Pica
- Restless legs syndrome
- Periodic movements of limbs
- Fatigue
- Impaired concentration
- Diminished work performance

American Academy of Pediatrics (AAP): Screening recommendations

- Current: AAP Report on Prevention & Diagnosis of IDA, 2010
  - Universal laboratory screening at 12 months
  - Other well child time points - assess risk factors & screen
- Future: AAP/ASPHO Report on Treatment of IDA, 2020?
  - Universal laboratory screening at 9 to 12 months
  - Repeat screening at 15 to 18 months
    - High risk transition period from breastfeeding / formula
    - Children with excessive cow milk intake often present (age 20 to 22 months)
  - Universal laboratory screening of adolescent girls

Screening Recommendations from Other Medical Organizations

Organization	Children	Women
American College of Obstetricians and Gynecologists (ACOG)	Screen adolescents with heavy menstrual bleeding	Prenatal screening in the earliest prenatal visit and early in third trimester
Centers for Disease Control and Prevention (CDC)	Screen for IDA in high-risk infants, high-risk preschool children	Screen pregnant women and non-pregnant women of childbearing age
American Academy of Family Physicians (AAFP)	Screen high-risk infants & young children whose diet is primarily cow milk	--
United States Preventive Services Task Force (USPSTF)	No recommendation due to insufficient evidence	No recommendation due to insufficient evidence

IDA CASE PRESENTATIONS

Case 1: Can’t quit the bottle

- An 18 month old Latino boy appears for WCC
- Picky eater, only wants milk
- Exam:
  - Well-nourished but pale
  - Drinking from large bottle of milk
  - Systolic flow murmur
- POC Hgb at 12 month WCC normal (12 g/dL)

Excessive cow milk intake and IDA

- Contains little iron (<1 mg/L)
- Iron poorly absorbed (5-10%)
  - Iron in breast milk has 50% absorption
- Excess milk
  - reduced intake of other foods
  - reduced absorption of supplemental iron
- May cause GI bleeding, milk-protein enteropathy
- **Limit to 2 cups per day (16 ounces)**

Additional risk factors: young children

- Prematurity (more premature, higher risk)
- Exclusive breastfeeding beyond 4 to 6 months of age without iron supplementation
- Bottle-fed beyond 1 year of age
- Obesity
- *Protective factor: Daycare attendance*

Brotanek et al. Pediatrics 2007;
Arch Pediatr Adolesc Med 2005.

Case 2: Taking a knee

- 14 year old African American girl presents with complaints of fatigue
- Star athlete but tiring out during basketball practice
  - Getting winded more rapidly compared to peers
  - Parents think she is out of shape, not pushing herself
  - Coach suggested iron pills
- Hgb 6.5, Hct 18, MCV 58, RDW 22; Ferritin 2

Chlorosis in young women

- Chlorosis or “green sickness” described in young women – pale, tired, faint
- Medicinal syrup – iron filings steeped in cold wine – used to treat
- *“…when one gives [iron] in the pale color the pulse becomes at once fuller and slower, the pallor disappears and once again the face is rosy and ruddy”*

  – Sydenham, 1661
- **First successful therapeutic iron trial!**

IDA risk factors: adolescent girls & young women

- Menstrual blood loss
  - Heavy menstrual bleeding (HMB)
  - Acute and/or chronic
- Adolescent growth spurts
- Poor or low iron diet
- Athlete’s anemia
  - Gastrointestinal & renal losses
  - High endurance athletes, long-distance runners

Original Study

Iron Deficiency Anemia in Adolescents Who Present with Heavy Menstrual Bleeding

Amanda G. Cooke MD [1], Timothy L. McCavit MD, MS [2], George R. Buchanan MD [3], Jacquelyn M. Powers MD, MS [4,*]

[1] *Department of Pediatrics, Johns Hopkins All Children's Hospital, St Petersburg, Florida*
[2] *Division of Hematology-Oncology, Department of Pediatrics, Cook Children's Hospital, Fort Worth, Texas*
[3] *Division of Hematology-Oncology, Department of Pediatrics, UT Southwestern Medical Center and Children's Medical Center, Dallas, Texas*
[4] *Division of Hematology-Oncology, Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, Houston, Texas*

Original Study

Hematologic Considerations and Management of Adolescent Girls with Heavy Menstrual Bleeding and Anemia in US Children's Hospitals

Jacquelyn M. Powers MD, MS [1,2,*], Joseph R. Stanek MS [3], Lakshmi Srivaths MD [1,2], Fareeda W. Haamid DO [4,5], Sarah H. O'Brien MD, MS [3,5]

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[3] *Division of Hematology/Oncology, Nationwide Children's Hospital, Columbus, Ohio*
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[5] *Department of Pediatrics, The Ohio State University, Columbus, Ohio*

Cooke, et al. JPAG 2017; Powers, et al. JPAG, 2018

Case 3: “Sonic ice is my favorite”

- A 19 year old woman currently at home from college for fall break presents due to her mom’s concerns for abnormal / “stress-related” behavior
  - Eating toilet paper, family running out more quickly than normal
  - Chewing on ice incessantly
- The patient joined a number of organizations at school, is primarily dieting on cheese pizza, and recently participated in a blood drive on campus

Pica: compulsive eating of non-food items

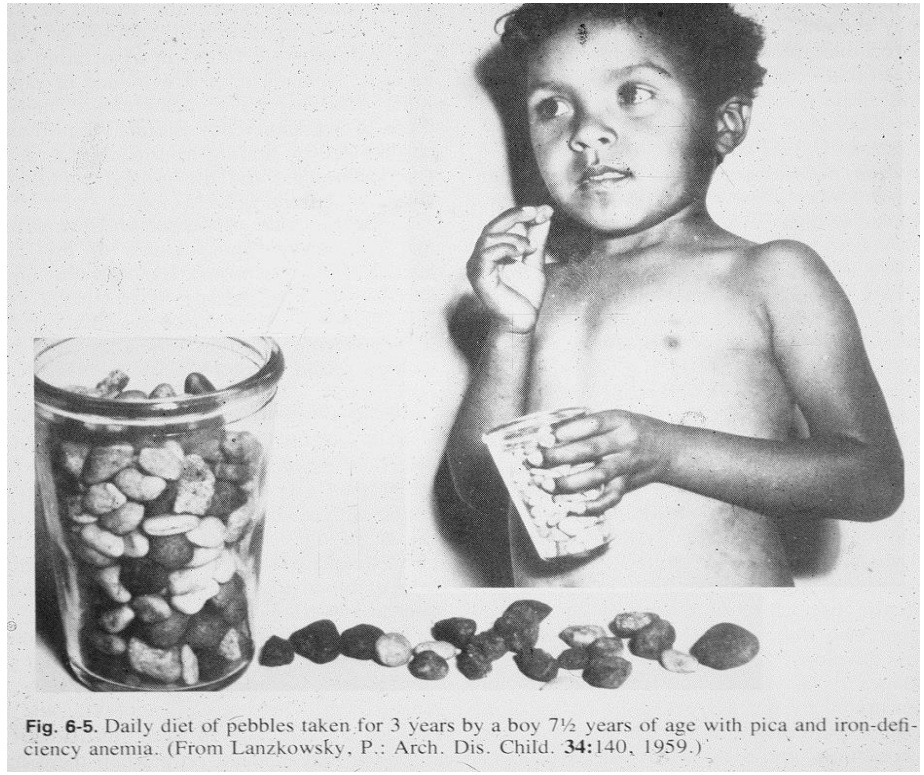
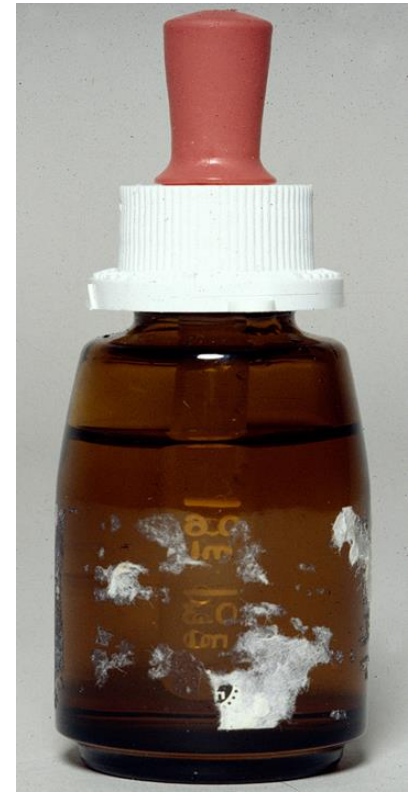


Fig. 6-5. Daily diet of pebbles taken for 3 years by a boy 7½ years of age with pica and iron-deficiency anemia. (From Lanzkowsky, P.: Arch. Dis. Child. **34:**140, 1959.)

