Iron Therapy

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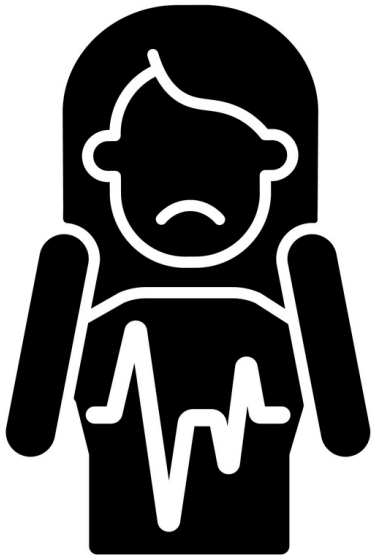
Iron Deficiency

Fatigue

Palpitations

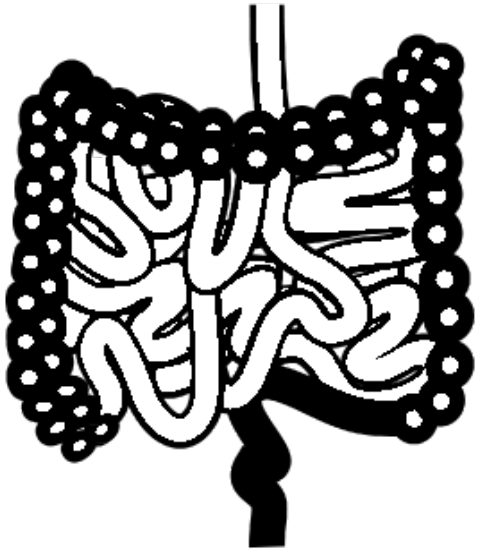


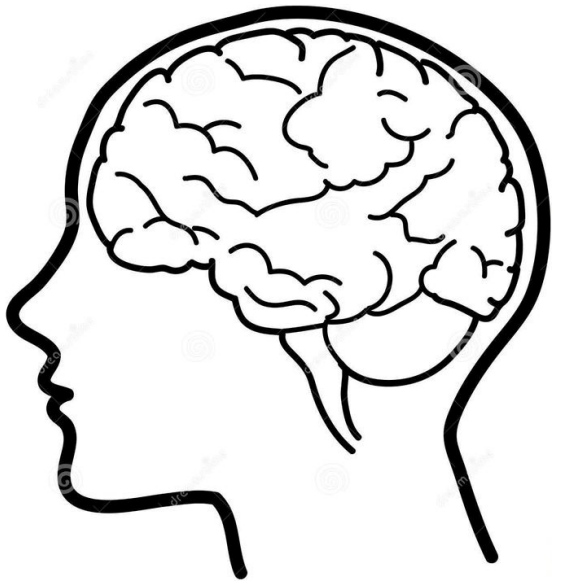
Dyspnea

Other Symptoms

Angina

Motility Disorders





Vertigo
Lethargy
Cognitive dysfunction

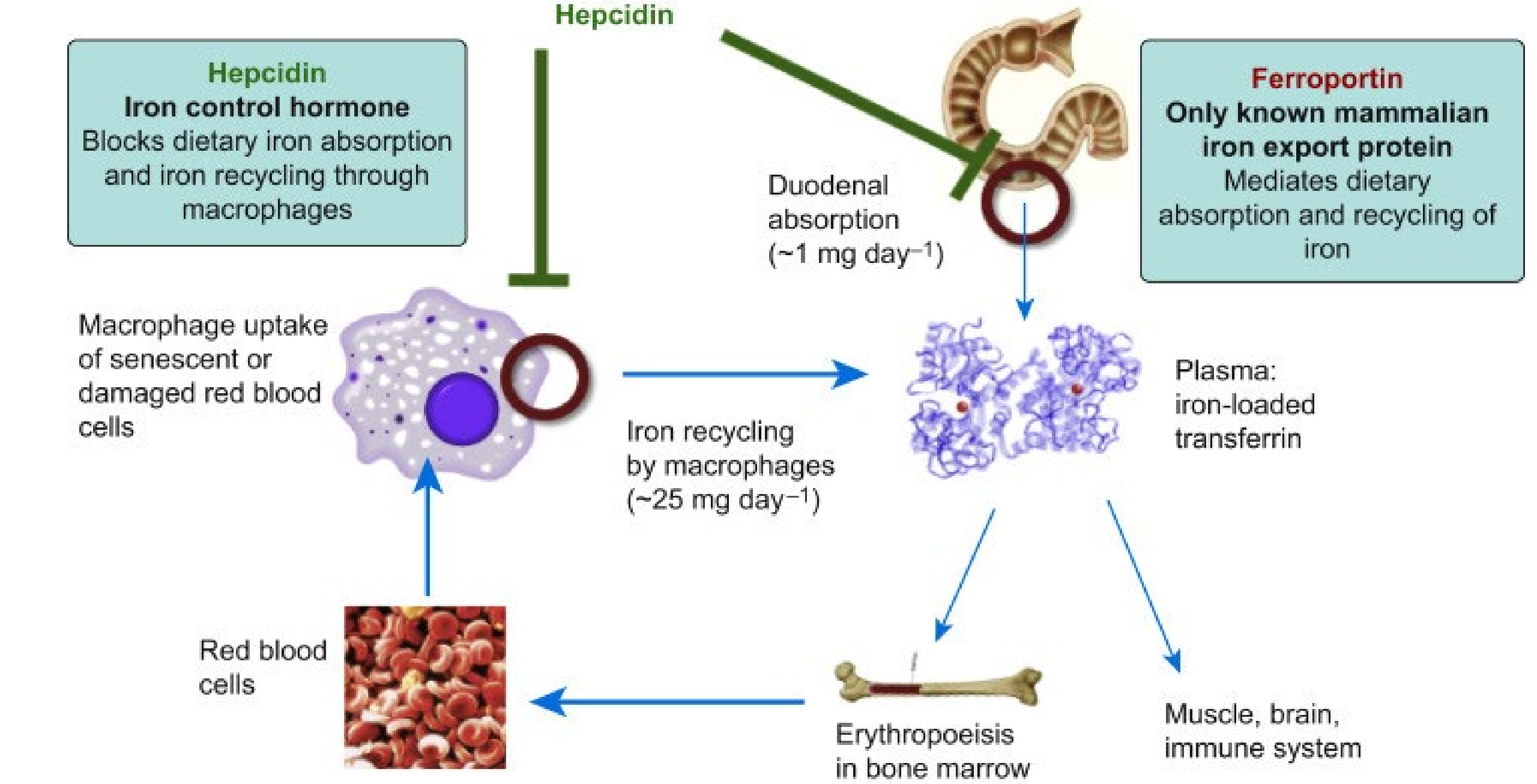
Kumar, Aditi, et al. "Iron deficiency anaemia: pathophysiology, assessment, practical management." *BMJ open gastroenterology* 9.1 (2022): e000759.

