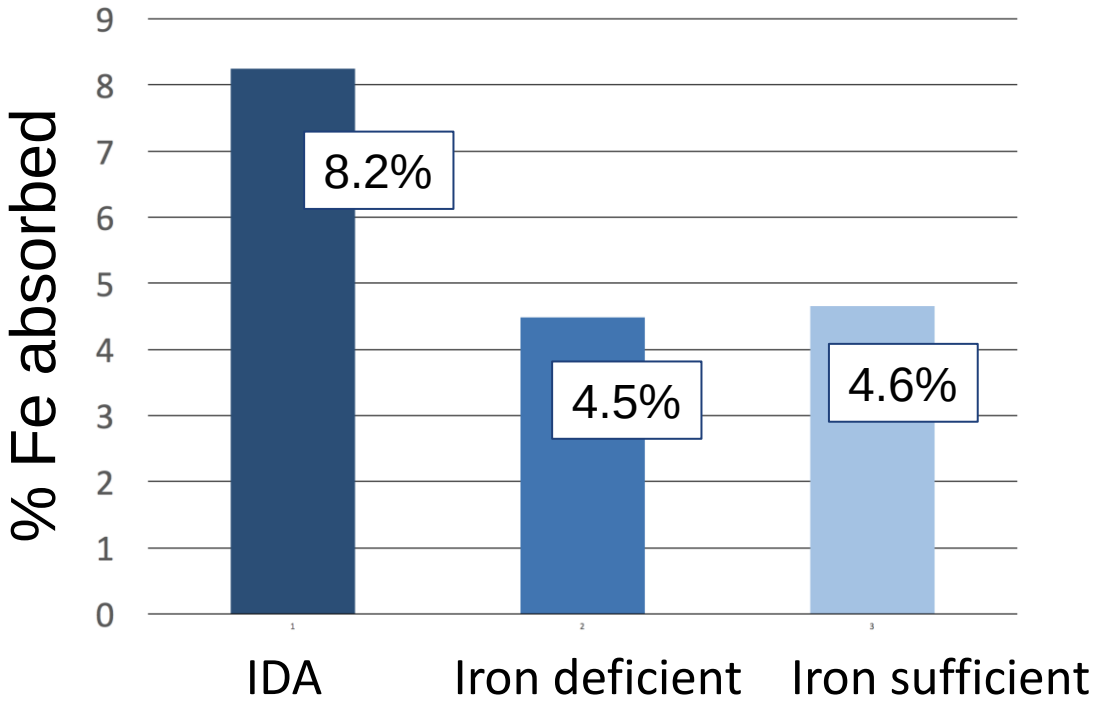
ETH zürich

Improving bioavailability and safety of oral iron

Prof. Michael Zimmermann, MD

ETH Zurich, Switzerland

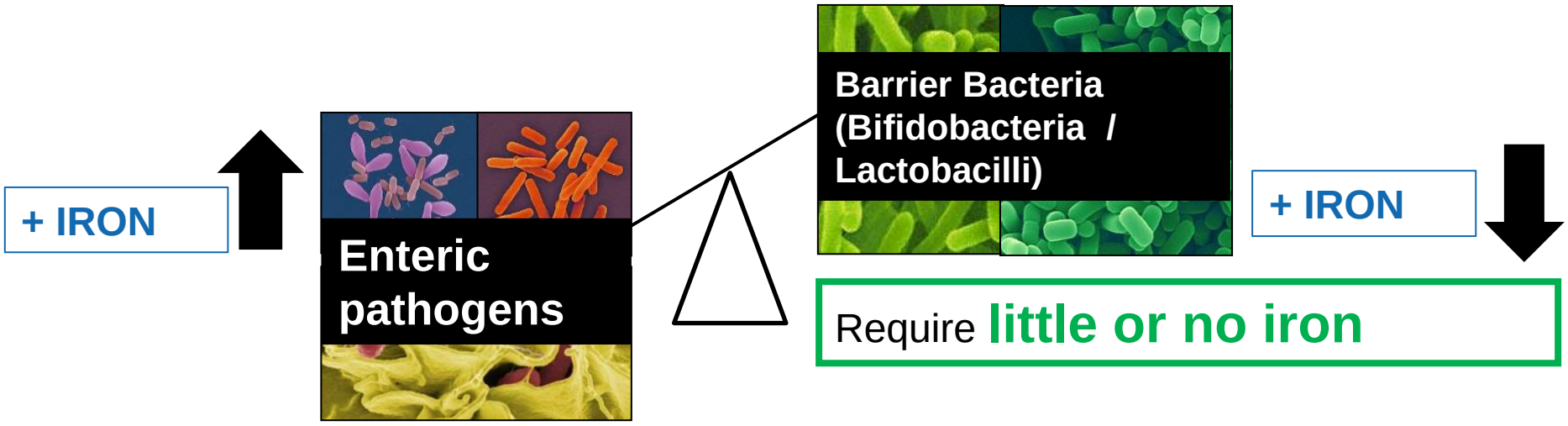
Iron fortificants and supplements are poorly absorbed and >80-90% of the dose passes unabsorbed into the colon