Ice, dirt, drywall, cardboard, paper, wipes, erasers, cornstarch, soap, laundry detergent



Blood donation and iron deficiency

- Adolescent and young adult donors (16 years and older) contribute substantially to the U.S. blood supply
- Frequent blood donors at risk for iron deficiency
  - Hgb screening prevents donation by anemic donors but misses those who are iron deficient but not anemic
  - Multiple trials demonstrate benefit of iron supplementation following blood donation (faster recovery to pre-donation levels)

IDA MANAGEMENT

Principles of IDA Management

1. Confirm the diagnosis
2. Identify its cause
3. Correct or manage the primary cause
4. Provide iron therapy (oral versus intravenous)
5. Confirm therapy success

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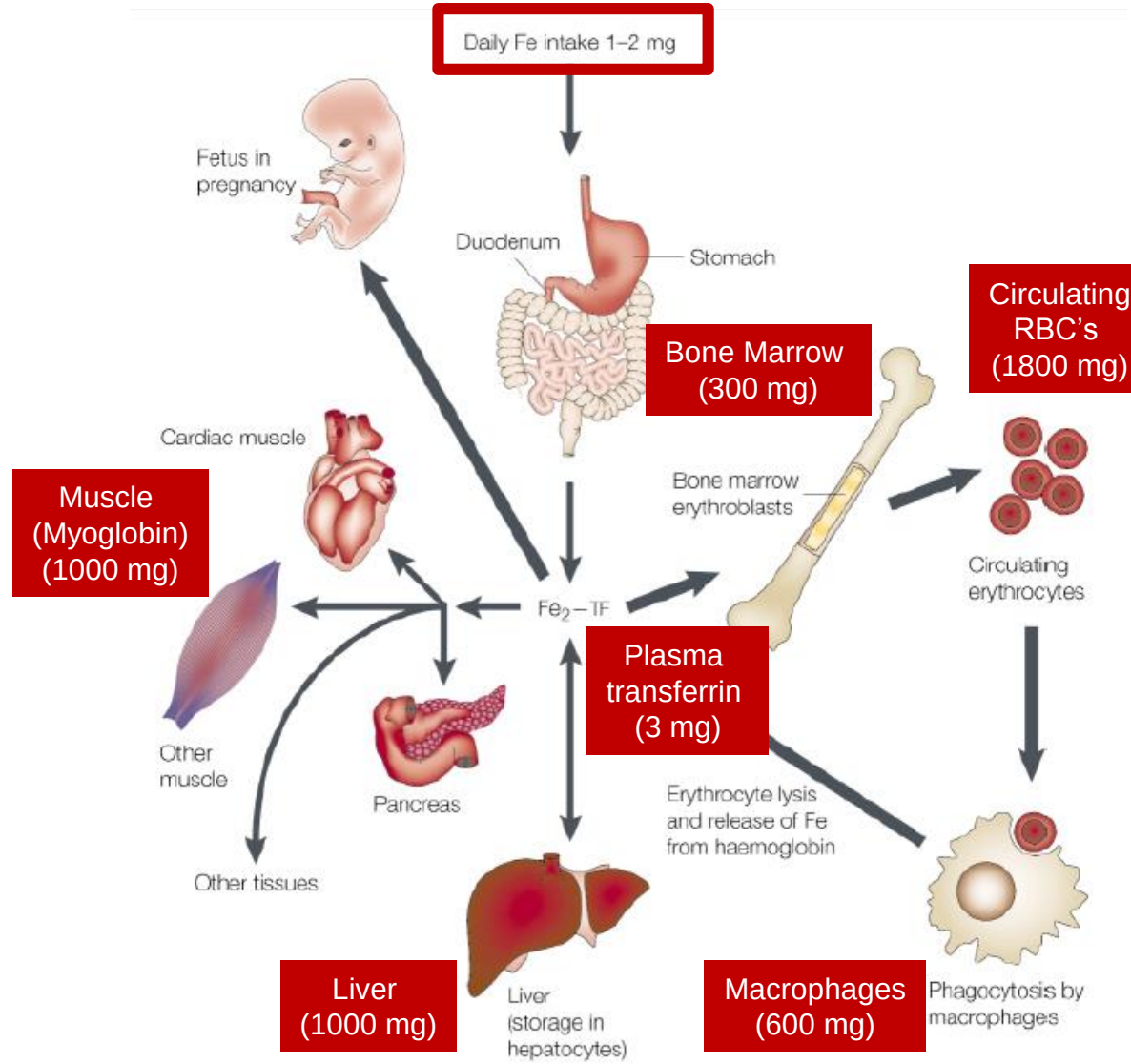
Iron in the body

- Healthy adults ~3-5 grams total body iron
- Daily intake 1-2 mg, balanced with losses
- Majority in RBC's & bone marrow
- Storage iron in liver
- Circulating iron bound to transferrin limited (0.1% total body iron)

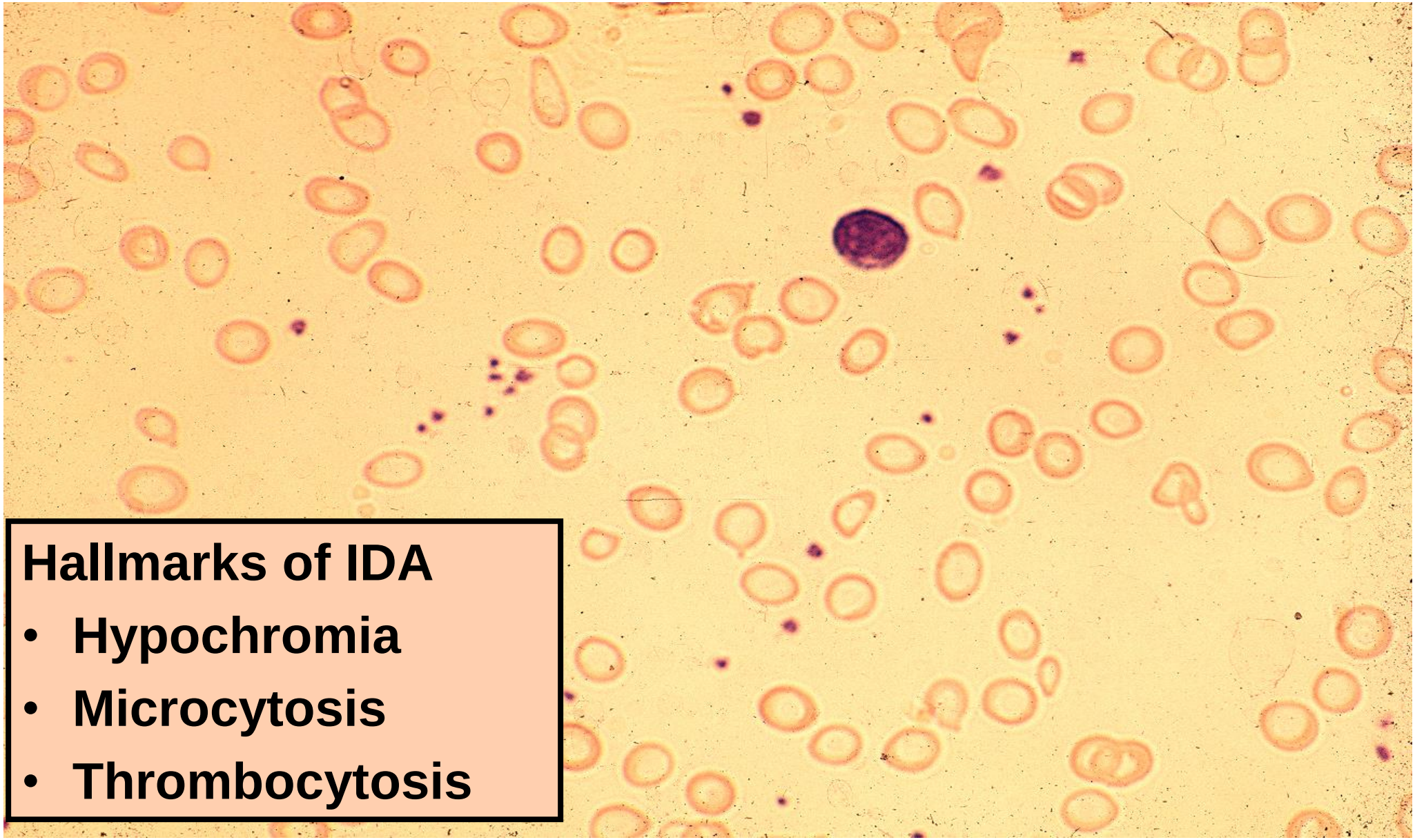


Andrews, NC. *Nature Reviews Genetics*. 2000.