Iron Deficiency Without Anemia

- Ferritin <30 ug/L
  - Inflammation: ferritin <100 ug/L
- Tsat <20%

- Single dose oral iron on alternating days
  - Repeat iron studies in 6-8 weeks

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, randomised controlled trials. *Lancet Haematol* 2017;4:e524–33.



Shah, A., A. Acheson, and R. C. F. Sinclair. "Perioperative iron deficiency anaemia." *BJA education* 23.10 (2023): 372-381.

Oral iron preparations

- Many oral iron supplements are available, efficacy is equal
- Take on an empty stomach
- Avoid slow-release formulations

Carbonyl iron (iron pentacarbonyl)
Ferric citrate
Ferrous ascorbate
Ferrous chloride
Ferrous fumarate
Ferrous gluconate
Ferrous succinate
Ferrous sulfate
Ferrous sulfate anhydrous
Polysaccharide-iron complex

Auerbach M, Adamson JW. How we diagnose and treat iron deficiency anemia. Am J Hematol. 2016 Jan;91(1):31-8. doi: 10.1002/ajh.24201. Epub 2015 Nov 17. PMID: 26408108.

Case 1

- 63yo woman with CHF referred for progressively worsening anemia

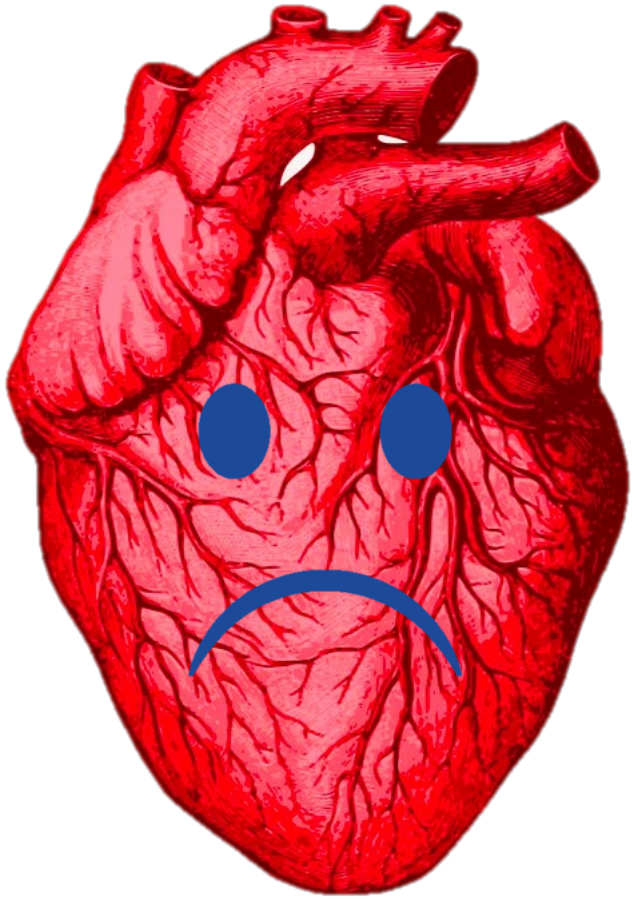
Component	Ref Range & Units	13 d ago (3/5/24)
Ferritin	5 - 200 NG/ML	17

