Iron!

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GENERAL HEMATOLOGY

OHSU

DISCLOSURE

Current Relevant Financial Relationship(s)

None

Key Concepts

- Iron is good!
- Iron deficiency – diagnosis and treatment

Iron Deficiency alone – without anemia – leads to symptoms

Non Blood Effects of Fe Deficiency

- Iron is important in a variety of enzyme system
- Muscle second greatest user of iron
- CNS iron also important
- Iron deficiency important above and beyond just anemia

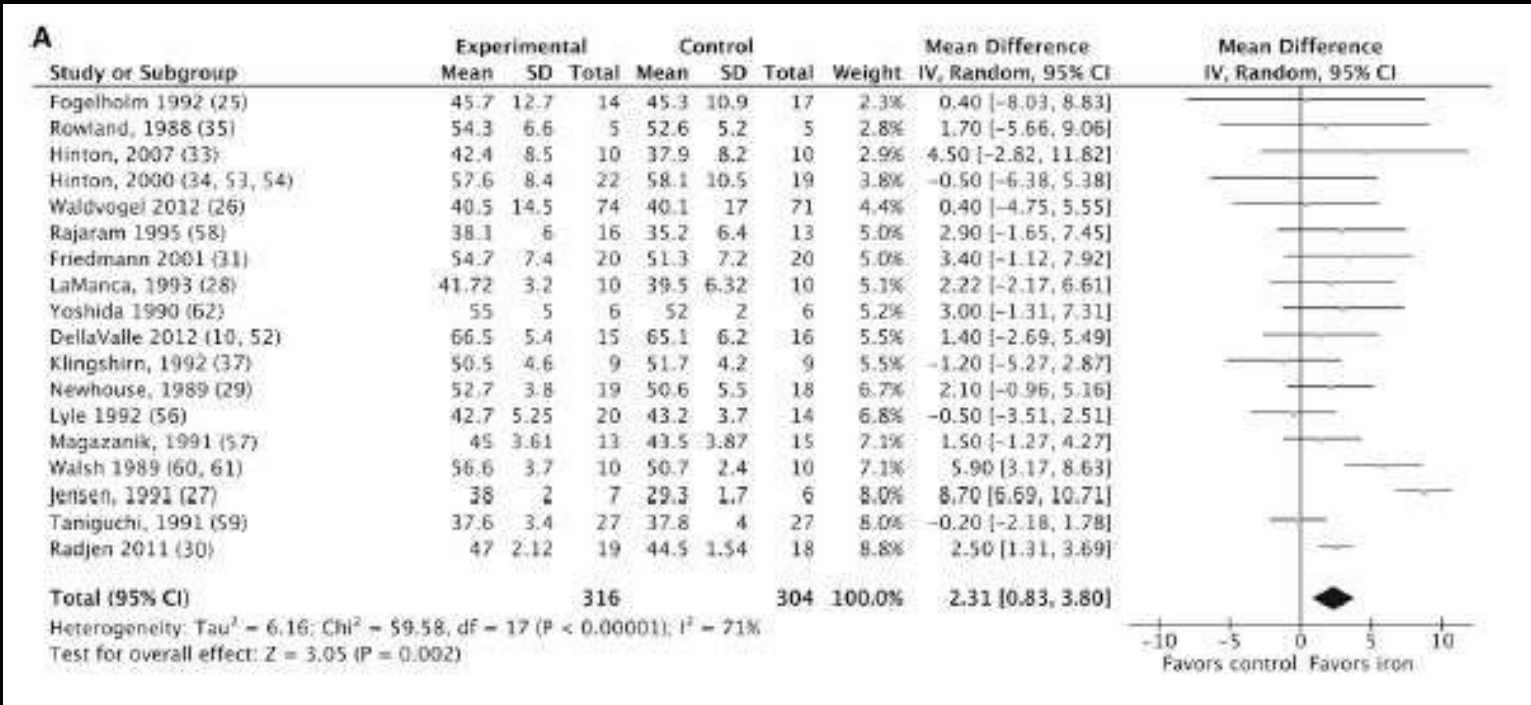
Iron for Fatigue

- Two RCT with oral iron show benefit with ferritin < 50 ng/mL
- Should be consider for fatigue and ferritin < 50 ng/mL

Iron and Athletes

- 33-80% of female athletes and 10-17% of male iron deficient
- Lack of iron effects:
  - Maximal exercise ability
  - Endurance
  - Strength
  - Cold tolerance

Benefit of treating Non-Anemic Fe Def: VO_2max



A

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Fogelholm 1992 (25)	45.7	12.7	14	45.3	10.9	17	2.3%	0.40 [-8.03, 8.83]
Rowland, 1988 (35)	54.3	6.6	5	52.6	5.2	5	2.8%	1.70 [-5.66, 9.06]
Hinton, 2007 (33)	42.4	8.5	10	37.9	8.2	10	2.9%	4.50 [-2.82, 11.82]
Hinton, 2000 (34, 53, 54)	57.6	8.4	22	58.1	10.5	19	3.8%	-0.50 [-6.38, 5.38]
Waldvogel 2012 (26)	40.5	14.5	74	40.1	17	71	4.4%	0.40 [-4.75, 5.55]
Rajaram 1995 (58)	38.1	6	16	35.2	6.4	13	5.0%	2.90 [-1.65, 7.45]
Friedmann 2001 (31)	54.7	7.4	20	51.3	7.2	20	5.0%	3.40 [-1.12, 7.92]
LaManca, 1993 (28)	41.72	3.2	10	39.5	6.32	10	5.1%	2.22 [-2.17, 6.61]
Yoshida 1990 (62)	55	5	6	52	2	6	5.2%	3.00 [-1.31, 7.31]
DellaValle 2012 (10, 52)	66.5	5.4	15	65.1	6.2	16	5.5%	1.40 [-2.69, 5.49]
Klingshirn, 1992 (37)	50.5	4.6	9	51.7	4.2	9	5.5%	-1.20 [-5.27, 2.87]
Newhouse, 1989 (29)	52.7	3.8	19	50.6	5.5	18	6.7%	2.10 [-0.96, 5.16]
Lyle 1992 (56)	42.7	5.25	20	43.2	3.7	14	6.8%	-0.50 [-3.51, 2.51]
Magazanik, 1991 (57)	45	3.61	13	43.5	3.87	15	7.1%	1.50 [-1.27, 4.27]
Walsh 1989 (60, 61)	56.6	3.7	10	50.7	2.4	10	7.1%	5.90 [3.17, 8.63]
Jensen, 1991 (27)	38	2	7	29.3	1.7	6	8.0%	8.70 [6.69, 10.71]
Taniguchi, 1991 (59)	37.6	3.4	27	37.8	4	27	8.0%	-0.20 [-2.18, 1.78]
Radjen 2011 (30)	47	2.12	19	44.5	1.54	18	8.8%	2.50 [1.31, 3.69]
Total (95% CI)			**316**			**304**	**100.0%**	**2.31 [0.83, 3.80]**

Heterogeneity: $Tau^2 = 6.16$; $Chi^2 = 59.58$, $df = 17$ ($P < 0.00001$); $I^2 = 71\%$

Test for overall effect: $Z = 3.05$ ($P = 0.002$)