Laboratory values suggestive of IDA

Iron Compartment	Conventional Test	Value suggestive of IDA
Storage	Serum ferritin	< 15 mg/L
Plasma	Serum iron (Fe)	< 40 mg/dL
	Total iron binding capacity (TIBC)	> 400-425 μg/dL
	Transferrin saturation (Fe/TIBC)	< 15%
	Serum transferrin receptor (sTfr)	> 35 nmol/L
RBC's	Hemoglobin concentration (Hgb)	< 11 g/dL (increases with age)
	Mean corpuscular volume (MCV)	< 70 fl (increases with age)
	Red cell distribution width (RDW)	> 16%
	Reticulocyte hemoglobin equivalent (Ret-He) or content (CHr)	< 26 pg (also low in thalassemia trait)
Other	Hepcidin (serum or urine)	Reduced

Anemia is the final stage of iron deficiency



Hallmarks of IDA

- **Hypochromia**
- **Microcytosis**
- **Thrombocytosis**

Other etiologies of microcytic anemia

Common

- Thalassemia trait
- Anemia of inflammation

Less common

- Hemoglobinopathies (Hgb C, Hgb E)

Diagnosis	Clinical history	Laboratory measurements	Distinguishing features
IDA	Low-iron diet Blood loss	Elevated RDW Low serum ferritin or TSAT	Improvement with oral iron
Thalassemia trait	Not c/w IDA Ethnicity Family history	Normal iron panel +Hgb Barts on NBS (alpha) Elevated Hgb A2 on Hgb analysis (beta)	Minimal to no change with oral iron
Anemia of inflammation or chronic disease	Recent acute and/or chronic illness Inflammation Tissue injury	MCV - normal or low Serum ferritin – normal or high Transferrin/TIBC may be low sTfR/$\log_{10}$ferritin index low	Improves as inflammation decreases May benefit from IV iron

Case 4: Is he iron deficient if his ferritin is normal?

- 28 year old young man presents with recent diagnosis of Crohn’s disease.
- He received pRBC transfusion at initial presentation and initiated immune-modulating therapy but not yet in remission.
- Recently discontinued iron pills due to abdominal pain.
- Current labs: Hgb 10, MCV 80, Ferritin 55, TSAT 10%

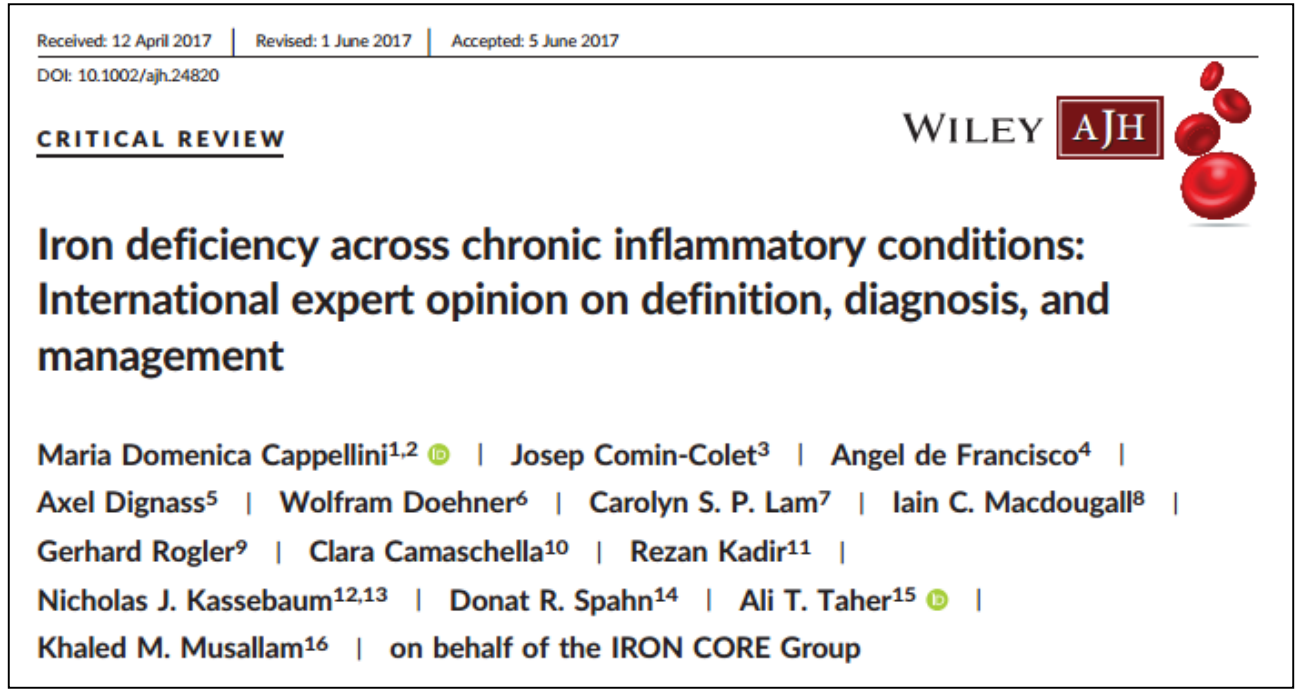
IDA in school-aged kids, adolescent boys, and adult men → *think GI blood loss*

- Gastrointestinal disease and/or blood loss
  - Inflammatory bowel disease
  - GERD, Ulcers
  - History of intestinal failure, TPN dependence, anatomic abnormalities
- Other external blood loss (recurrent epistaxis)
- *Adolescent boys: rapid growth, iron poor diet, athlete's anemia*

Inflammatory bowel disease

- Anemia and iron deficiency common
- Inflammation makes iron deficiency difficult to detect
  - Many iron parameters may be affected by inflammation
- Important to assessment for:
  - Ongoing blood loss
  - Symptoms (i.e. fatigue)

Iron deficiency in chronic disease



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CRITICAL REVIEW

WILEY AJH

Iron deficiency across chronic inflammatory conditions: International expert opinion on definition, diagnosis, and management

Maria Domenica Cappellini[1,2] | Josep Comin-Colet[3] | Angel de Francisco[4] | Axel Dignass[5] | Wolfram Doehner[6] | Carolyn S. P. Lam[7] | Iain C. Macdougall[8] | Gerhard Rogler[9] | Clara Camaschella[10] | Rezan Kadir[11] | Nicholas J. Kassebaum[12,13] | Donat R. Spahn[14] | Ali T. Taher[15] | Khaled M. Musallam[16] | on behalf of the IRON CORE Group

- Important to identify iron deficiency in patients with chronic disease
- Algorithms for evaluation & treatment

Cappellini, et al. AJH 2017

Iron deficiency in chronic disease: sTfR

- First line therapy: Treatment of underlying disease
- If difficult to control, assess soluble transferrin receptor (sTfR)
  - Quantitative measure of total erythropoietic activity
  - Normal in patients with anemia of inflammation/chronic disease
  - Elevated in those with concomitant iron deficiency
- sTfR-ferritin index (sTfR/log ferritin) also helpful
  - Level <1 suggests inflammation alone
  - Level >2 suggests presence of iron deficiency

Key Points: Making the diagnosis

- Clinical history + Microcytic anemia → IDA
- Iron studies can be used for confirmation
  - Serum ferritin for total body iron status
    → Low ferritin always diagnostic for iron deficiency
  - Other markers available for complex cases
- History inconsistent / normal iron panel
    → Consider other causes of microcytic anemia

Principles of IDA Management

1. Confirm the diagnosis
2. **Identify its cause**
3. **Correct or manage the primary cause**
4. Provide iron therapy (oral versus intravenous)
5. Confirm therapy success

Principles of IDA Management

1. Confirm the diagnosis
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4. **Provide iron therapy** (**oral** vs intravenous)
5. Confirm therapy success

Oral iron formulations

- Iron salts (ferrous sulfate, ferrous fumarate)
  - Ferrous form (Fe^{2+})
- Iron polysaccharide complex
  - Ferric form (Fe^{3+}), better taste
- Carbonyl iron
  - Less available

Blaud's iron pills introduced in 1831

Finally, P. Blaud in a paper read before the Royal Academy of Medicine in Paris, Aug. 23, 1831, raised iron to the position of practically a specific in chloroses. After describing the symptoms of chlorosis he states:* "But in all these cases it comes from a vicious sanguinification, the result of which is an imperfect fluid, where the serosity predominates, where the coloring principle is lacking and which is no longer suited to excite suitably the organism and carry on the regular exercise of its functions. The treatment is ferruginous preparations, modifiers of the organism, which give back to the blood the exciting principle which it has lost, that is to say the coloring substance. When one knows the importance of the blood and the rôle which it plays in the organic scene of life, when one knows that this fluid is the exciting agent of all our parts, and the prime mover of all their functions, one is little astonished at the trouble manifested when the conditions necessary to its influence no longer exist in its composition and that it lacks some one of the elements. Here the coloring matter is lacking. It is a clinical fact, which we know to be beyond doubt and from here arise all the functional disorders."