Component	Ref Range & Units	13 d ago (3/5/24)
Iron	50 - 170 ug/dL	17 ↓
Transferrin	140 - 330 mg/dL	391 ↑
Percent Saturation	16 - 48 %	3 ↓

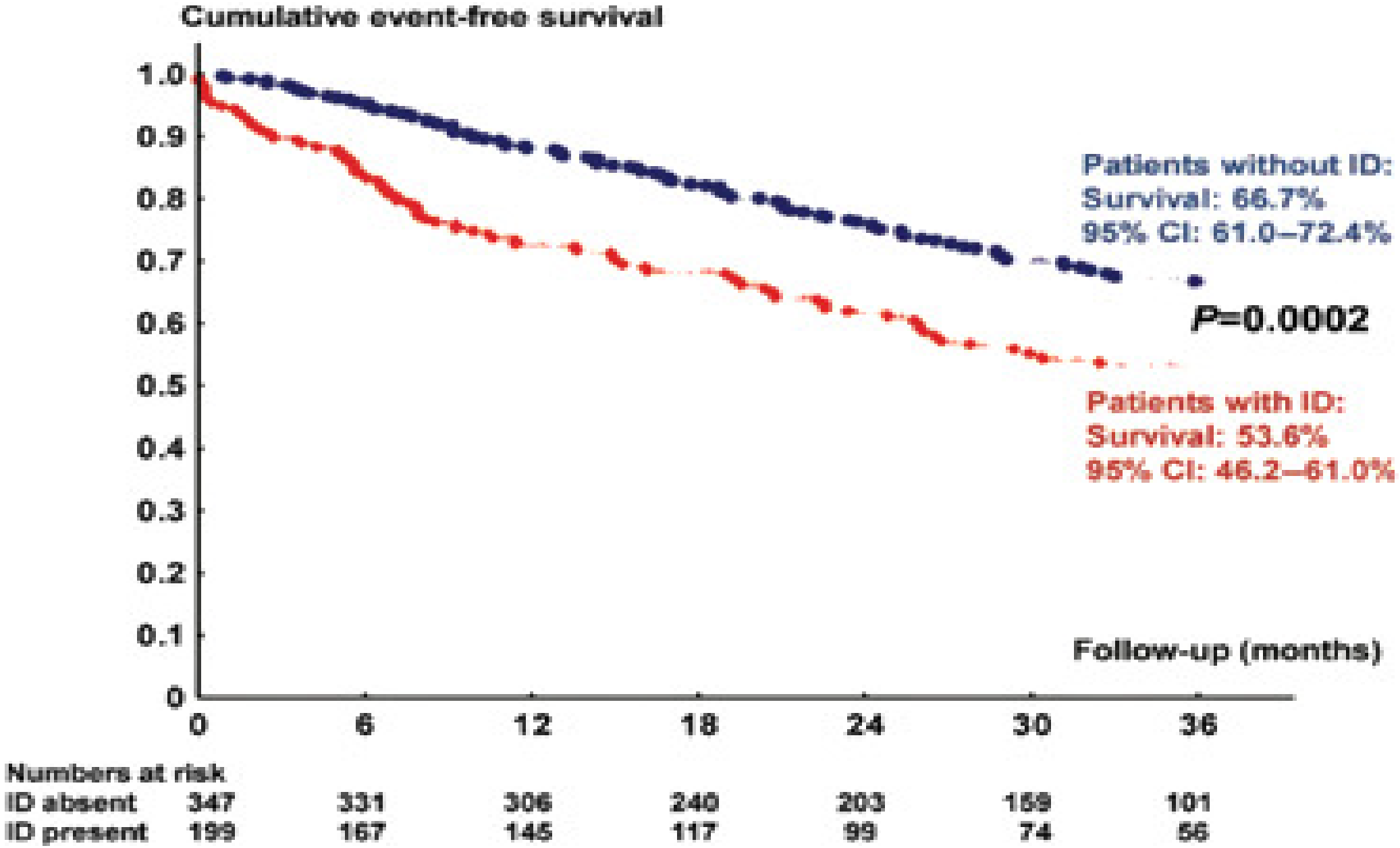
Component	Ref Range & Units	13 d ago (3/5/24)
WBC	4.00 - 11.00 K/UL	6.78
RBC	4.20 - 5.20 M/UL	2.84 ↓
Hemoglobin	12.0 - 16.0 G/DL	7.1 ↓
Hematocrit	35.0 - 47.0 %	23.5 ↓
MCV	83.0 - 95.0 FL	82.7 ↓
MCH	28.0 - 32.0 PG	25.0 ↓
MCHC	32.0 - 36.0 G/DL	30.2 ↓
RDW	11.0 - 14.0 %	17.6 ↑

Iron in Heart Failure

- Effects 30-50% of patients
- Depleted iron stores cause anemia
- Multifactorial etiology