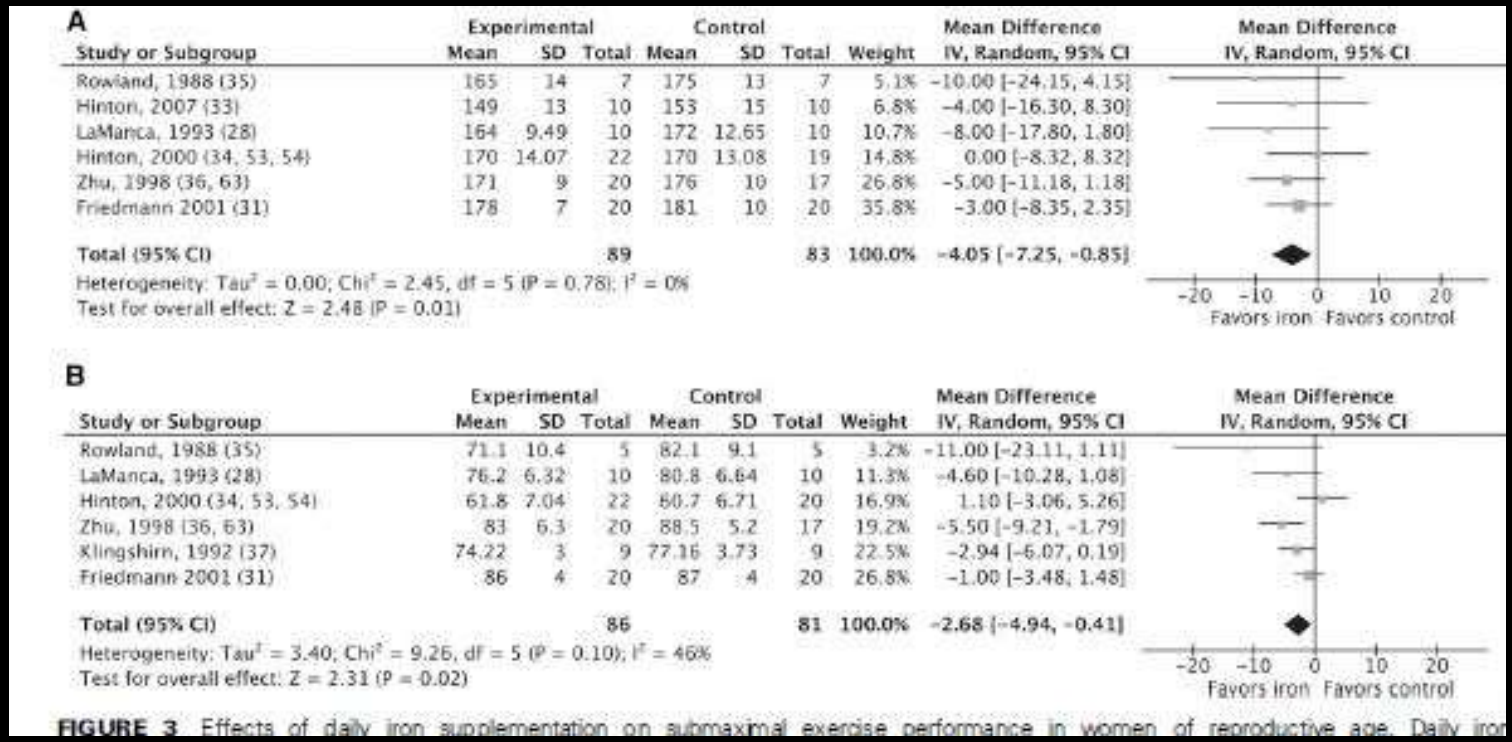
Mean Difference IV, Random, 95% CI

-10 -5 0 5 10

Favors control Favors iron

J. Nutr. 144: 906–914, 2014.

Submaximal



A

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Rowland, 1988 (35)	165	14	7	175	13	7	5.1%	-10.00 [-24.15, 4.15]
Hinton, 2007 (33)	149	13	10	153	15	10	6.8%	-4.00 [-16.30, 8.30]
LaManca, 1993 (28)	164	9.49	10	172	12.65	10	10.7%	-8.00 [-17.80, 1.80]
Hinton, 2000 (34, 53, 54)	170	14.07	22	170	13.08	19	14.8%	0.00 [-8.32, 8.32]
Zhu, 1998 (36, 63)	171	9	20	176	10	17	26.8%	-5.00 [-11.18, 1.18]
Friedmann 2001 (31)	178	7	20	181	10	20	35.8%	-3.00 [-8.35, 2.35]
Total (95% CI)			**89**			**83**	**100.0%**	**-4.05 [-7.25, -0.85]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.45$, df = 5 (P = 0.78); $I^2 = 0\%$
Test for overall effect: Z = 2.48 (P = 0.01)

Mean Difference IV, Random, 95% CI

-20 -10 0 10 20
Favors iron Favors control

B

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Rowland, 1988 (35)	71.1	10.4	5	82.1	9.1	5	3.2%	-11.00 [-23.11, 1.11]
LaManca, 1993 (28)	76.2	6.32	10	80.8	6.64	10	11.3%	-4.60 [-10.28, 1.08]
Hinton, 2000 (34, 53, 54)	61.8	7.04	22	60.7	6.71	20	16.9%	1.10 [-3.06, 5.26]
Zhu, 1998 (36, 63)	83	6.3	20	88.5	5.2	17	19.2%	-5.50 [-9.21, -1.79]
Klingshirn, 1992 (37)	74.22	3	9	77.16	3.73	9	22.5%	-2.94 [-6.07, 0.19]
Friedmann 2001 (31)	86	4	20	87	4	20	26.8%	-1.00 [-3.48, 1.48]
Total (95% CI)			**86**			**81**	**100.0%**	**-2.68 [-4.94, -0.41]**

Heterogeneity: $Tau^2 = 3.40$; $Chi^2 = 9.26$, df = 5 (P = 0.10); $I^2 = 46\%$
Test for overall effect: Z = 2.31 (P = 0.02)

Mean Difference IV, Random, 95% CI

-20 -10 0 10 20
Favors iron Favors control

FIGURE 3 Effects of daily iron supplementation on submaximal exercise performance in women of reproductive age. Daily iron

J. Nutr. 144: 906–914, 2014.

Iron and Athletes

- Low iron even without anemia affects performance
  - Decrease muscle stores?
- Consider screening female athletes
- Check fatigued athletes
- RCT show improvement in performance treating non-anemic iron deficiency

Other Effects of Low Iron

- Restless legs
  - Ferritins < 100 ng/mL
  - Lack of CNS Iron
- Alopecia
  - Ferritins < 100 ng/mL
- Pulmonary hypertension
- Heart failure
- Acute mountain sickness

Most women are iron deficient

Statistical Iron Deficiency

- Laboratory values for ferritin reflect arbitrary criteria and not physiology
- Ranges of "normal" unrealistic for:
  - Women
  - Older patients