*Blaud (P.) Sur les maladies chlorotiques, et sur un mode de traitement spécifique dans ces affections. *Rev. méd. franç, et étrang., Par.*, 1832, i, pp. 337-367.

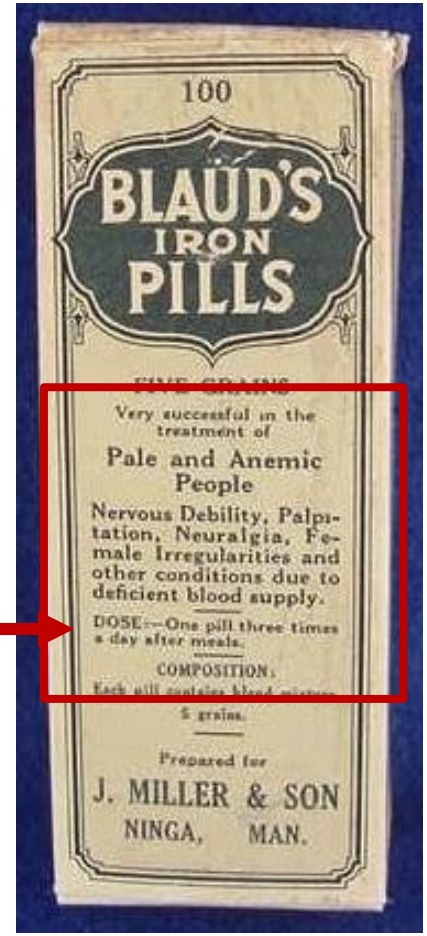
The prescription he advises is:

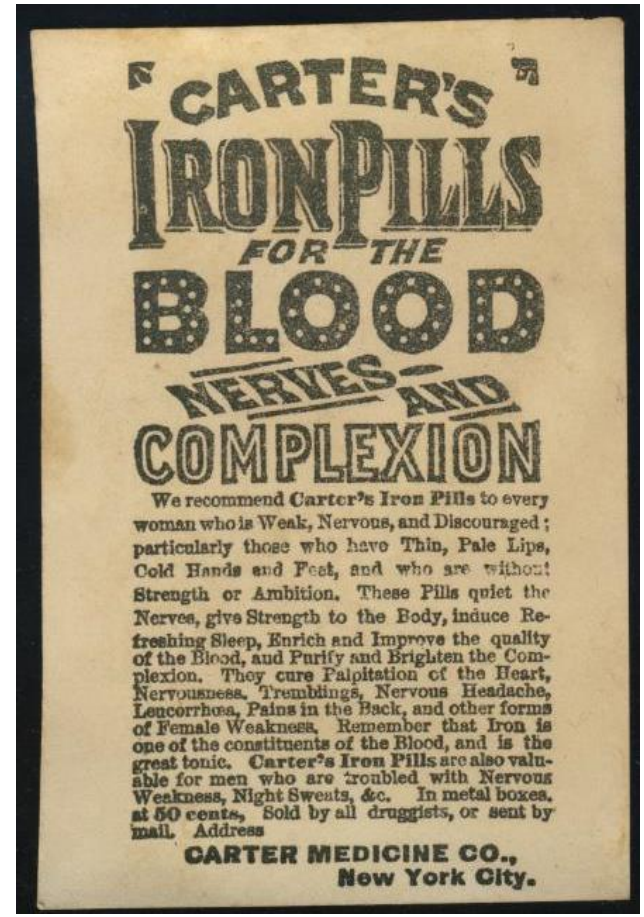
"℞ Sulfate de fer.....ʒss
Sous-carbonate de potasse.....ʒss
Powder and mix—add
Mucilage adragant .....q.s.
Divide into 48 boluses or pills.

Sig.: 1st, 2d and 3d day, 1 pill on rising, 1 pill on retiring; 4th, 5th and 6th day, 1 pill t.i.d.; 7th, 8th and 9th day, 2 pills twice a day; 10th, 11th and 12th day, 2 pills t.i.d.; 13th, 14th and 15th day, 3 pills twice a day; 16th and following, 4 pills t.i.d., continue until symptoms disappear and then return in inverse order to minimal dose and no treatment."

Blaud claims that iron is not a new treatment for chlorosis but that this form is new and its almost universal success, often where other forms of iron have failed, is sufficient to render it a new treatment.