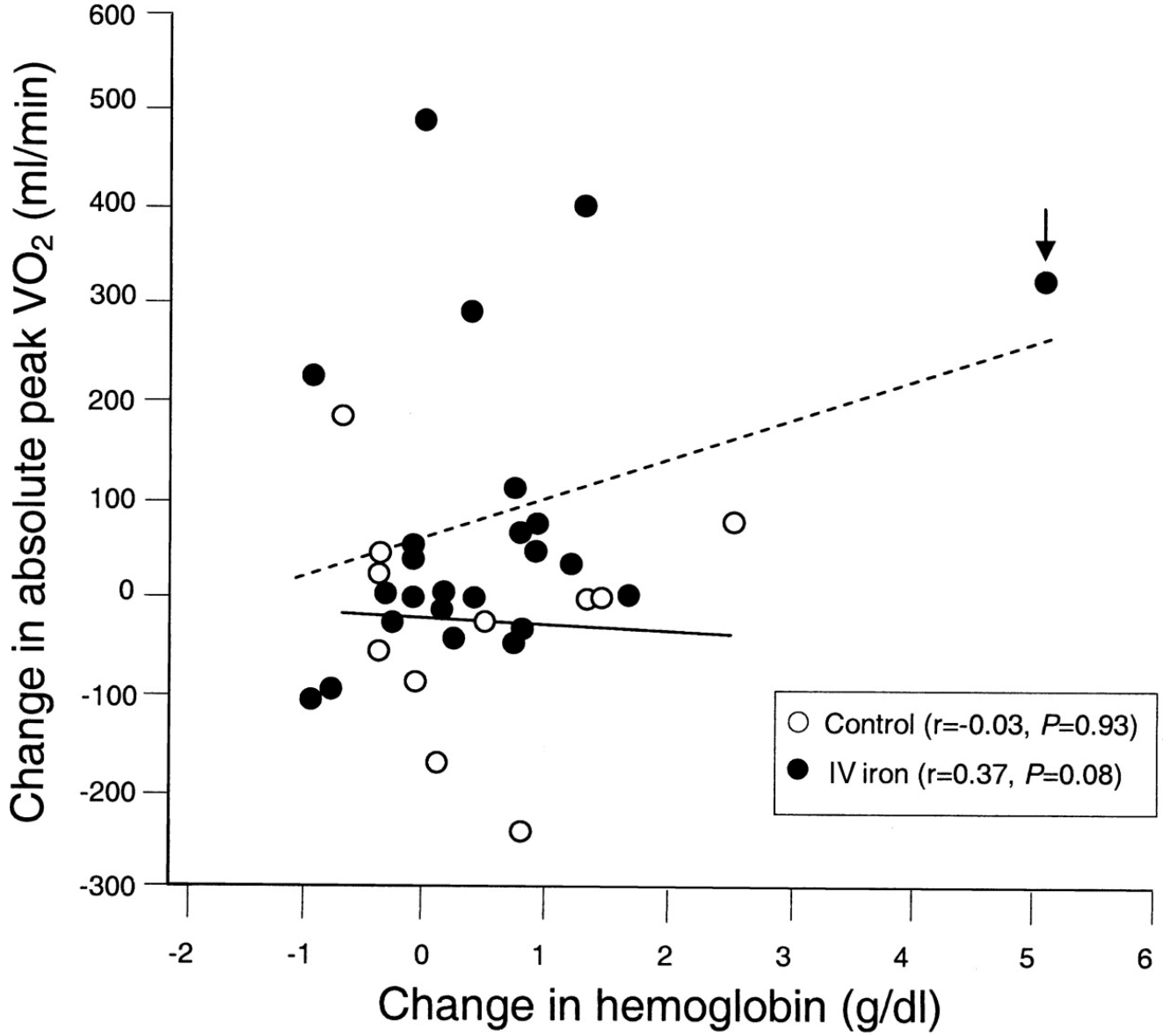
Loncar, Goran, et al. "Iron deficiency in heart failure." *ESC heart failure* 8.4 (2021): 2368-2379.



Cardiovascular Therapeutics, Volume: 35, Issue: 6, First published: 24 August 2017, DOI: (10.1111/1755-5922.12301)

Iron repletion

- Oral iron is rarely successful and is not recommended
- IV iron is safe and effective



Lewis GD, Semigran MJ, Givertz MM, et al. Oral iron therapy for heart failure with reduced ejection fraction: design and rationale for oral iron repletion effects on oxygen uptake in heart failure. *Circ Heart Fail*. 2016; **9**:pii: e000345.

Okonko DO, Grzeslo A, Witkowski T, et al. Effect of intravenous iron sucrose on exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure and iron deficiency FERRIC-HF: a randomized, controlled, observer-blinded trial. J Am Coll Cardiol. 2008; 51: 103-112.

