Improving bioavailability and safety of oral iron

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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.

Barrier Bacteria (Bifidobacteria / Lactobacilli)

Require little or no iron

Kortman et al. 2014   Weinberg ED 1997
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

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

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

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- **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

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*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

Next iron dose should be given when hepcidin subsides?
Hepcidin increases >5 fold after a single oral dose of iron

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.

<table>
<thead>
<tr>
<th>Total iron absorbed (mg)</th>
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<tbody>
<tr>
<td>daily</td>
<td>67  (39, 114)</td>
</tr>
<tr>
<td>alternate</td>
<td>88  (56, 138)</td>
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GI side effects 33% less frequent in the alternate day group.

* p < 0.001

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).