Absorption from 12.5 mg iron as ferrous fumarate **in Ghanaian infants**

Am J Clin Nutr 2004; 80(5): 1436-1444

Iron is a growth-limiting nutrient for many gut pathogens, but beneficial bacteria require little or no iron



iron acquisition plays an essential role in virulence and colonization

Kortman et al. 2014 *Weinberg ED 1997*

THE LANCET

Effect of provision of daily zinc and iron with several micronutrients on growth and morbidity among young children in Pakistan: a cluster-randomised trial

Sajid Soofi, Simon Cousens, Saleem P Iqbal, Tauseef Akhund, Javed Khan, Imran Ahmed, Anita K M Zaidi, Zulfiqar A Bhutta

Lancet 2013; 382: 29–40

- Cluster randomized, ca. 2700 infants at 6 mo age
- 'In-home' fortification with a micronutrient powder (MNP) 12.5 mg Fe/day, one year trial

In the MNP groups:

- **increased days with diarrhea** (p=0.001)
- increased incidence of bloody diarrhea (p=0.003) and severe diarrhea (p=0.07)

Iron fortification adversely affects the gut microbiome, increases pathogen abundance and induces intestinal inflammation in Kenyan infants

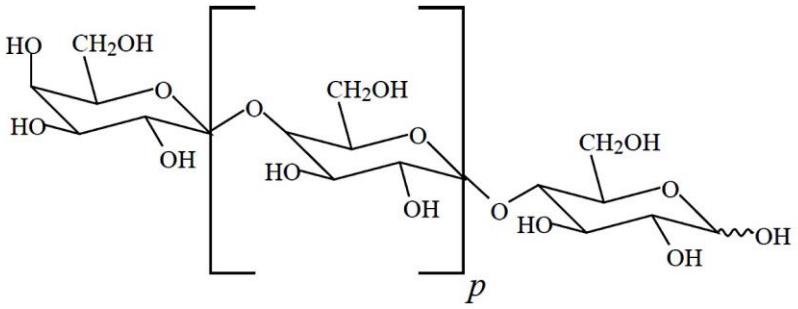
Tanja Jaeggi,[1] Guus A M Kortman,[2] Diego Moretti,[1] Christophe Chassard,[1] Penny Holding,[3] Alexandra Dostal,[1] Jos Boekhorst,[4] Harro M Timmerman,[4] Dorine W Swinkels,[2] Harold Tjalsma,[2] Jane Njenga,[5] Alice Mwangi,[5] Jane Kvalsvig,[6] Christophe Lacroix,[1] Michael B Zimmermann[1]

Gut 2015;64:5 731-742

Iron-containing MNPs (12.5 mg Fe/day) adversely affect the infant gut microbiome:

- decrease beneficial commensal microbiota
- increase entropathogens and inflammation
- may increase risk of diarrhea

Prebiotic galacto-oligosaccharides (GOS)



- GOS: a chain of 2 to 8 galactose units
- undigestible by the human gut, pass intact into the colon
- stimulates growth of favorable commensal colonic bacteria, e.g. Bifidobacteria, Lactobacilli