Compound	Brand name	Recommended amount per dose	Infusion time	Availability
Low-molecular-weight iron dextran	INFeD	100 mg after uneventful 25-mg test dose	2-6 h (+ test dose)	United States, Europe
Ferrous gluconate	Ferrlecit	125 mg	12.5 mg/min	United States, Europe, Canada
Iron sucrose	Venofer	200-300 mg	100 mg/30 min	United States, Europe, Canada
Ferumoxytol	Feraheme	510 mg	15 min	United States, Europe
Ferric carboxymaltose	Injectafer	750 mg	15 min	United States, Europe
	Ferinject	1000 mg	15 min	United States, Europe
Iron isomaltoside	Monofer	≤1000 mg	>15 min	United States, Europe

Case 1

- We plan for administration of IV iron, her insurance requires trial of Iron Sucrose

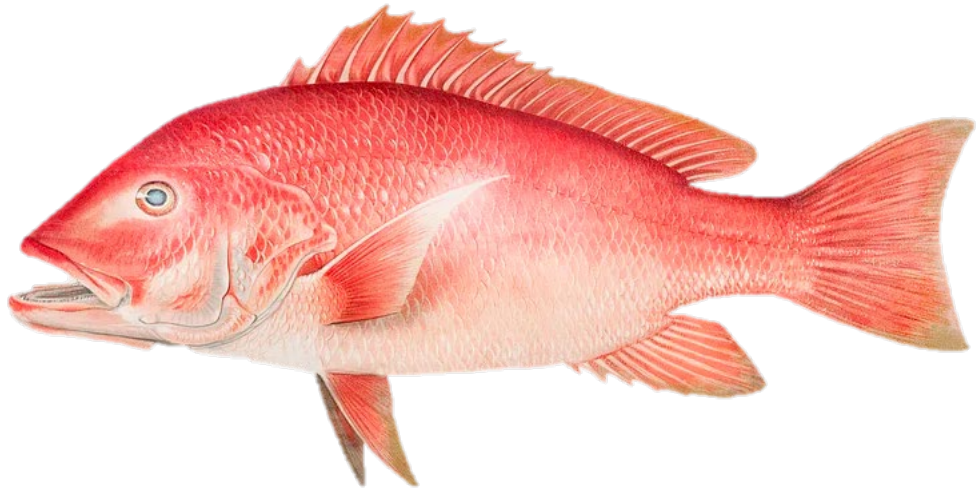
Studies on Iron in HF

CONFIRM-HF	Ferric carboxymaltose 2–5 doses over 36 weeks vs placebo
EFFECT-HF	Ferric carboxymaltose up to 3 doses over 12 weeks vs standard of care
Dhoot et al.	Ferric carboxymaltose single dose vs placebo
AFFIRM-AHF	Ferric carboxymaltose 2–4 doses over 24 weeks vs placebo
IRONMAN	Isomaltoside 1–9 doses over 20 months vs usual care
Mollace et al.	Ferric carboxymaltose 500 mg at 0 and 4 weeks vs placebo
HEART-FID	Ferric carboxymaltose 2,316 ± 1,366 mg cumulative dose over 3 years vs placebo

Lakhal-Littleton, Samira, and John GF Cleland. "Iron deficiency and supplementation in heart failure." *Nature Reviews Cardiology* (2024): 1-24.

Case 1

- Our patient comes in for her first dose of iron sucrose with a plan for 5 total doses
- Shortly after the infusion begins she develops chest tightness and flushing of the face and neck
- The infusion is held



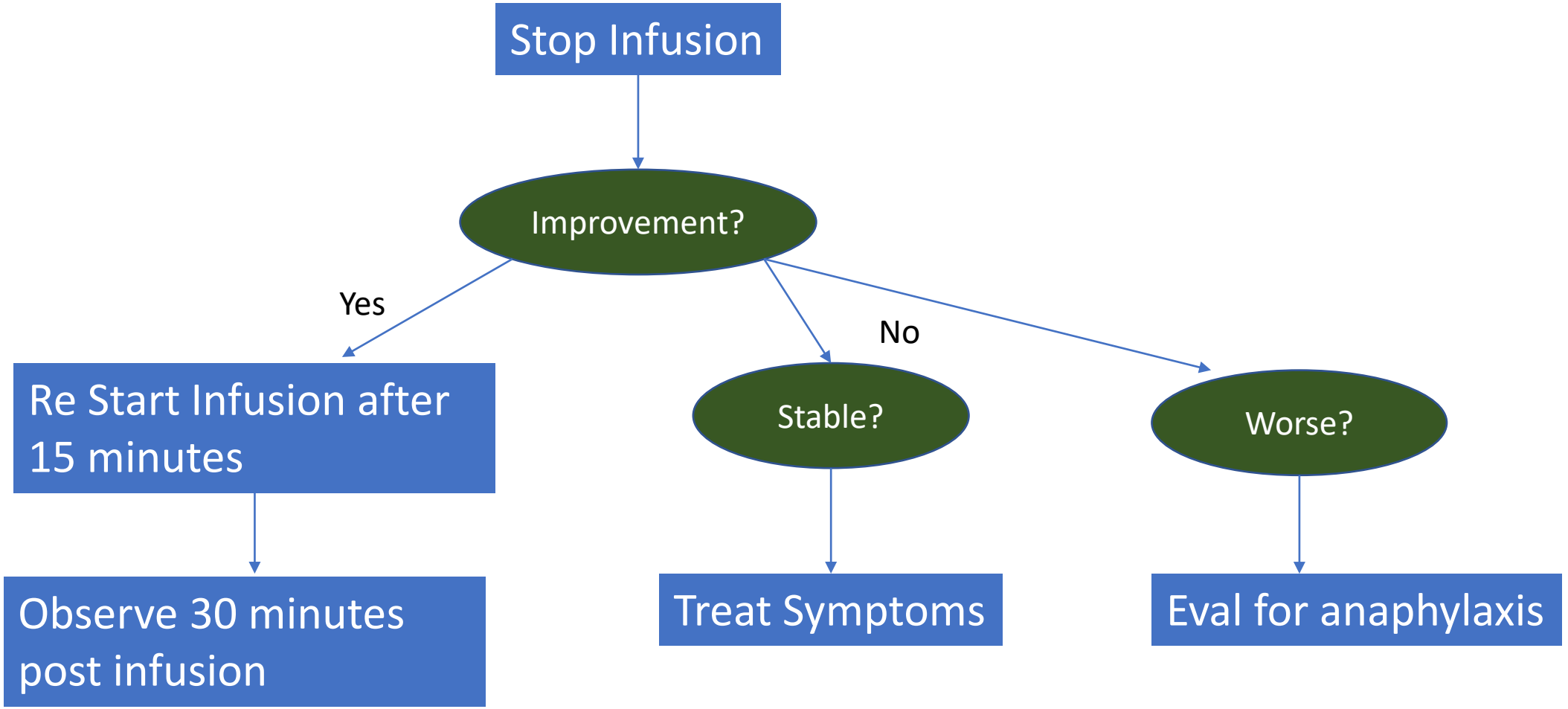
Fishbane!