Blaud's iron pills introduced in 1831



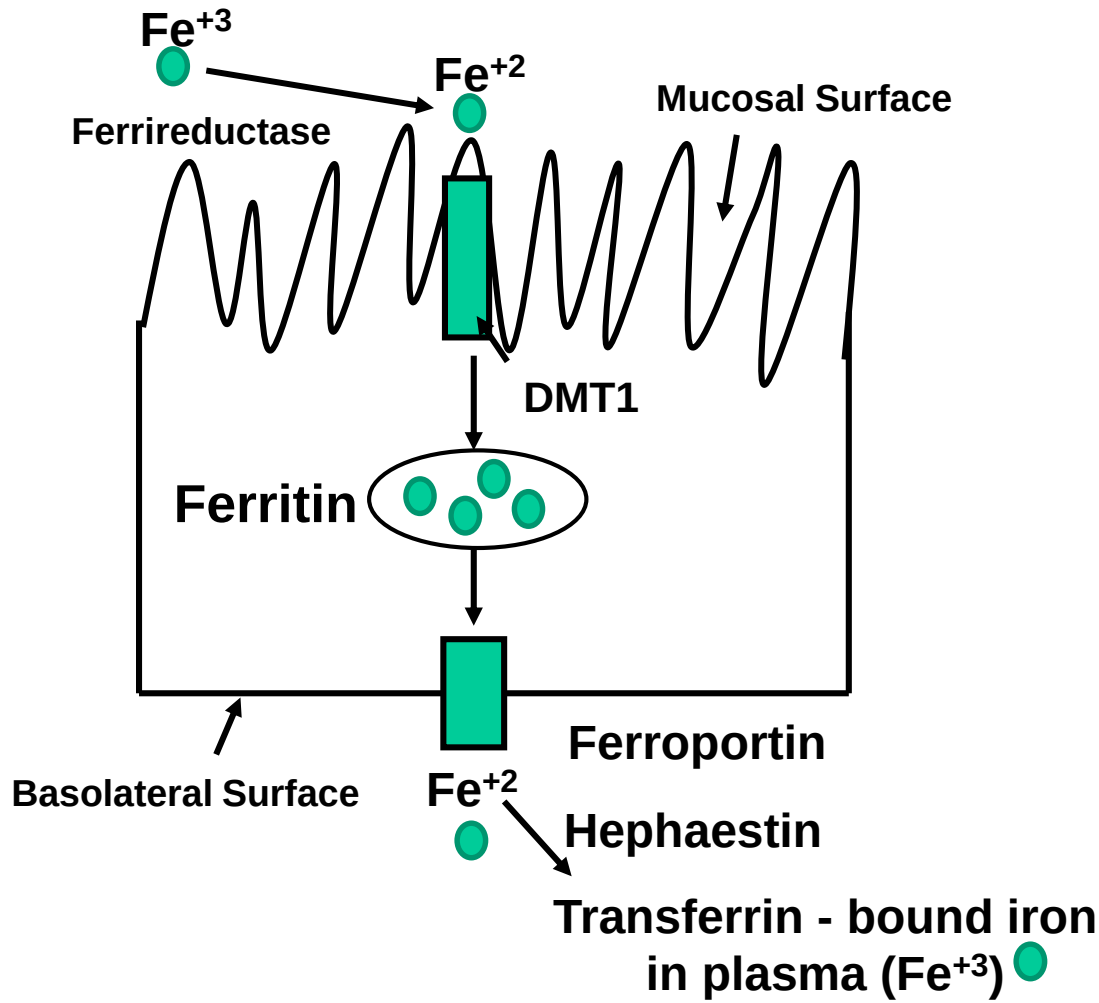


Old dosing recommendations non-specific

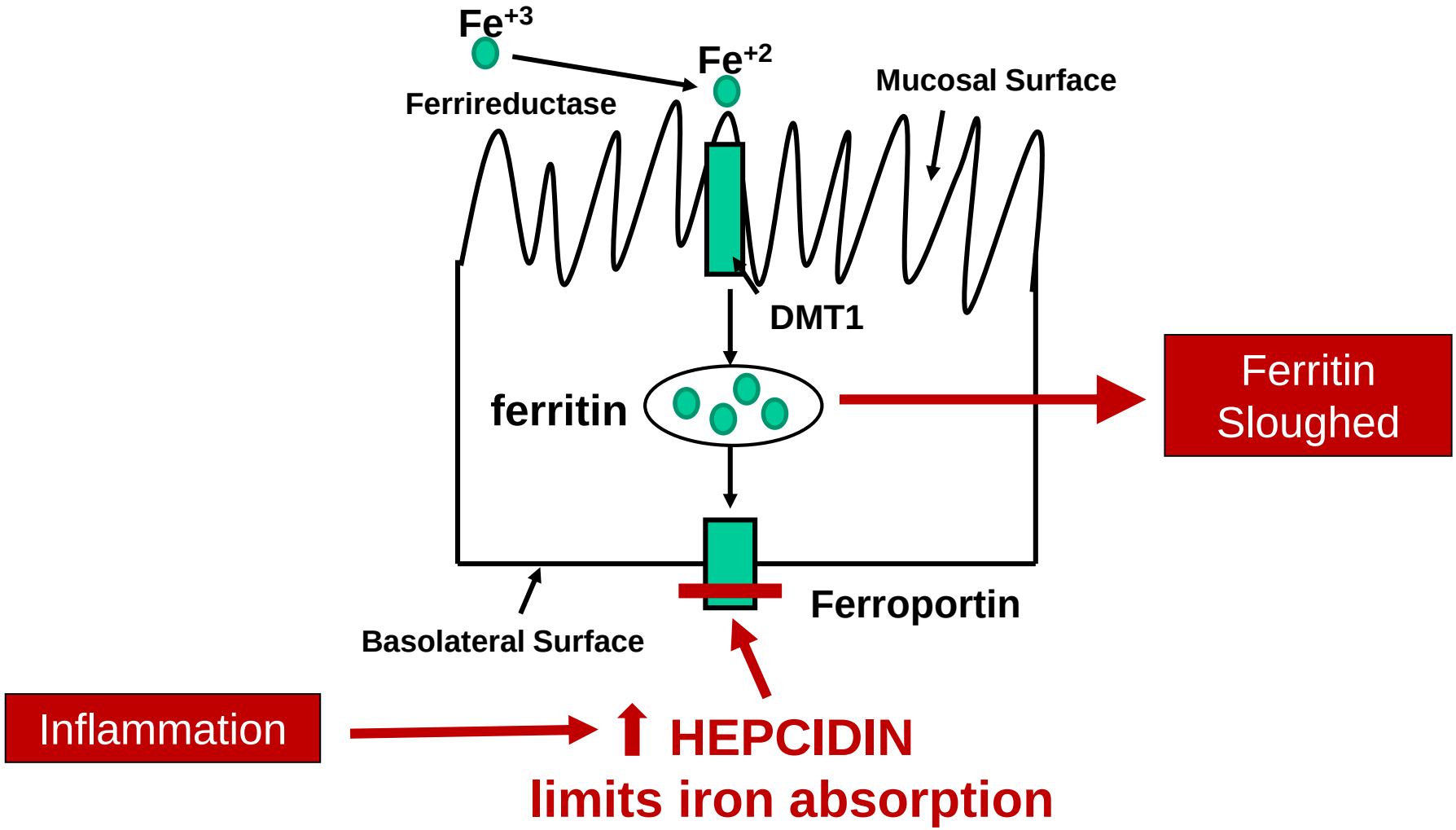
Recommendations for oral iron dosing in select medical textbooks

Reference	Total Daily Dose (Elemental Iron)		Number of Daily Doses
	Children	Adults	
Nelson Textbook of Pediatrics	3–6 mg/kg/d		3
Rudolph's Pediatrics	3–6 mg/kg/d		"Divided"
The Harriet Lane Handbook	3–6 mg/kg/d	60–100 mg/dose	1 to 4
Harrison's Principles of Internal Medicine		200–300 mg/d	
Nathan & Oski's Hematology of Infancy and Childhood	3 mg/kg/d		1 or 3
Manual of Pediatric Hematology & Oncology	4.5–6 mg/kg/d	100–200 mg daily (adolescents)	3
Hoffman: Hematology Basic Principles & Practice	3 mg/kg/d	60–200 mg/d	3 or 4
Williams Hematology	6 mg/kg/d	150–200 mg/d	"Divided" 3 or 4

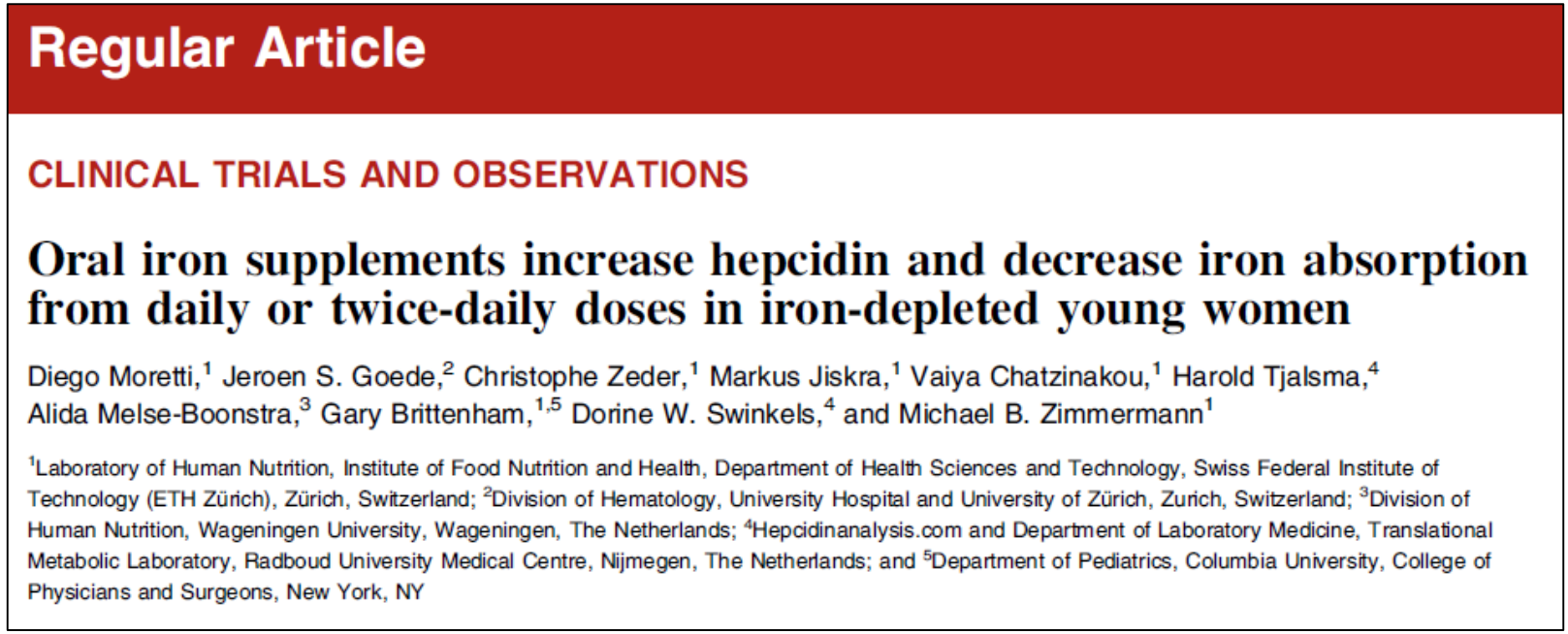
Absorption of iron occurs in duodenum



Regulation of iron absorption by hepcidin



Oral iron dosing, hepcidin, and absorption



Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women

Diego Moretti,[1] Jeroen S. Goede,[2] Christophe Zeder,[1] Markus Jiskra,[1] Vaiya Chatzinakou,[1] Harold Tjalsma,[4] Alida Melse-Boonstra,[3] Gary Brittenham,[1,5] Dorine W. Swinkels,[4] and Michael B. Zimmermann[1]

[1]Laboratory of Human Nutrition, Institute of Food Nutrition and Health, Department of Health Sciences and Technology, Swiss Federal Institute of Technology (ETH Zürich), Zürich, Switzerland; [2]Division of Hematology, University Hospital and University of Zürich, Zurich, Switzerland; [3]Division of Human Nutrition, Wageningen University, Wageningen, The Netherlands; [4]Hepcidinanalysis.com and Department of Laboratory Medicine, Translational Metabolic Laboratory, Radboud University Medical Centre, Nijmegen, The Netherlands; and [5]Department of Pediatrics, Columbia University, College of Physicians and Surgeons, New York, NY

- Healthy women, ages 18 to 45
- Hemoglobin >11.7 g/dL, Serum ferritin <20 ng/mL

Moretti, et al. Blood 2015.126(17):1981-9.