Gut microbiota
Original Article

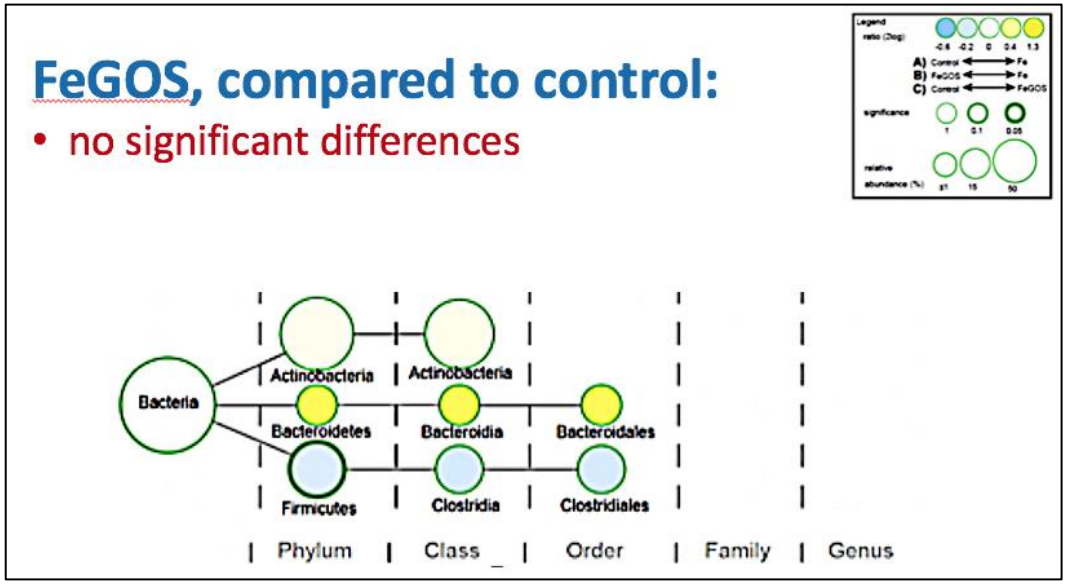
Gut

Prebiotic galacto-oligosaccharides mitigate the adverse effects of iron fortification on the gut microbiome: a randomised controlled study in Kenyan infants FREE

Daniela Paganini[1], Mary A Uyoga[2], Guus A M Kortman[3], Colin I Cercamondi[1], Diego Moretti[1], Tanja Barth-Jaeggi[4], Clarissa Schwab[1], Jos Boekhorst[3], Harro M Timmerman[3], Christophe Lacroix[1], Simon Karanja[2], Michael B Zimmermann[1]

Gut 2017;66(11):1956-1967

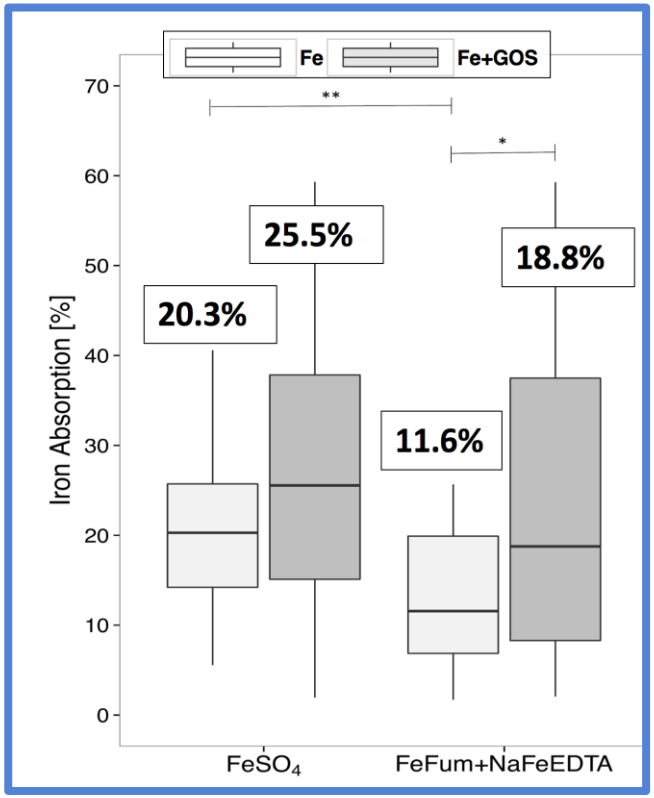
- **Prebiotic GOS** given with iron-containing MNPs in may be beneficial to **maintain a healthy commensal gut microbiome and reduce enteropathogens**



The American Journal of CLINICAL NUTRITION

Consumption of galacto-oligosaccharides increases iron absorption from a micronutrient powder containing ferrous fumarate and sodium iron EDTA: a stable-isotope study in Kenyan infants