Hypersensitivity

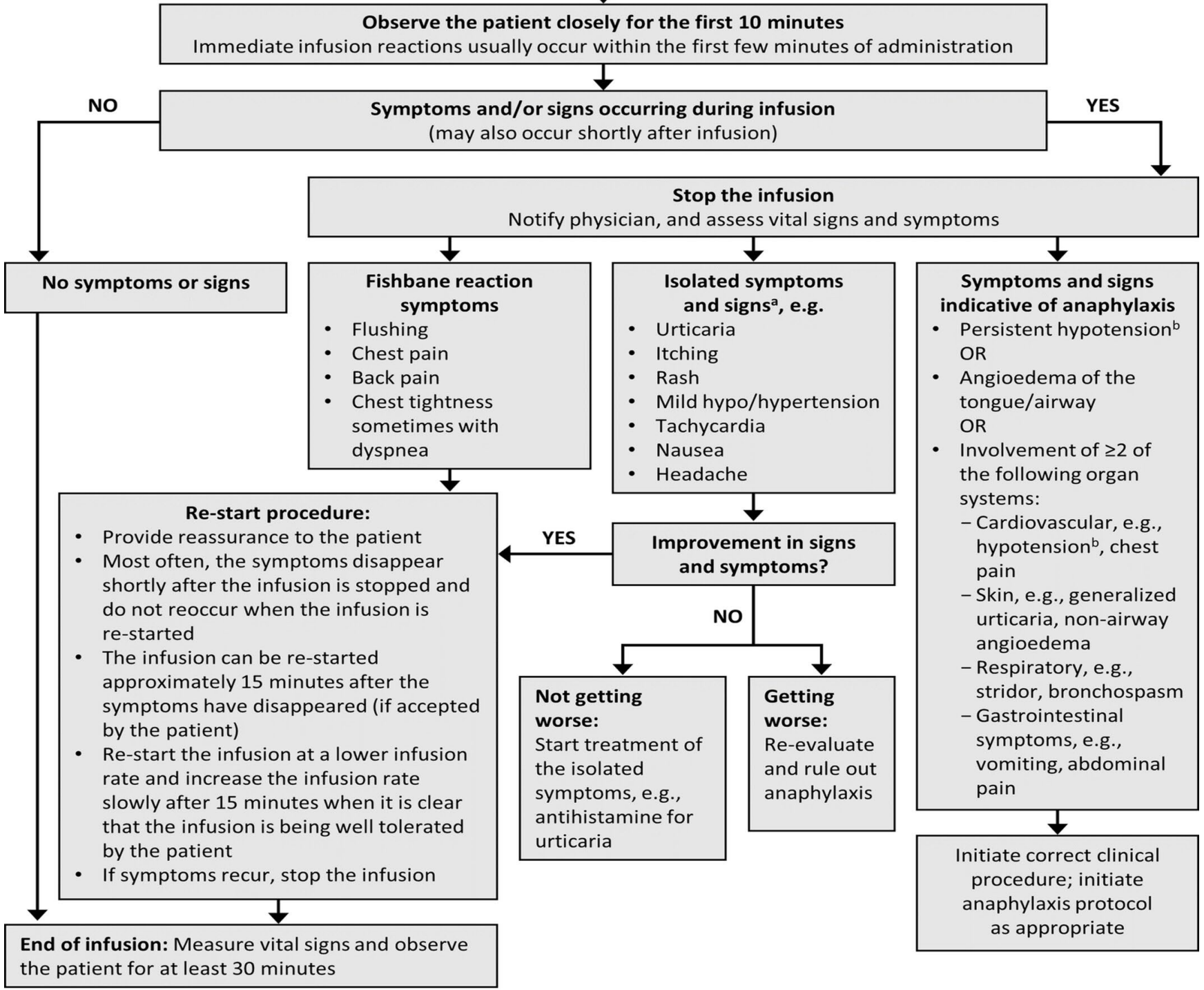
- Rates of true IgE mediated hypersensitivity are very low < 0.1%
  - Risk similar among agents
- Complement activation-related pseudo-allergy (CARPA) 1%
  - Fishbane reaction
  - Flushing, myalgias, throat fullness
  - Caused by labile free iron
- Avoid premedications in the absence of multiple drug allergies