Oral iron dosing, hepcidin, and absorption

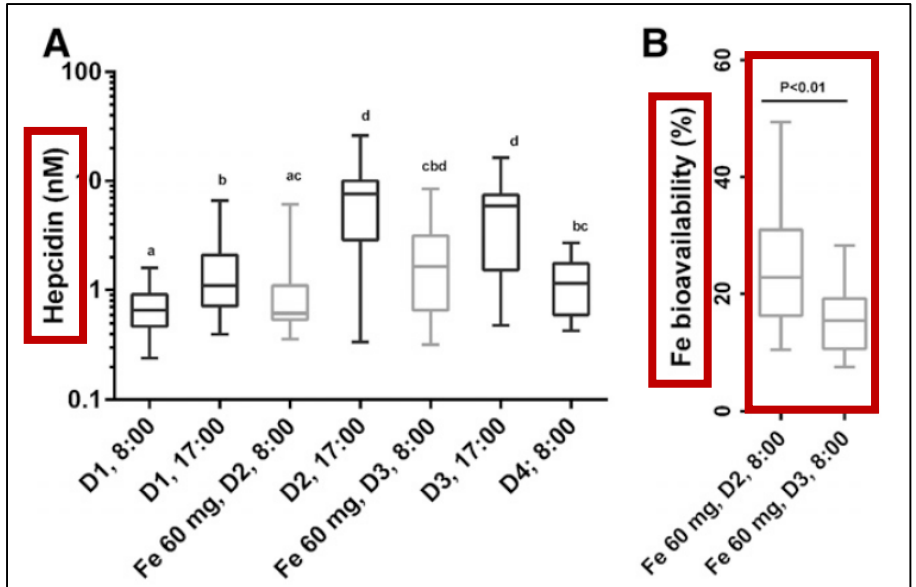


Figure 3. A supplemental iron dose of 60 mg Fe results in an increase in hepcidin after 24 hours and in a decreased iron absorption from the consecutive dose (n = 16). Doses are given both at 8:00 AM on consecutive days 2 and 3 and compared with day 1 (control day) (study 2). (A) Hepcidin profiles during the observation period: boxes indicate median and interquartile ranges, whiskers describe the range of the data (min to max); boxes with different subscript letter differ significantly ($P < .05$). (B) Fractional iron absorption measured on days 2 and 3 from the 60-mg Fe dose. D1, day 1.

Iron absorption studies

- Iron doses ≥60 mg increase hepcidin for up to 24 hours, reducing iron absorption the following day

- To maximize fractional absorption of iron:
  - Administer lower doses of iron (40-80 mg daily)
  - Avoid divided (i.e. BID) dosing

Consecutive versus alternate day dosing

Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomised controlled trials

Nicole U Stoffel, Colin I Cercamondi, Gary Brittenham, Christophe Zeder, Anneke J Geurts-Moespot, Dorine W Swinkels, Diego Moretti*, Michael B Zimmermann*

- 14 doses of iron given either
  - Consecutive days (14 doses in 14 days)
  - Alternate days (14 doses in 28 days)
- Alternate-day dosing → 34% greater total iron absorption
- Split dosing (60 mg twice daily vs 120 mg once) did *not* increase absorption

Stoffel, et al. Lancet Haemotol 2017.

BESTIRON trial

JAMA | Original Investigation

Effect of Low-Dose Ferrous Sulfate vs Iron Polysaccharide Complex on Hemoglobin Concentration in Young Children With Nutritional Iron-Deficiency Anemia

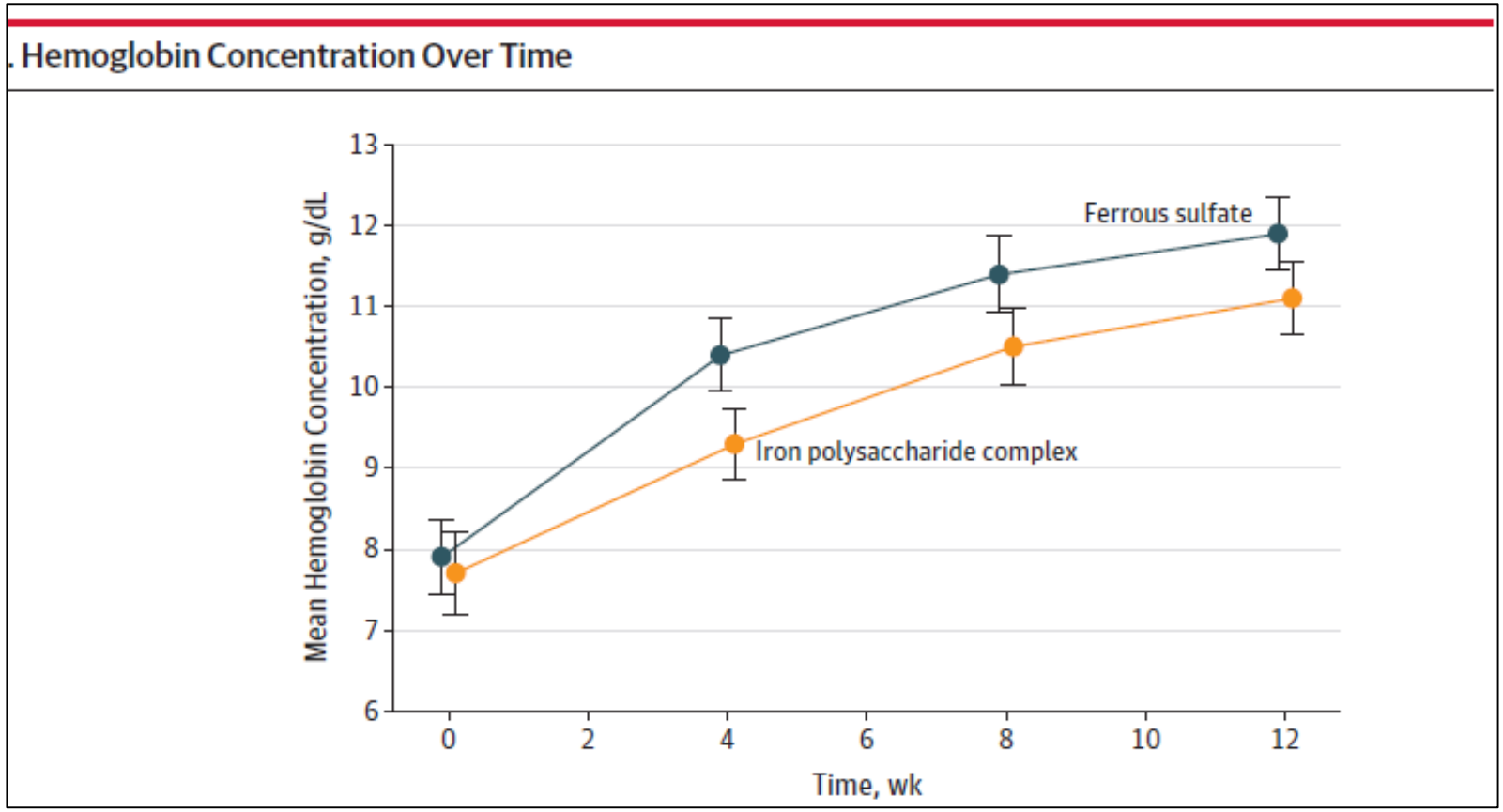
A Randomized Clinical Trial

Jacquelyn M. Powers, MD, MS; George R. Buchanan, MD; Leah Adix; Song Zhang, PhD; Ang Gao, MS; Timothy L. McCavit, MD, MS

- Single center, double-blind superiority trial
- 80 children (9 months to 4 years) with nutritional IDA
- Randomized to 3 mg/kg once daily of ferrous sulfate or iron polysaccharide complex (IPC) drops for 12 weeks

Powers, et al. JAMA. 2017.

Hemoglobin concentration



Significant difference in change in hemoglobin over time between groups (1.0 g/dL [95% CI, 0.4-1.6 g/dL]; p<0.001), favoring ferrous sulfate.

BESTIRON trial

- **Ferrous sulfate** is superior to iron polysaccharide complex in improving Hgb concentration in young children with nutritional IDA

- **Low dose iron therapy of 3 mg/kg once daily** corrects anemia in the majority of affected patients

Key points: Oral iron therapy

- Standard guidelines based on historic treatment
  - Limited data to support high-dose or divided dosing
- My approach:
  - Young children: 3 mg/kg ferrous sulfate once daily
  - Adolescents/Adults: 65 mg (1 tablet) ferrous sulfate once daily
- Higher doses for initial treatment ok but give once daily
  - If patient no longer anemic (but still iron deficient), may consider dosing every other day or 3x/week

Reasons for “persistent” IDA

- Incorrect diagnosis
- Persistence of etiology
  - Poor diet (milk intake)
  - Ongoing blood loss
- Insufficient iron dose
  - Dosing incorrect
  - Duration too short
- Non-adherence
  - Difficult schedule (TID)
  - Side effects/taste
- Malabsorption
  - Rarely primary etiology
  - Inflammation/underlying GI condition
  - Very rare genetic condition

Facilitators of adherence in young children

- Qualitative study in caregivers of children with IDA
- Barriers to adherence
  - Difficulty administering (poor taste, side effects)
  - Forgetfulness, complex regimen
- Facilitators of adherence
  - Simplified regimens, specific instructions
  - Provider and caregiver support
  - Motivation to improve child's health, minimize trauma

Powers, et al. J Pediatr. 2020

Principles of IDA Management

1. Confirm the diagnosis
2. Identify its cause
3. Correct or manage the primary cause
4. **Provide iron therapy (**oral vs **intravenous)**
5. Confirm therapy success

History of intravenous iron therapy

- Initially introduced in the 1950s
  - High rates of adverse reactions limited use
- During 1990s, safer IV preparations developed
  - Primary indication: chronic kidney disease in adults
- Past 10 years, additional preparations
  - Improved safety, larger doses, shorter infusion times
  - None perfect (without adverse effects)
  - Higher cost, potentially decreased ancillary infusion costs

Intravenous iron

Pros

- Effective for majority, including patients with concurrent inflammation
- 3 formulations allow for full treatment via a single or “total-dose” infusion
- Adverse effects uncommon

Cons

- Expensive
- Though rare, adverse effects may be severe (i.e. hypersensitivity reaction)

Intravenous iron preparations in the U.S.