Women and Iron

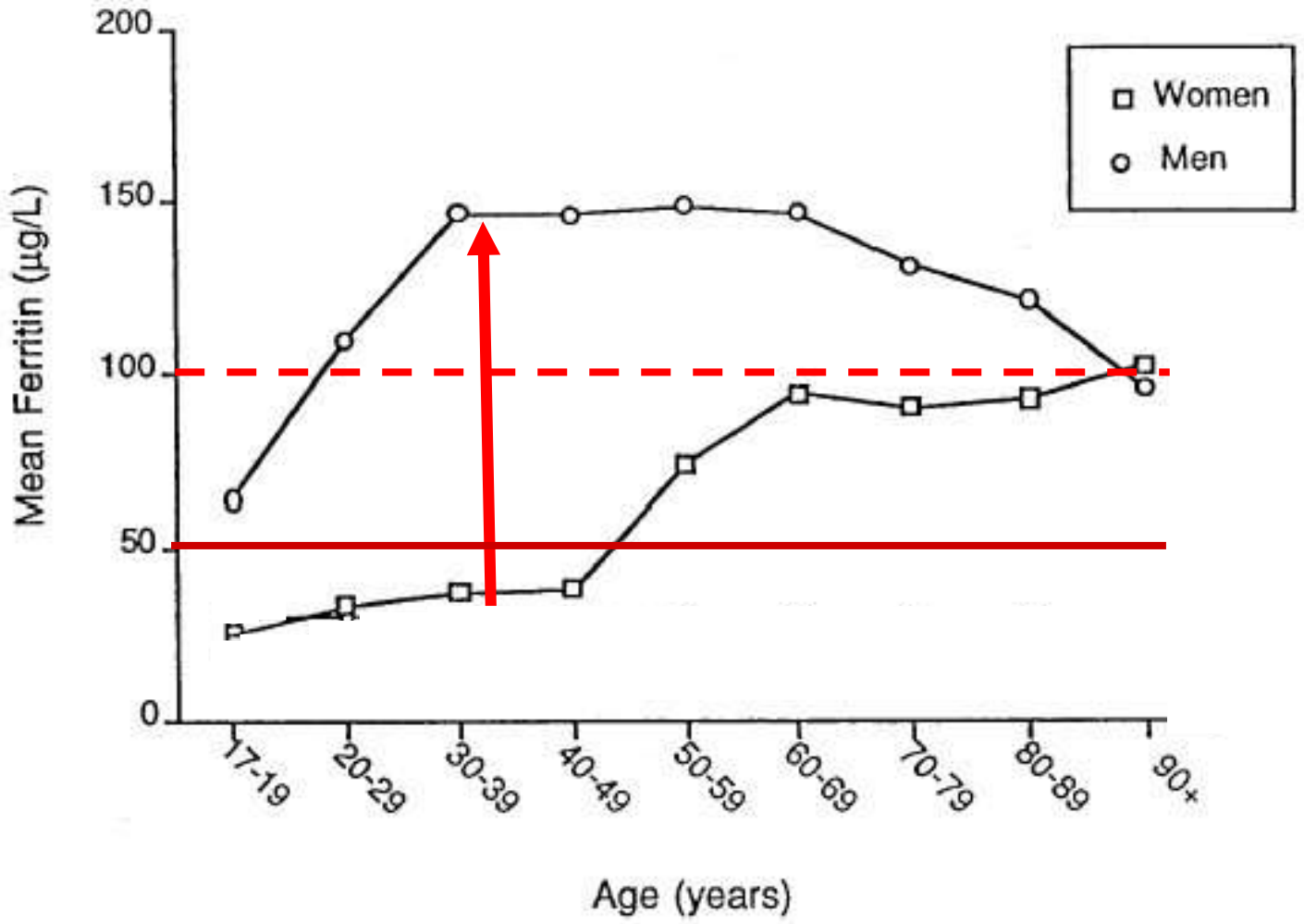
- No physiologic reason that women should have different ranges of normal for ferritin
  - 85% of 20 year old men have ferritin over 50 ng/mL
  - 25% of 20 year old women do
- Often overlooked cause of fatigue
  - Benefit of raising ferritin > 50 ng/mL