Achebe, Maureen, and Thomas G. DeLoughery. "Clinical data for intravenous iron–debunking the hype around hypersensitivity." Transfusion 60.6 (2020): 1154-1159.
Szebeni J, Fishbane S, Hedenus M, et al. Hypersensitivity to intravenous iron: classification, terminology, mechanisms and management. Br J Pharmacol. 2015;172:5025–5036.

Insfusion Reactions:
1. Warn patient about CARPA Symptoms



Achebe, Maureen, and Thomas G. DeLoughery. "Clinical data for intravenous iron–debunking the hype around hypersensitivity." Transfusion 60.6 (2020): 1154-1159.



Transfusion, Volume: 60,
Issue: 6, Pages: 1154-1159,
First published: 01 June 2020,
DOI: (10.1111/trf.15837)

Case 1

- We document “intolerance” to iron sucrose and proceed with two doses of ferric carboxymaltose

Case 2

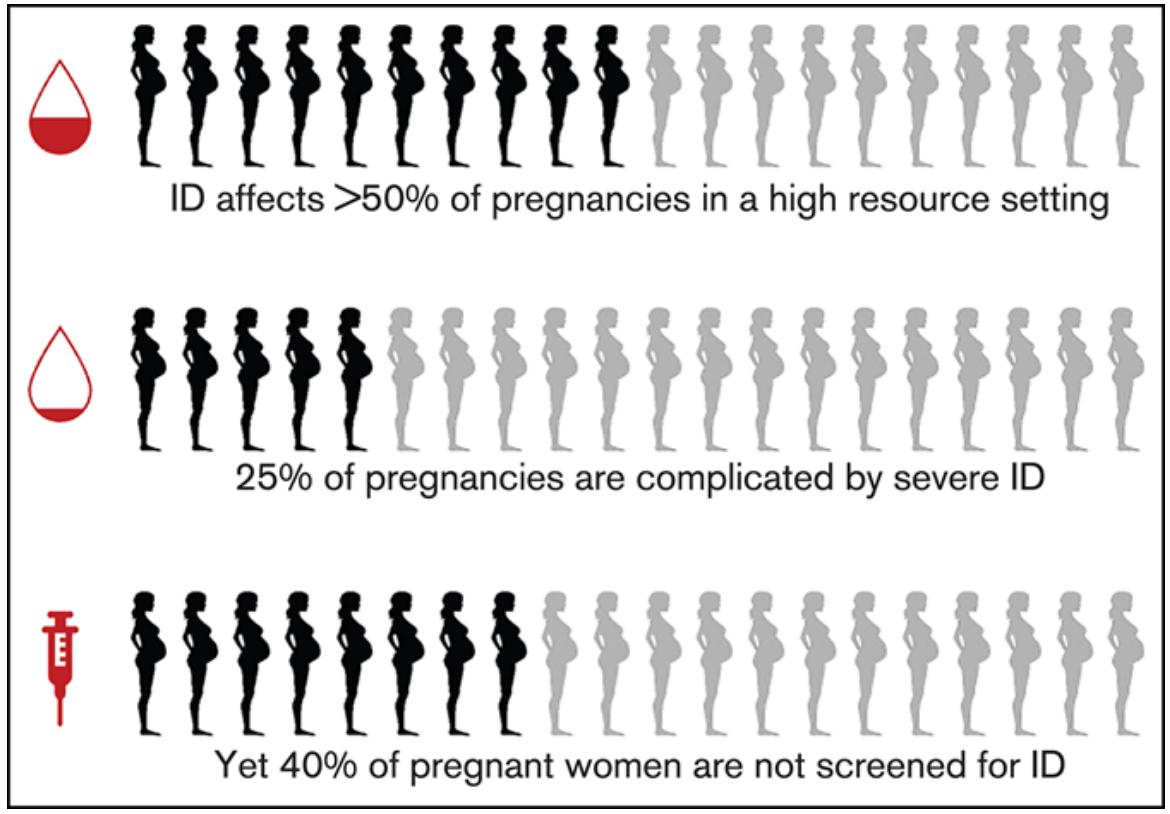
- 26yo G1P0 woman, 23 weeks gestation, found to be anemic on routine prenatal despite oral iron supplement and referred to heme for iron infusions

Component Ref Range & Units	1 mo ago
Iron 50 - 170 ug/dL	16 ⌄
Transferrin 200 - 340 mg/dL	399 ^
Percent Saturation 16 - 48 %	3 ⌄
Resulting Agency	UVA MED LABS
Ferritin 5 - 200 NG/ML	8