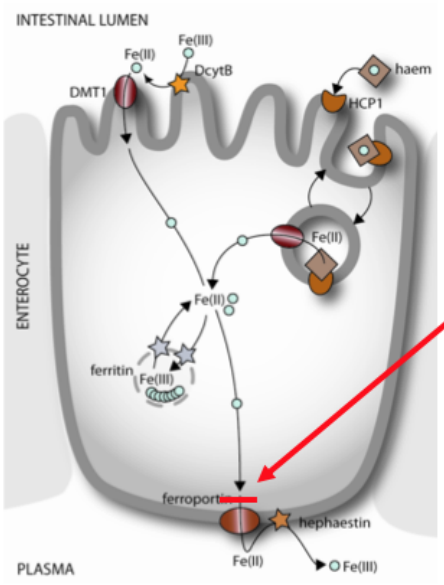
Daniela Paganini,[1] Mary A Uyoga,[3] Colin I Cercamondi,[1] Diego Moretti,[1] Edith Mwasi,[4] Clarissa Schwab,[2] Salome Bechtler,[1] Francis M Mutuku,[5] Valeria Galetti,[1] Christophe Lacroix,[2] Simon Karanja,[3] and Michael B Zimmermann[1]



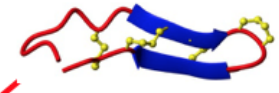
- **In Kenyan infants, addition of GOS** to a MNP with 5 mg Fe **increases absorption by 40 %**
- Fractional absorption is **nearly 20%**, compared to 4-8 % from current MNPs

Am J Clin Nutr 2017;106(4):1020-1031

What is the best dosing regimen for oral iron to maximize absorption?



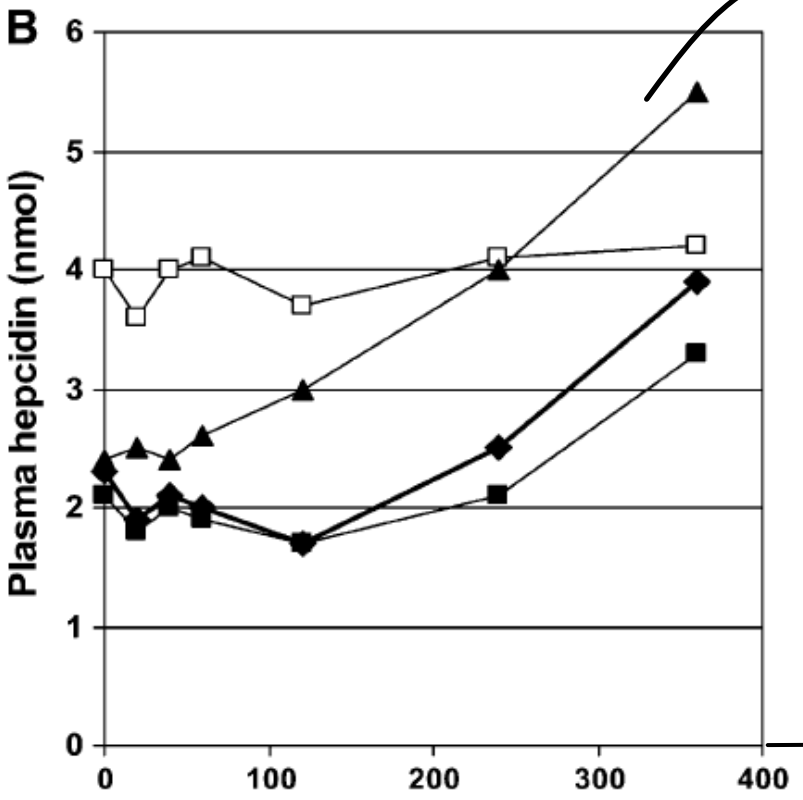
High circulating hepcidin reduces iron absorption