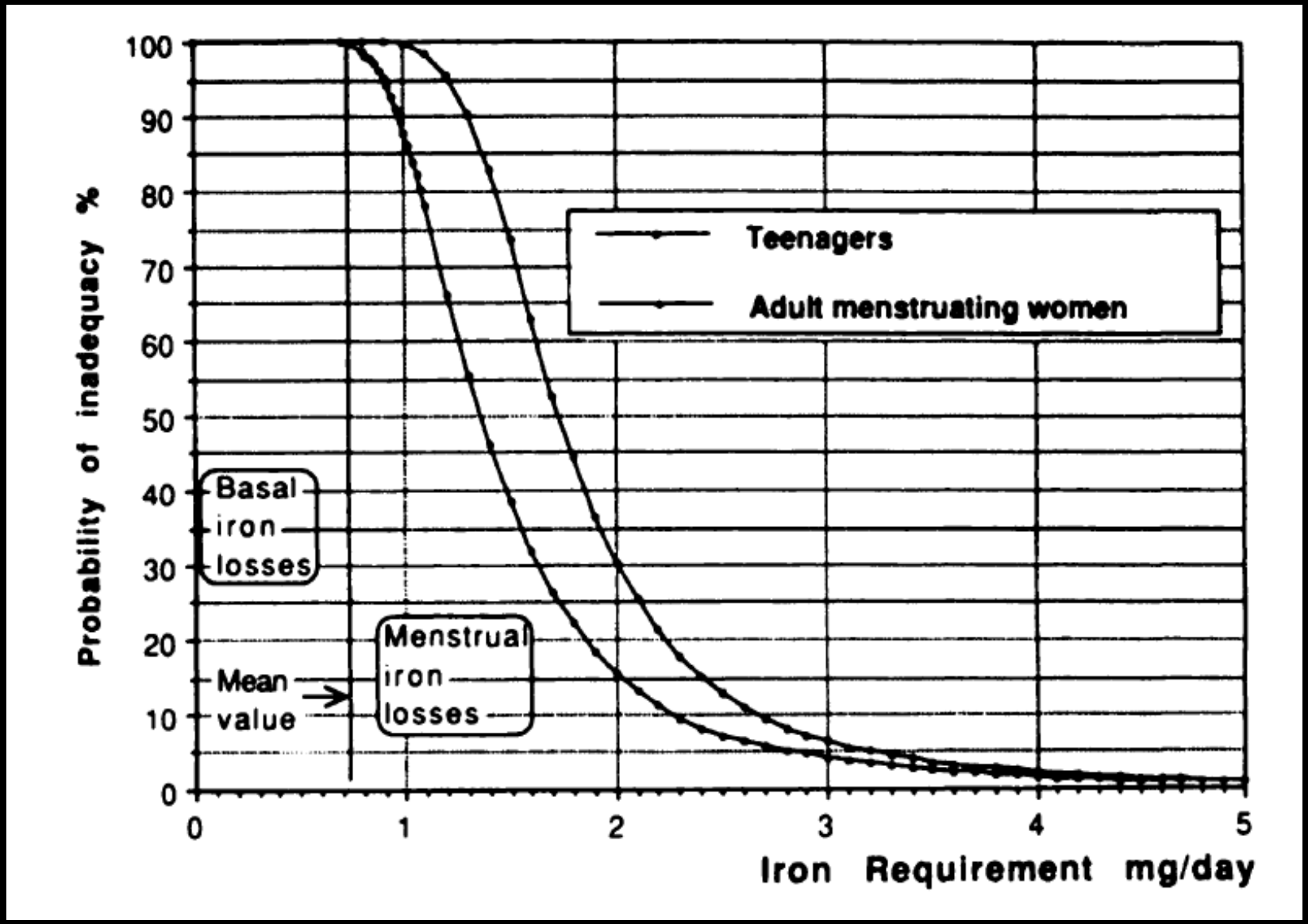
Iron Requirements

- **Men: 14 ug/kg/day**
  - **~ 1mg/day**
- **Women:**
  - **~2.4-3.4 mg/day**

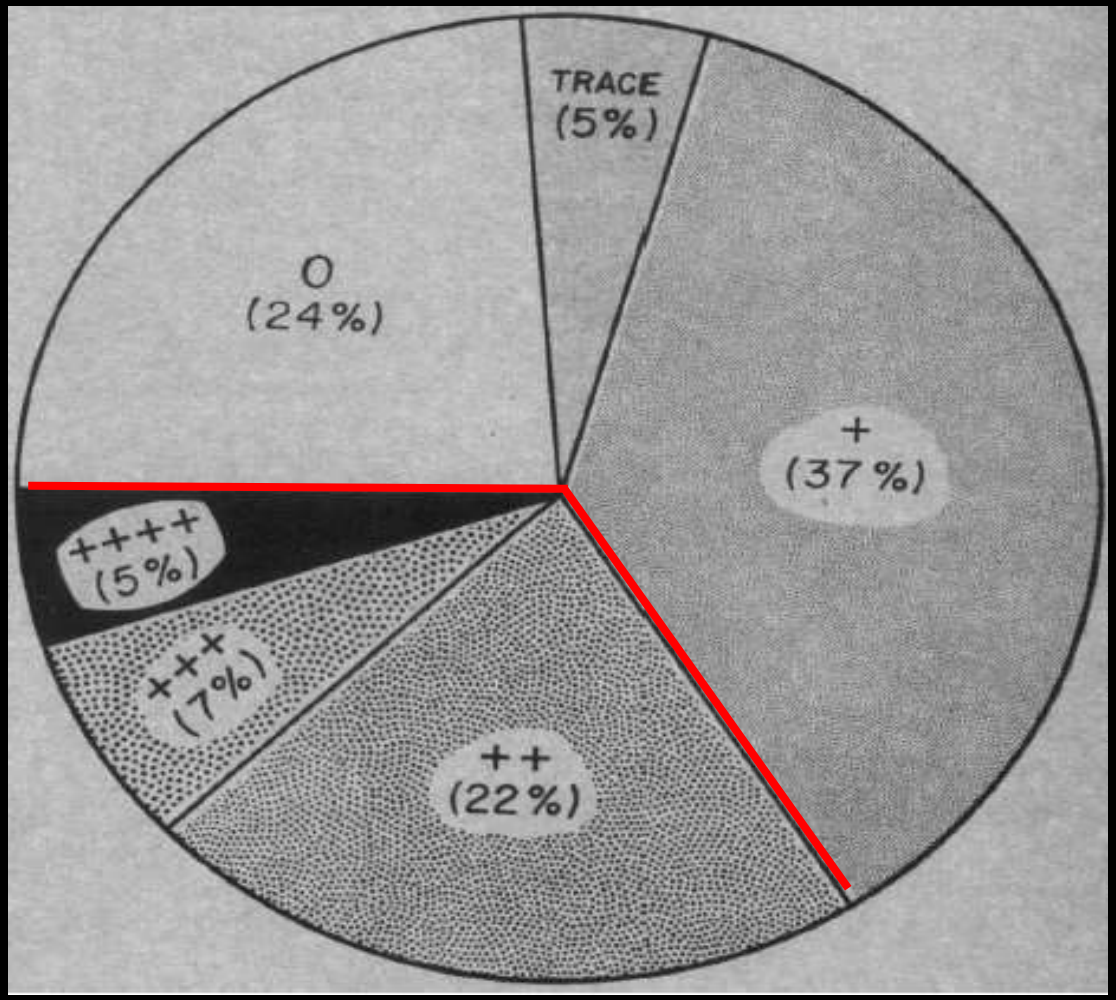
Gender and Ferritin

Figure 1




Probability of inadequacy %
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
Iron Requirement mg/day
Teenagers
Adult menstruating women
Basal iron losses
Menstrual iron losses
Mean value

Most Women have Low Iron Stores



JAMA, Mar 1967; 199: 897 - 900

The serum ferritin is the best – and only test-needed to diagnose iron deficiency

Diagnosis of Iron Deficiency Anemia

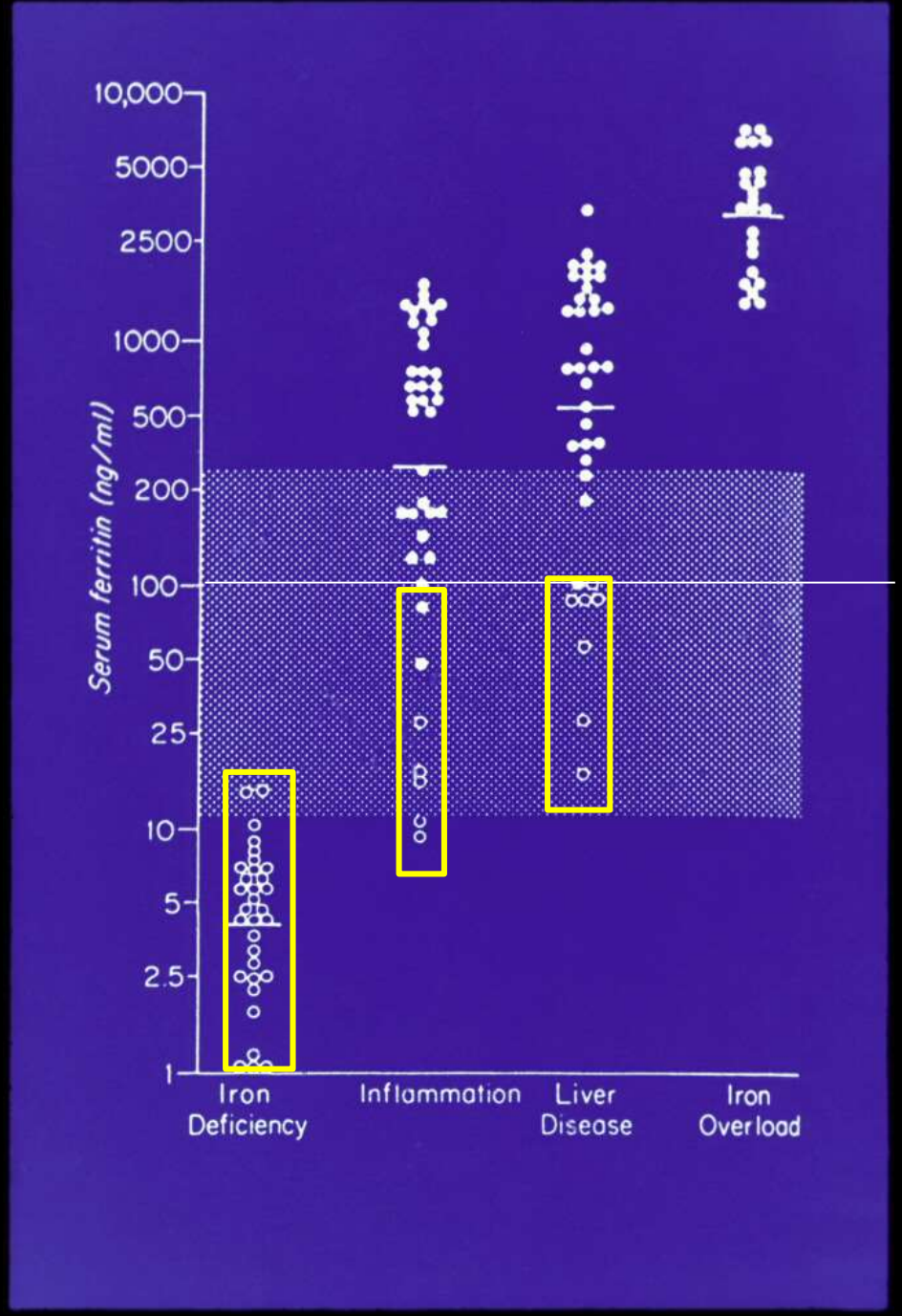
- MCV
- Serum iron
- TIBC
- Iron saturation
- Ferritin
- Bone marrow tests

Testing for Iron Deficiency

- "Classic" tests only helpful in few patients
- Tests affected by concurrent illness and age
  - Fe: VARIES WILDLY
  - MCV: lacks sensitivity and specificity
  - RDW: totally and completely worthless
  - Saturation: low in both ACD and iron deficiency

Serum Ferritin

- Serum ferritin proportional to iron stores
- Needs iron to be produced
  - –Acute phase reactant only in presence of iron
- Most accurate non-invasive test of iron stores!