Generic Name	Ferric gluconate	Iron sucrose	Low Molecular Weight Iron Dextran (LMWID)	Ferumoxytol	Ferric Carboxymaltose
FDA Indication (Adult)	CKD on dialysis + ESAs	CKD	Oral iron administration is unsatisfactory or impossible	CKD	Intolerance or unsatisfactory response to oral iron; NDD-CKD
FDA Approved (Pediatrics)	Yes, >6 years	Yes, >2 years	Yes, >4 months	No	No – *Planning Pediatric study in U.S.*
Total dose infusion	No	No	Yes	Yes	Yes
Maximum Dose	125 mg	200 – 300 mg	100 mg (1000 mg off-label)	510 mg	750 mg (1000 mg Europe)
Infusion Time	60 minutes	2-5 minutes (Typically 60)	60 minutes	15-60 minutes	15 minutes
Test Dose	No	No	Yes	No	No
Black Box	No	No	Yes	Yes	No

*Total dose infusion: Patient's entire iron deficit (treatment course) can be given in one infusion

Table modified from Auerbach and Ballard. ASH Education Program. 2010.

Indications for intravenous iron

- Chronic kidney disease
- Failure or intolerance of oral iron
- Severe anemia, ongoing / uncontrolled blood loss
- Concurrent inflammation / chronic disease
  - Inflammatory bowel disease / GI conditions
  - Heart failure
- Symptomatic iron deficiency (fatigue, restless legs)

TRANSFUSION

BLOOD MANAGEMENT: Large-dose intravenous ferric carboxymaltose injection for iron deficiency anemia in heavy uterine bleeding: a randomized, controlled trial

David B. Van Wyck, Antoinette Mangione, John Morrison, Phillip Earl Hadley, Judi A. Jehle, Lawrence Tim Goodnough

First published: 01 December 2009 | https://doi.org/10.1111/j.1537-2995.2009.02327.x | Cited by: 88

Lawrence Tim Goodnough, MD, Stanford University Medical Center, Pasteur Drive, Room H-1402, 5626, Stanford, CA 94305; e-mail: ltgoodno@stanford.edu.

ClinicalTrials.gov Trial Identifier: NCT00395993.

International Journal of GYNECOLOGY & OBSTETRICS

Clinical articles

Randomized controlled trial comparing ferric carboxymaltose and iron sucrose for treatment of iron deficiency anemia due to abnormal uterine bleeding

Reeta Mahey, Alka Kriplani, Krishna D. Mogili, Neerja Bhatla, Garima Kachhawa, Renu Saxena

First published: 23 December 2015 | https://doi.org/10.1016/j.ijgo.2015.09.007 | Cited by: 3

IV iron in children who have failed oral iron

Pediatr Blood Cancer 2011;56:615–619

Intravenous Iron Sucrose for Children With Iron Deficiency Failing to Respond to Oral Iron Therapy

Shelley E. Crary, MD, MSCS,[1,2]* Katherine Hall, BS,[1,2] and George R. Buchanan, MD[1,2]

Pediatr Blood Cancer 2013;60:1747–1752

Intravenous Low Molecular Weight Iron Dextran in Children With Iron Deficiency Anemia Unresponsive to Oral Iron

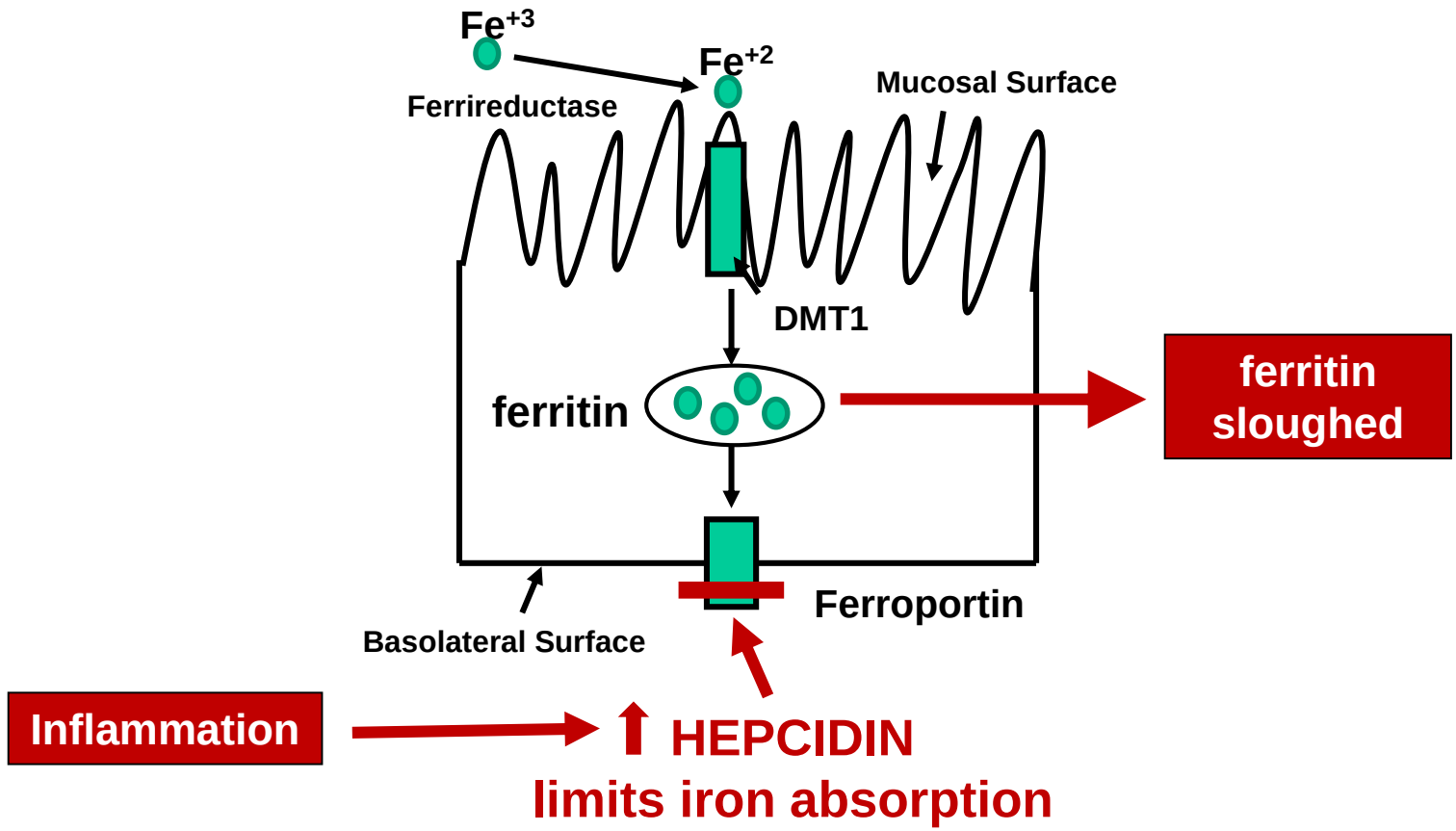
Ellen S. Plummer, MD,[1,2] Shelley E. Crary, MD, MSCS,[3]* Timothy L. McCavit, MD,[1,2] and George R. Buchanan, MD[1,2]

THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

Intravenous Ferric Carboxymaltose in Children with Iron Deficiency Anemia Who Respond Poorly to Oral Iron

Jacquelyn M. Powers, MD, MS[1,2,3], Mark Shamoun, MD[4,5], Timothy L. McCavit, MD, MS[6,7], Leah Adix, CCRP[5], and George R. Buchanan, MD[4,5,8]

Regulation of iron absorption by hepcidin



Inflammatory bowel disease

- Oral iron for those with well controlled disease, mild anemia
- Many cannot tolerate oral iron → intravenous iron preferred
  - Worse IBD disease activity; increased abdominal pain
  - Poor absorption due to ongoing inflammation; impact on gut microbiome
- Patients with other gastrointestinal conditions may also require intravenous iron therapy (gastric bypass, gastric surgery)