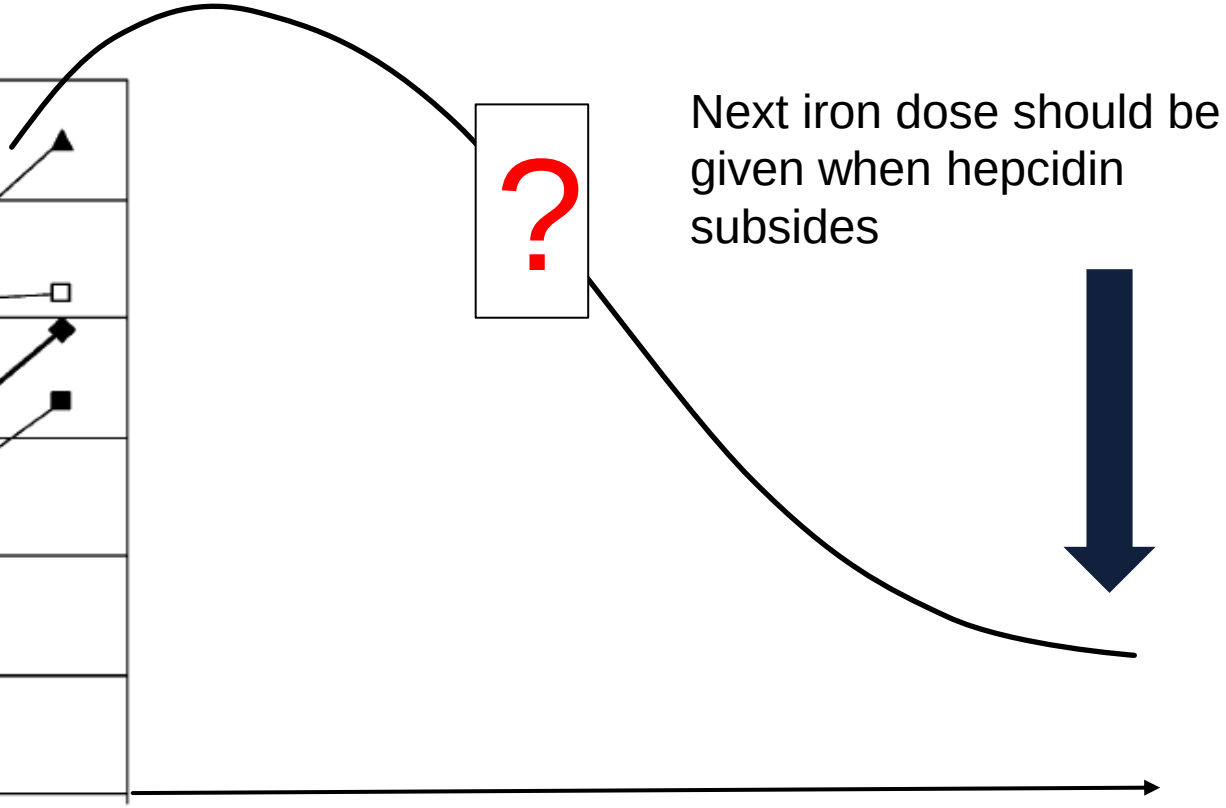


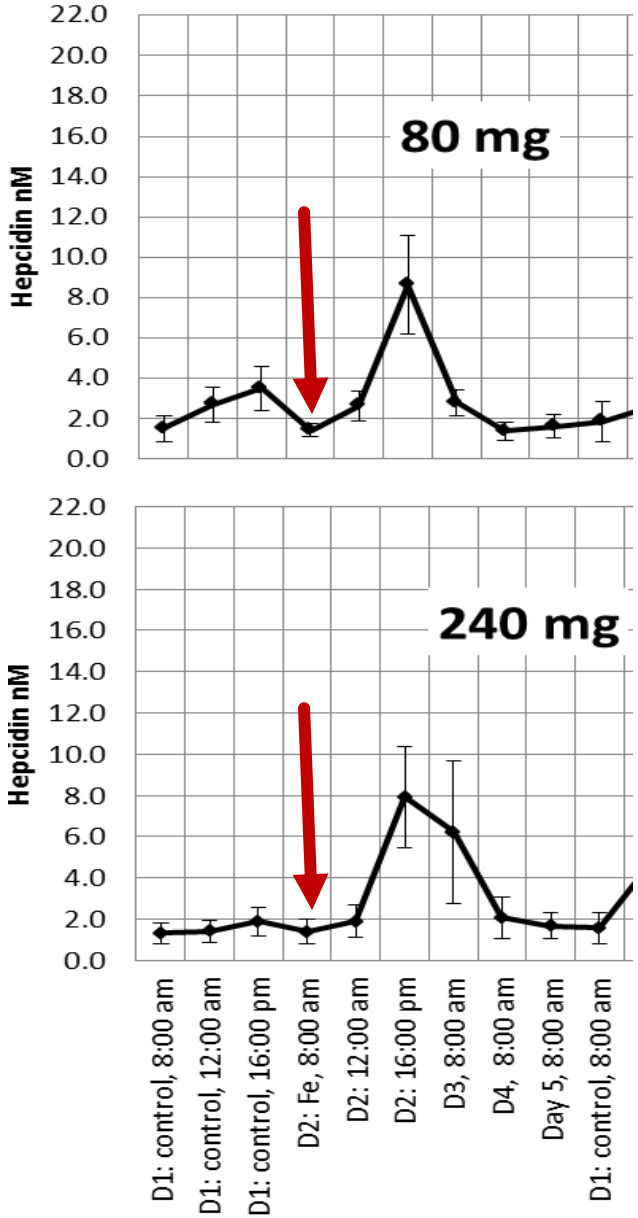
Blocks ferroportin-mediated efflux of iron into the blood