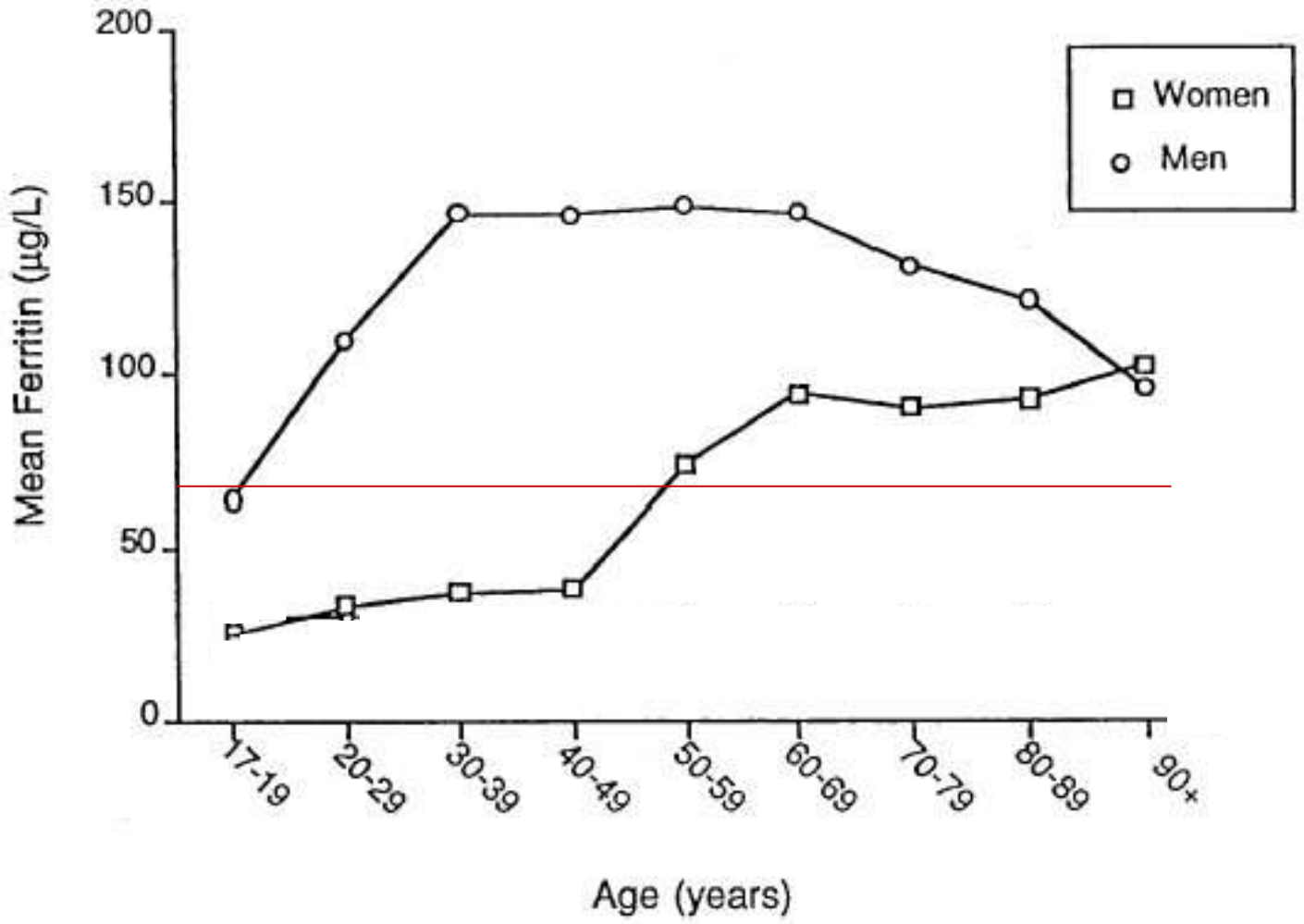
N Engl J Med. 1974 May 30;290(22):1213-6.

Iron Deficiency

- Serum ferritin is BEST non-invasive test of iron status
  - > 100 ng/mL rules out iron deficiency
  - Lower limit changes with age and condition
    - Patient over 65 with ferritin < 50 ng/mL all iron deficient

Age and Ferritin

Figure 1



Guyatt Review

- Ferritin only blood test to order
- Laboratory cut-off not optimal
- Likelihood of iron deficiency does not fall until ferritins > 40ng/mL
  - > 70ng/mL with inflammation
- Ferritins > 100 ng/mL rule-out iron deficiency

J Gen Intern Med. 1992 Mar-Apr;7(2):145-53

Ferritin: Bottom Line

- Ignore lab reference ranges!
  - < 15 ng/ml 100% specific
  - > 100 ng/ml rules-out
- In older patients ferritins < 100ng/ml consider GI work-up

Athletes: Ferritin

- All agree ferritins < 20ng/dl
- Literature goes up to 60ng/dl
- Two choices
  - < 50ng/dl if symptomatic
  - < 20ng/dl or < 35ng/dl and < 20% saturation

Functional Iron Deficiency

- Ferritins < 100: lack of marrow iron
- Ferritins > 100 but low sat: Failure to mobilize iron
  - Epo treatment
  - Heart failure
  - Anemia of chronic disease
- Hepcidin blockers?
- Aggressive IV iron