Inflammatory bowel disease

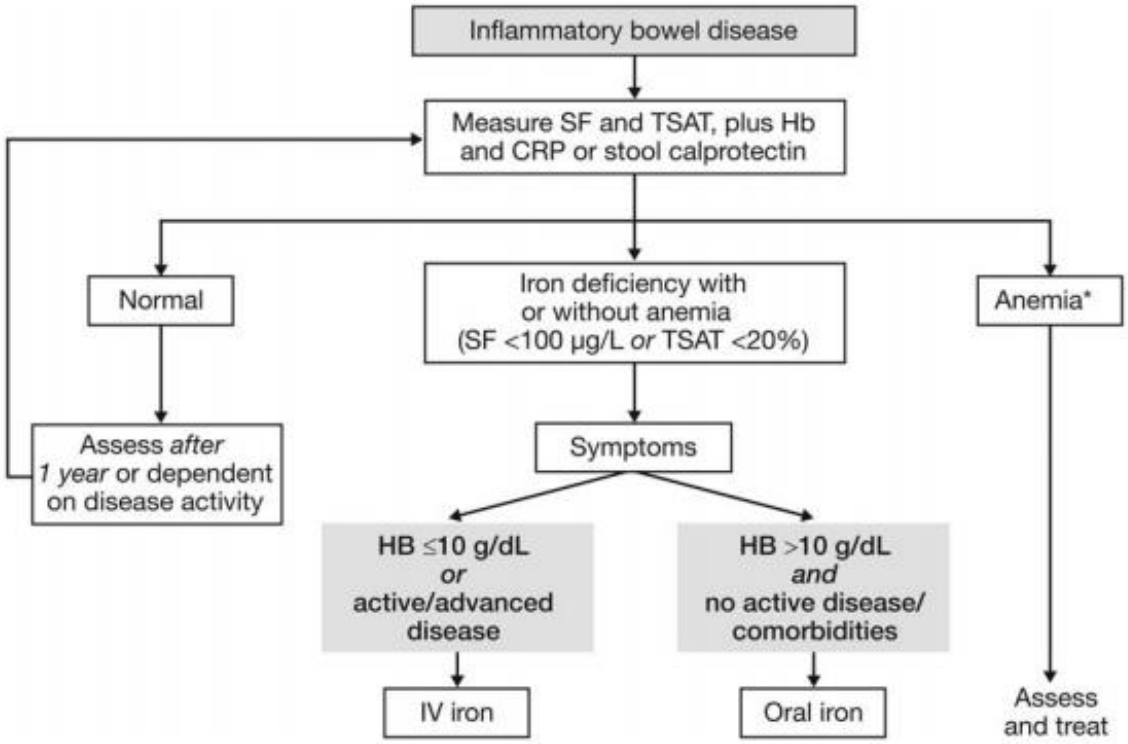


FIGURE 4 Diagnostic algorithm: iron deficiency in inflammatory bowel disease. *Look for other causes of anemia and treat accordingly. CRP, C-reactive protein; Hb, haemoglobin; IV, intravenous; SF, serum ferritin; TSAT, transferrin saturation

Cappellini, et al. AJH 2017

Heart failure: Iron therapy

European Journal of Heart Failure (2016)
doi:10.1002/ejhf.473

Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: a meta-analysis of randomized controlled trials

Ewa A. Jankowska[1,2*], Michał Tkaczyszyn[1,2], Tomasz Suchocki[3], Marcin Drozd[1,2], Stephan von Haehling[4], Wolfram Doehner[5,6], Waldemar Banasiak[2], Gerasimos Filippatos[7], Stefan D. Anker[4], and Piotr Ponikowski[2,8]

Research

JAMA | Original Investigation

Effect of Oral Iron Repletion on Exercise Capacity in Patients With Heart Failure With Reduced Ejection Fraction and Iron Deficiency
The IRONOUT HF Randomized Clinical Trial

Gregory D. Lewis, MD; Rajeev Malhotra, MD; Adrian F. Hernandez, MD, MHS; Steven E. McNulty, MS; Andrew Smith, MD; G. Michael Felker, MD, MHS; W. H. Wilson Tang, MD; Shane J. LaRue, MD; Margaret M. Redfield, MD; Marc J. Semigran, MD; Michael M. Givertz, MD; Peter Van Buren, MD; David Whellan, MD; Kevin J. Anstrom, PhD; Monica R. Shah, MD, MHS; Patrice Desvigne-Nickens, MD; Javed Butler, MD; Eugene Braunwald, MD; for the NHLBI Heart Failure Clinical Research Network

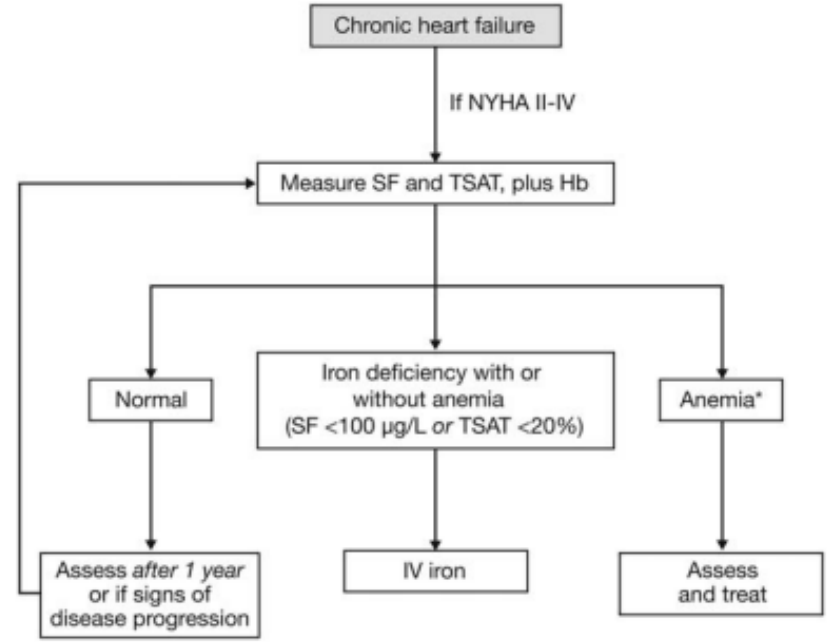


FIGURE 2 Diagnostic algorithm: iron deficiency in chronic heart failure. *Look for other causes of anemia and treat accordingly. Hb, haemoglobin; IV, intravenous; NYHA, New York Heart Association; SF, serum ferritin; TSAT, transferrin saturation

Cappellini, et al. AJH 2017

Key points: Intravenous iron therapy

- No intravenous iron formulation is “perfect”
- Newer formulations safer, provide additional options for patients failing oral iron
- My approach:
  - Recommend for long-standing or recurrent IDA
  - Patients with concomitant chronic inflammatory conditions
  - Additional indications → shared-decision making approach

Principles of IDA Management

1. Confirm the diagnosis
2. Identify its cause
3. Correct or manage the primary cause
4. Provide iron therapy, orally or parenterally
5. **Confirm therapy success**

Confirm therapy success

- Normalization of hemoglobin
  - Mild IDA → within 1 month
  - Moderate to severe → ≥2 g/dL improvement in 1 month
- Iron therapy must be continued for minimum 3 months
- Consider assessing ferritin prior to stopping iron therapy
- Counsel on recurrent symptoms
  - "Warning signs" of recurrence
  - Recurrent HMB, pica, fatigue

Conclusions

- Early recognition of and screening for ID and IDA in high-risk populations may prevent severe complications
- Low-dose and daily dosing strategies effective for majority of patients
- Intravenous iron therapy may be considered for long-standing IDA, failed oral iron therapy, or symptomatic iron deficiency without anemia

Review Articles

Camaschella C. Iron-deficiency anemia. *N Engl J Med* 2015;372(19):1832-43.

Powers JM, O'Brien SH. How I approach iron deficiency with and without anemia. *Pediatr Blood Cancer* 2019;66(3);E27544.

Hershko C, Camaschella C. How I treat unexplained refractory iron deficiency anemia. *Blood* 2014;123(30):326-33.

Pivotal Trials / Practice Changing Articles

Moretti D, Goede JS, Zeder C, et al. Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-repleted young women. *Blood* 2015;126(17):1981-9.

Powers JM, Buchanan GR, Adix L, et al. Effect of low-dose ferrous sulfate vs iron polysaccharide complex on hemoglobin concentration in young children with nutritional iron-deficiency anemia: a randomized clinical trial. *JAMA* 2017;317(22):2297-304.

Stoffel NU, Cercamondi CI, Brittenham G, et al. Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomized controlled trials. *Lancet Haematol* 2017;4(11):3524-33.

Thank you for your attention!

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