High plasma hepcidin sharply reduces iron absorption

A single oral dose of Fe induces a hepcidin rise







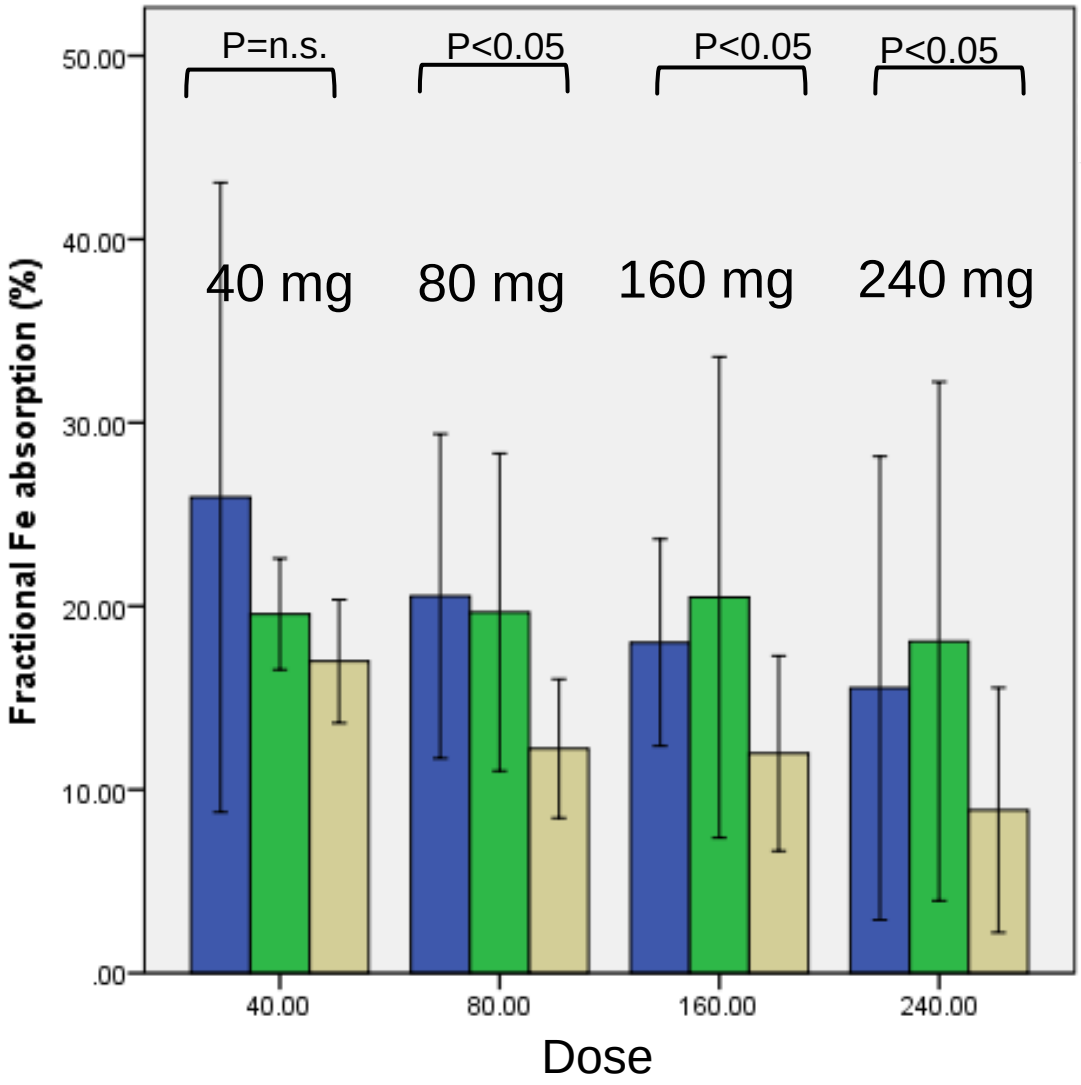
Change in plasma hepcidin after a single oral dose of iron