Trial of Oral Iron

- Effected by inflammation and compliance
- Useful in young women

Bone Marrow

- Direct measure of iron stores
- “Gold standard”
- Invasive and expensive

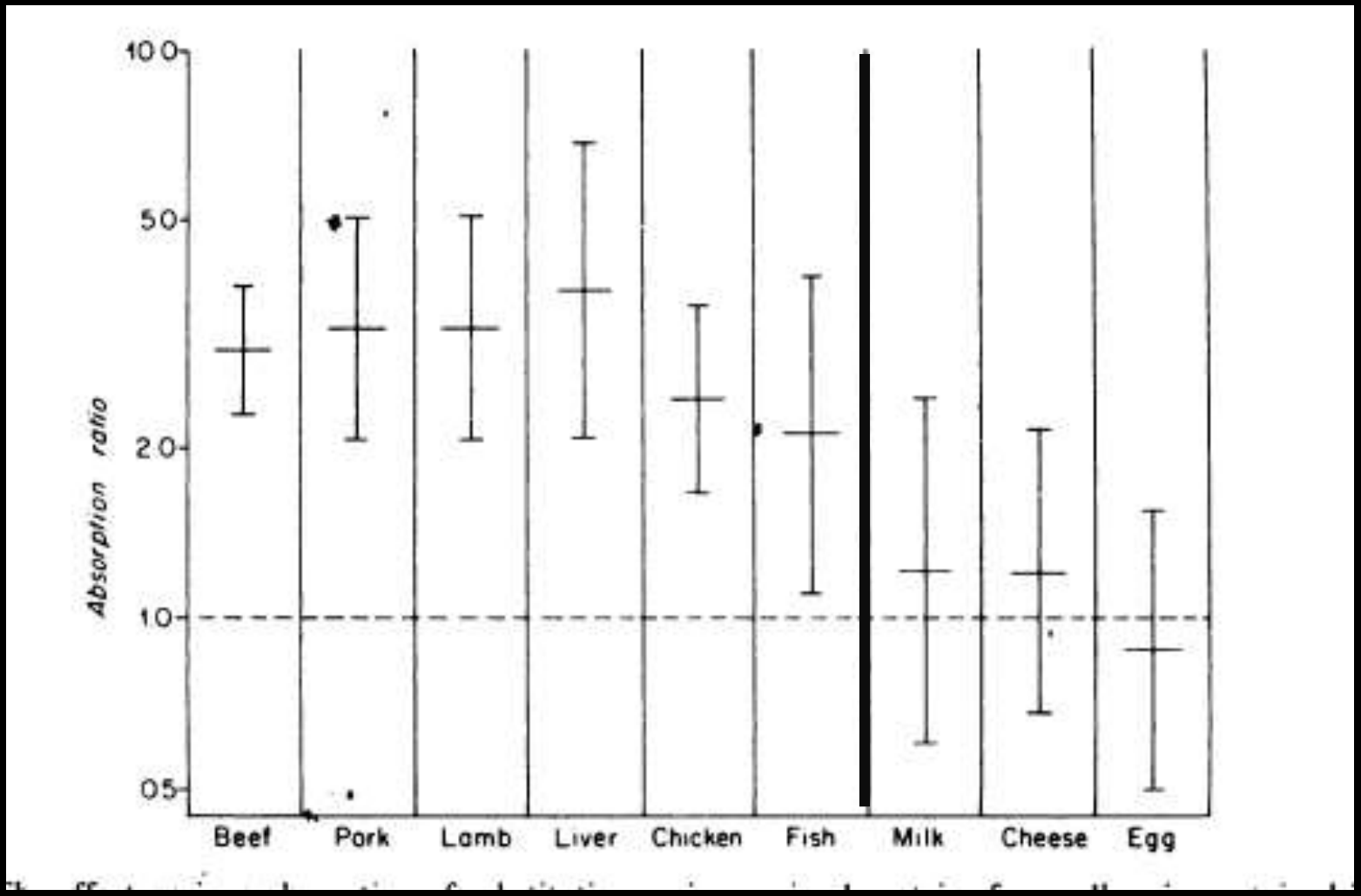
Summary

- RDW, serum iron, saturation: worthless
- TIBC: specific but not sensitive
- Ferritin: best non-invasive test
- Bone marrow: gold standard

Diet does matter

Dietary Iron

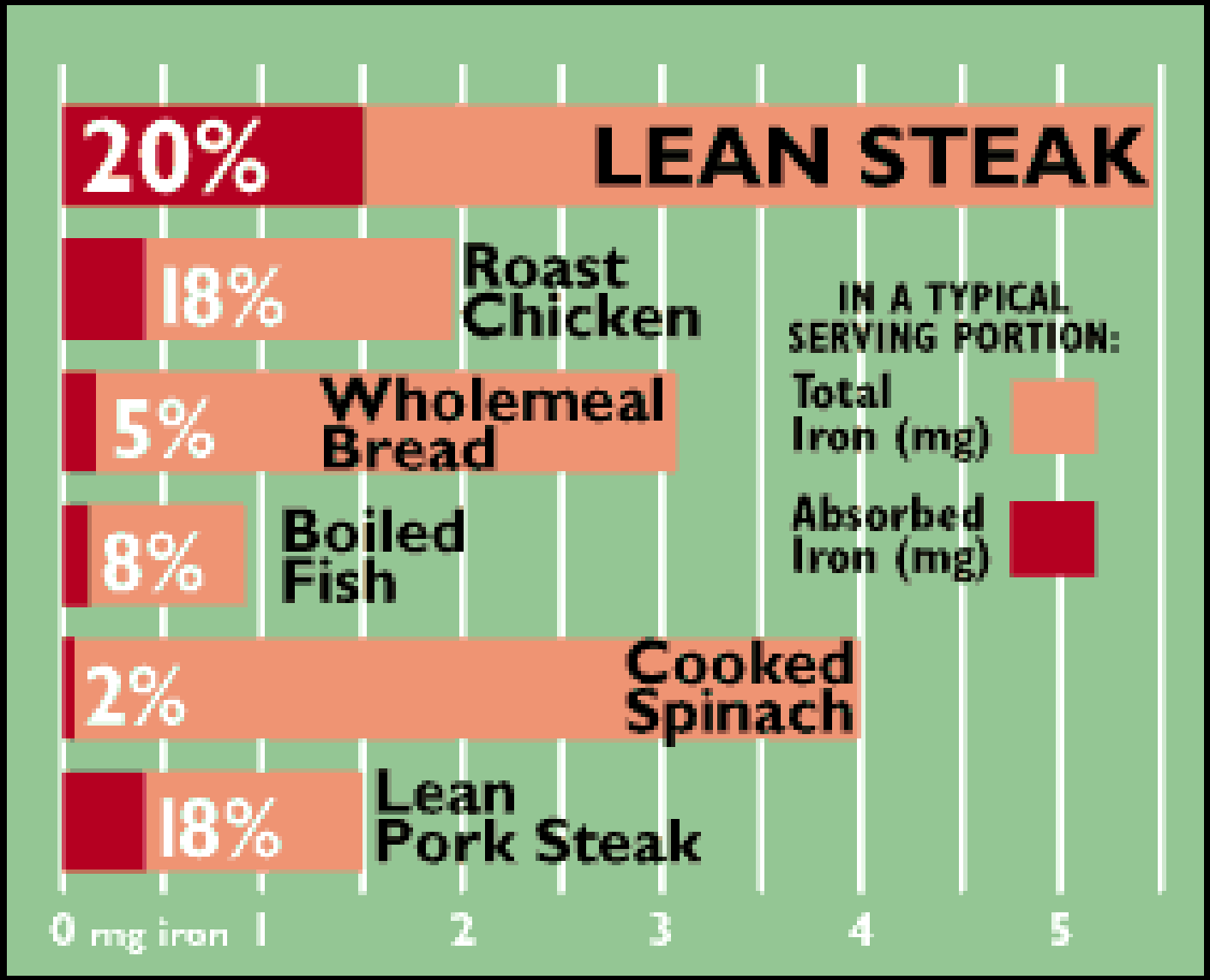
- Heme iron 10x better absorbed than non-heme iron
- Meat protein improves iron absorption



Am J Clin Nutr **August**
1976 vol. 29 no. 8
859-867

Dietary Iron

- Calcium, fiber can block iron absorption
  - Overcome by vitamin C
- Tea decreases 75-80%
- Coffee decreases 60% (5 oz!)


20%
LEAN STEAK
18%
Roast Chicken
5%
Wholemeal Bread
8%
Boiled Fish
2%
Cooked Spinach
18%
Lean Pork Steak
IN A TYPICAL SERVING PORTION:
Total Iron (mg)
Absorbed Iron (mg)
0 mg iron
1
2
3
4
5

What I Tell my Patients

- If feasible increase meat in diet
- Try not to drink tea or coffee with meat
- Vitamin C helps iron asorption