Hepcidin increases >5 fold after a single dose

Peaks at 8h,

Elevated at 24h, but not 48h

Moretti et al. Blood 2015



In ID women, doses of 40-240 mg Fe given on two consecutive mornings:

At doses of iron >40 mg, 30-50% decrease in absorption from the next morning's dose

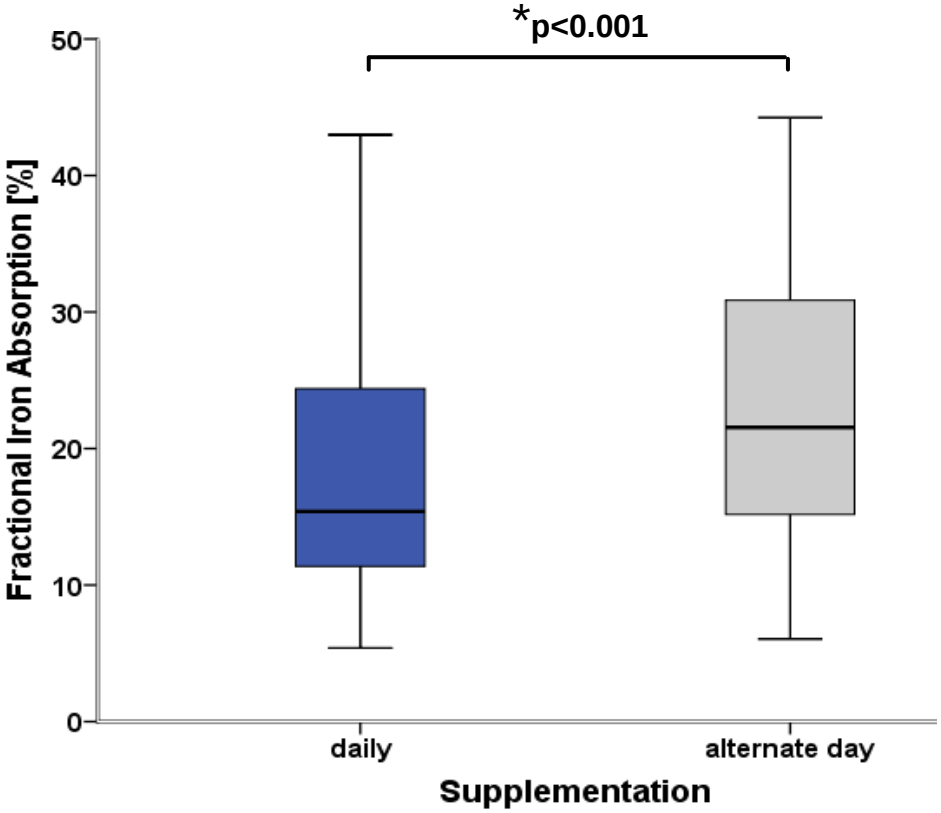
Moretti et al. Blood 2015

Alternate day dosing of 60 mg iron increases fractional and total absorption by 30%

14 doses of 60 mg given on alternate days deliver 20 mg more absorbed iron than when given daily

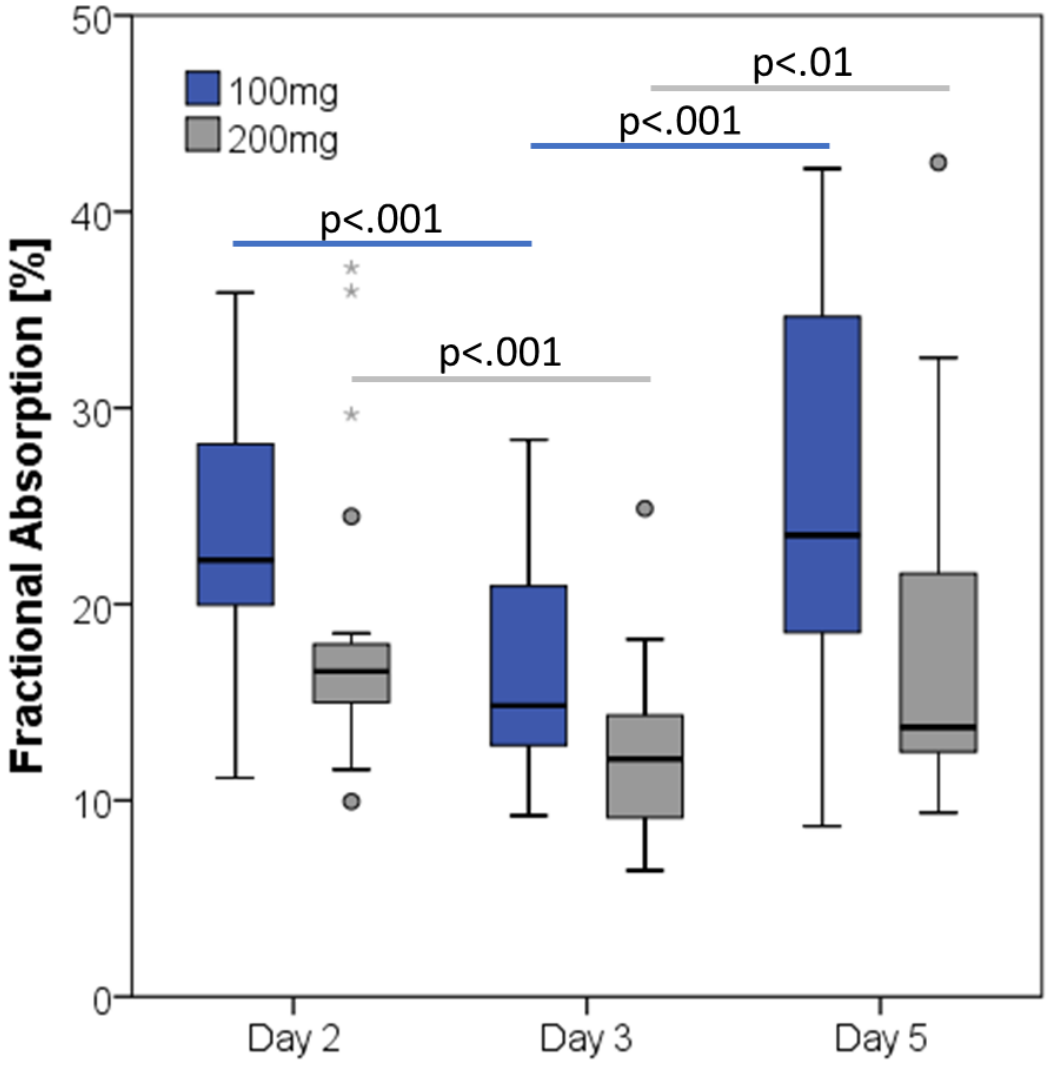
Total iron absorbed (mg)	
daily	67 (39, 114)
alternate	88 (56, 138)

GI side effects 33% less frequent in the alternate day group



Stoffel et al. Lancet Hematology 2018

In women with IDA, alternate day dosing of 100 or 200 mg increases absorption by 35-47%



Doses of 100mg ≈50% less GI side effects compared to 200mg

Stoffel et al. Hematologica 2020

Conclusions

- Large oral doses of Fe trigger an acute hepcidin surge that reduces iron absorption 24 hr later, but not 48 hr later

- Alternate day dosing increases iron absorption by 30-50% and may reduce side effects in women with ID (60 mg) and IDA (100 and 200 mg)

inside blood commentary

22 OCTOBER 2015 | VOLUME 126, NUMBER 17

CLINICAL TRIALS AND OBSERVATIONS

Comment on Moretti et al, page 1981

So you know how to treat iron deficiency anemia

Stanley L. Schrier STANFORD UNIVERSITY SCHOOL OF MEDICINE

In this issue of *Blood*, Moretti et al[1] provide data that challenge the entrenched oral treatment of iron deficiency anemia. The paper shows how the newer understanding of hepcidin and iron metabolism in general can lead to very practical improvements in the management of iron deficiency anemia, a disorder that may affect as many as 1 billion people.

dose of iron will cause an increase in plasma iron, which in turn will cause an increase in hepcidin, which in turn will interfere with iron absorption of the next dose of iron.

Using elegant technology based on their skills with 3 isotopes of iron, so that subjects could be their own controls, they measured total and fractional iron absorption in several scenarios testing varying doses of oral iron administered over a variety of schedules. Per prediction, they found that ingesting a substantial single dose of oral iron, when absorbed, led to an increase in plasma iron, which in turn led to an increase in hepcidin. The measured increase in hepcidin then impaired iron absorption from subsequent doses of oral