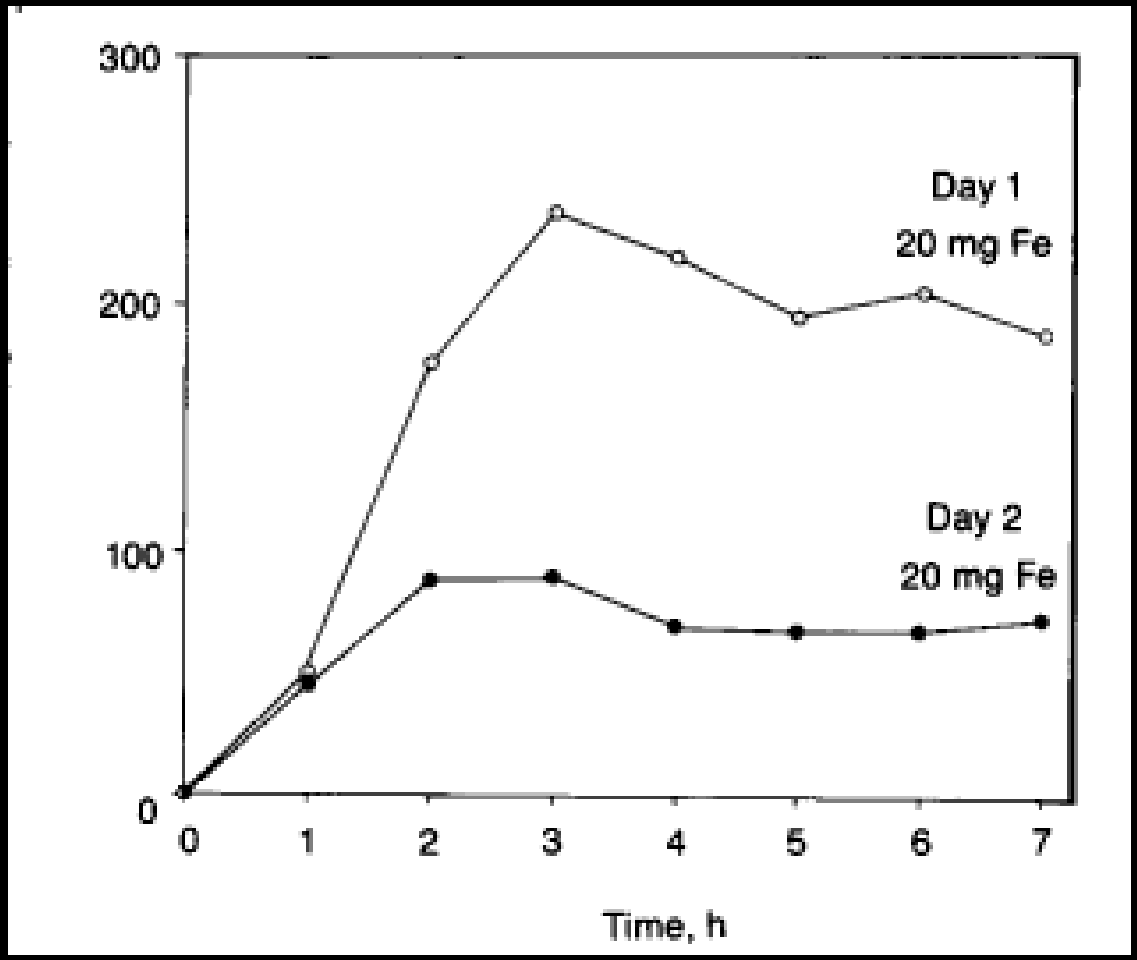
Iron Skillets

- Does increase iron in food
- Amount variable
  - Acidic food
  - Time cooked
- Spaghetti sauce
  - 0.22 mg fe/100g -> 2.10 mg fe/100g
- Apple sauce
  - 0.26 mg fe/100g -> 6.26 mg fe/100g
- Journal of Food Science 1991, 56 (2), 584-585

Iron pills – a little goes a long way

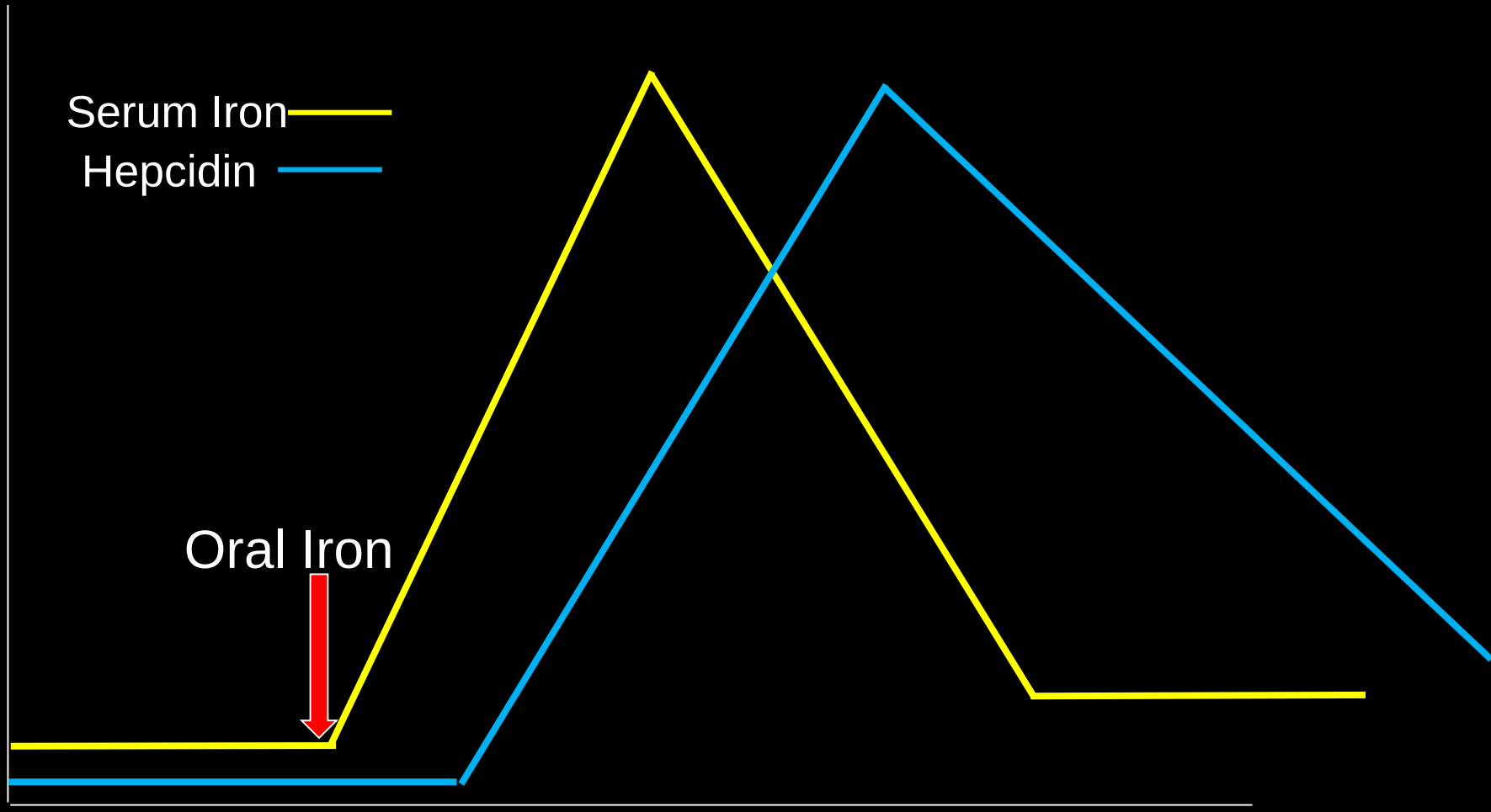
Oral Iron Pills

- Gut can only absorb a limited amount of iron
- Maxed out at ~ 10mg



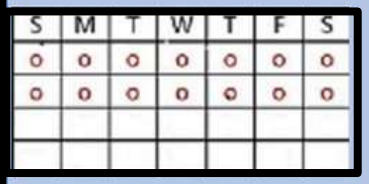
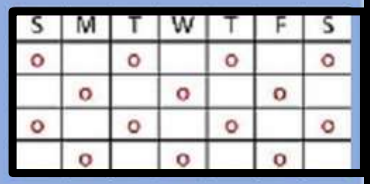
(*Arch Intern Med* 1987;147:489-491)

Hepcidin Response to Iron



Does Alternate-Day Dosing of Oral Iron Therapy Improve Iron Absorption?

Allan S. Brett, MD, reviewing Stoffel NU et al. *Lancet Haematol* 2017 Oct 9

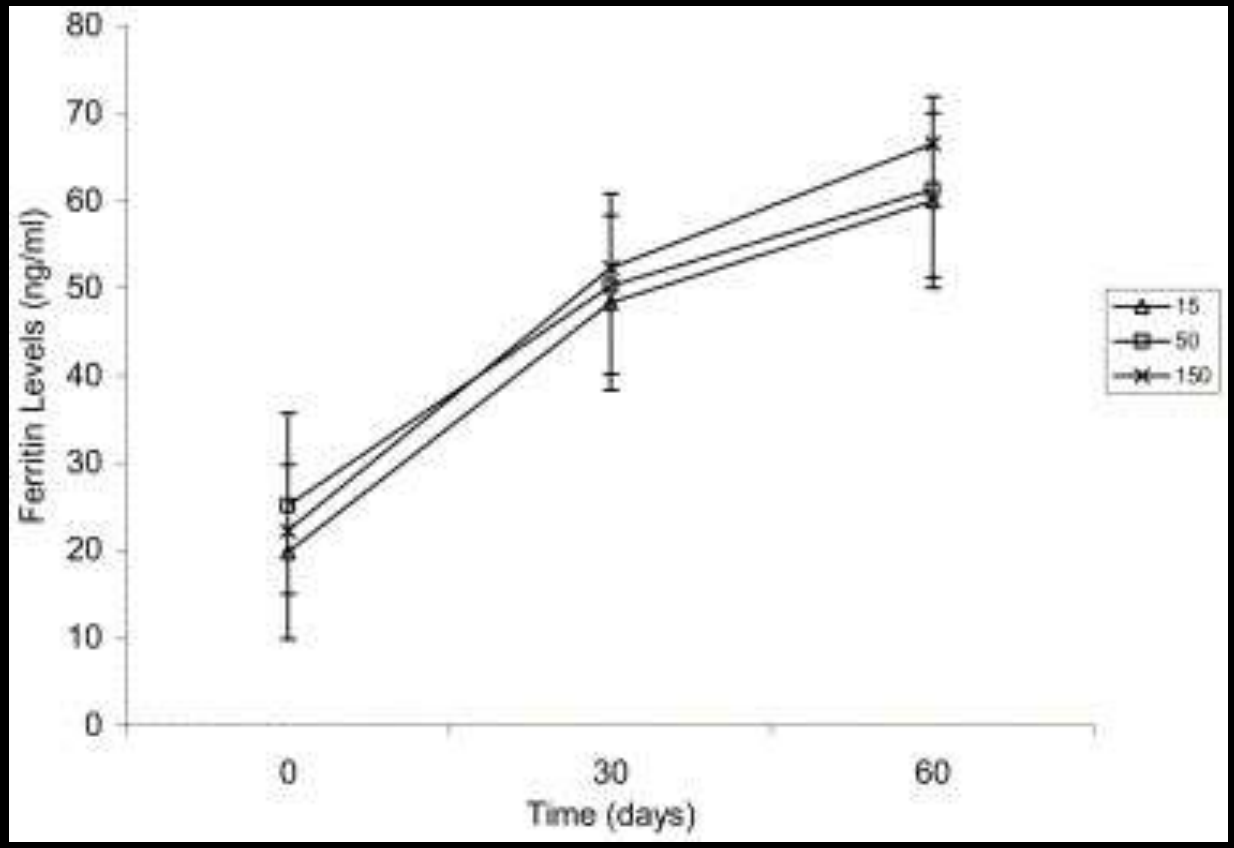
Daily Dosing 14 days		Alternate-Day Dosing 28 days
		
16%	Fractional Absorption	21%
131 mg	Total Absorption	175 mg

Comment: Fractional absorption was better with alternate-day dosing, but total absorption would still have been better with daily dosing if that group had received 28 days of iron. Alternate-day dosing likely enhanced gastrointestinal tolerability.

NEJM Journal Watch

But 28 days of daily iron = 262 mg absorbed

15 vs 50 vs 150mg Oral Iron



Am J Med. 2005 Oct;118(10):1142-7.

Oral Iron Pills

- Years of studies have shown that the best iron preparation is….

Oral Iron Pills

….the one that the patient can tolerate

- No consistent difference in any brand
- Many patients can’t tolerate any pill on an empty stomach
  - Ok with meals

What I Do

- Cheapest iron pill
  - Ferrous sulfate
- Once a day with meals
  - Vitamin C 500
  - No tea or coffee
- If intolerant can try lower dose

Response to Oral Iron

- Best predictor of response is rise in hemoglobin by 1 g/dl in two weeks

At What Ferritin are Iron Stores Replete?

- GI iron absorption goes back to backline only at ferritin of 60 ng/mL
- Falling from 70 to 35 ng/mL muscle loss iron
- Alopecia and restless legs seen at < 100 ng/mL
- Maybe 50-100 ng/mL a reasonable goal for repletion

All iron deficiency has a cause!

Contributors to Iron Deficiency

- GI
  - NSAIA 10-15%
  - Colon Ca 5-10%
  - Gastric Ca 5%
  - Ulcers 5%
  - Angiodysplasia 5%
  - Esophagitis 2-4%
  - Esophageal Ca 1-2%
- Non-GI
  - Menstruation 20-30%
  - Celiac disease 4-6%
  - Bariatric surgery 1%

Iron Deficiency: GI Evaluation

- Most patients with identifiable source of GI blood loss
- Very high number with tumors
- Most common cause of missed cancer diagnosis
- Who to evaluate?
  - All men
  - Women > 40 or with GI symptoms

Don’t be afraid to use IV iron

Parental Iron Therapy

- When to use
  - Refractory to oral iron
  - Unable to take oral iron
  - Cannot keep up with blood loss
    - Bariatric surgery
    - Inflammatory bowel disease
    - Chronic GI bleeding

IV Iron: Preparations

- Iron MW Iron Dextran: INFeD
- Iron Sucrose: Venofer
- Iron Gluconate: Ferrlecit
- Ferumoxytol: FeraHeme
- Ferric carboxymaltose: Injectafer
- Ferric derisomaltose: Monoferric

Dosing

- Iron dextran: 1-3 grams at once
- Venofer: 2-300 mg/day
- Ferrlecit: 250mg/day
- FeraHeme: 510 -1020mg mg/day
- Injectafer: 750mg/day
- Monoferric: 1000mg/day

Dosing IV Iron

- Replacement formulas inaccurate
- Give 1000mg
  - Recheck in 4 weeks
  - If severe anemia recheck in two weeks

Safety

- Minor infusion reactions common (~1-2%) but true anaphylaxis very rare
- Death rates (per 100,000)
  - INFeD 0.8 (0-1.9)
  - Ferrlecit 6.3 (1.311.4)
  - Venofer 6.6 (3.1-9)
  - FeraHeme 3.5 (0-7.8)

Reactions

- Complement mediated pseudo-allergy
- Drug non-specific activated complement
  - Similar to rituximab etc.
- True anaphylaxis very rare
  - Negative tryptase > 200 reactions

Implication

- No value test dose
- Premedication often doesn’t help
- Diphenhydramine makes things worse
- Treat as infusion reaction not allergy
- Studies show risk same with all iron preparations

Refractory Iron Deficiency

- Patient is “refractory” to IV iron
- Not getting enough iron
- Frequent ferritin checks
  infusions
- Goal ferritin > 100

Trends in Iron Deficiency

- Incidence of iron deficiency is increasing
  - Reduction in meat intake
  - Increase PPI/H2 blockers
  - Increase in bariatric procedures

Trends in Iron Deficiency

- Understanding variability in iron absorption
  - TMPRSS6
    - Key enzyme in iron metabolism
    - Multiple polymorphism in population
    - Homozygous mutations with refractory iron deficiency
    - Heterozygous with decrease absorption

Remember!

- Iron is good!
- Ferritins > 50 ng/mL are good
- Oral iron
  - One pill/day
  - With vitamin C
  - With meat if feasible