	Units	
WBC 4.00 - 11.00	K/UL	9.79
RBC 4.20 - 5.20	M/UL	3.49 ⌄
Hemoglobin 12.0 - 16.0	G/DL	7.7 ⌄
Hematocrit 35.0 - 47.0 %		26.9 ⌄
MCV 83.0 - 95.0 FL		77.1 ⌄
MCH 28.0 - 32.0 PG		22.1 ⌄
MCHC 32.0 - 36.0	G/DL	28.6 ⌄
RDW 11.0 - 14.0 %		20.4 ^
Platelets 150 - 450	K/UL	302

Iron Deficiency in Pregnancy

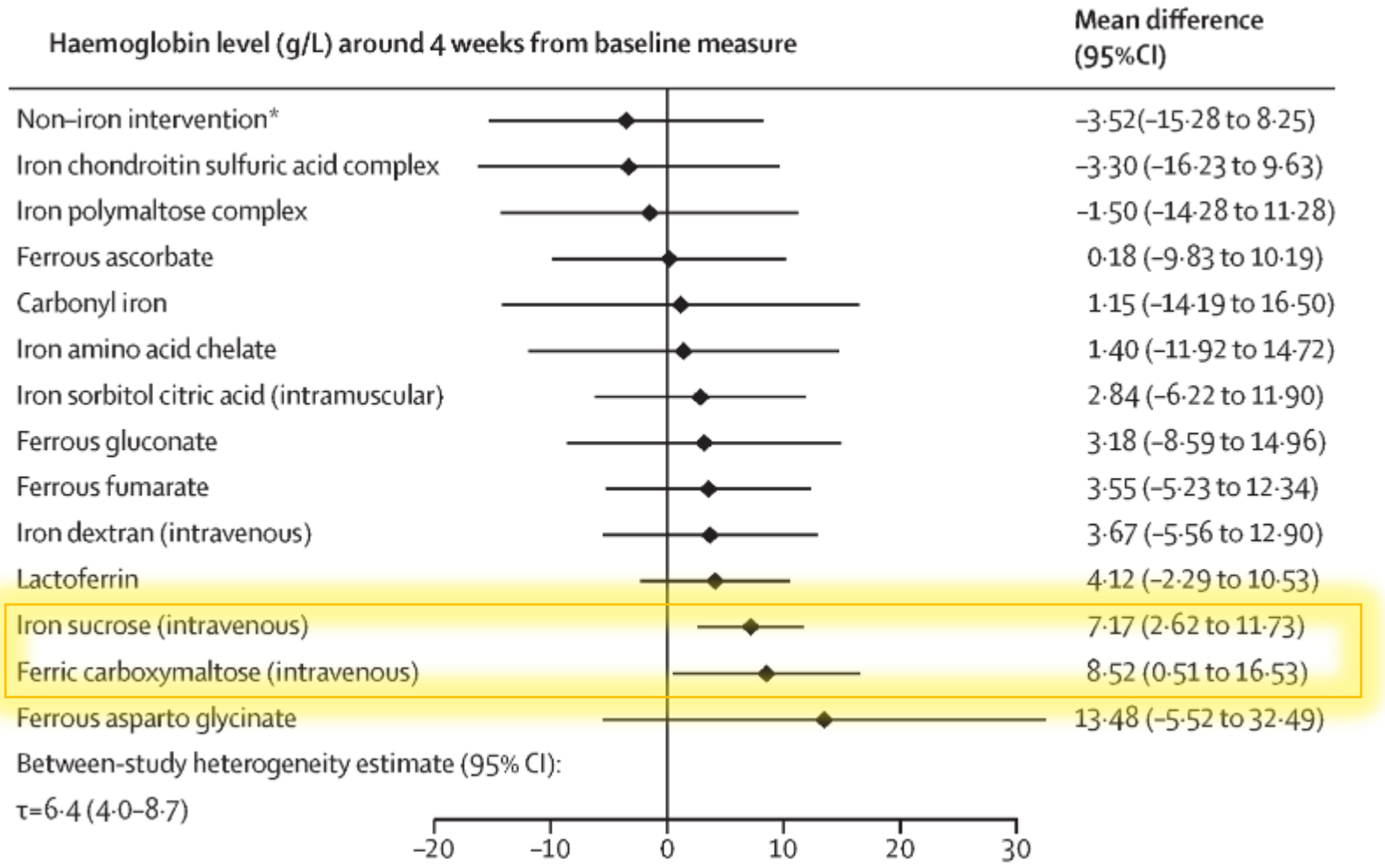
- serum ferritin concentration indexes the body's storage iron capacity but elevated ferritin is difficult to interpret
- % Saturation is useful because it is usually low prior to the development of anemia or microcytosis



James, Andra H. "Iron deficiency anemia in pregnancy." Obstetrics & Gynecology 138.4 (2021): 663-674.
Teichman, Jennifer, et al. "Suboptimal iron deficiency screening in pregnancy and the impact of socioeconomic status in a high-resource setting." *Blood Advances* 5.22 (2021): 4666-4673.

Treatment of Iron deficiency

- Parenteral iron is preferred from the 2nd trimester onward
  - More effective
  - Better tolerated than $FeSO_4$

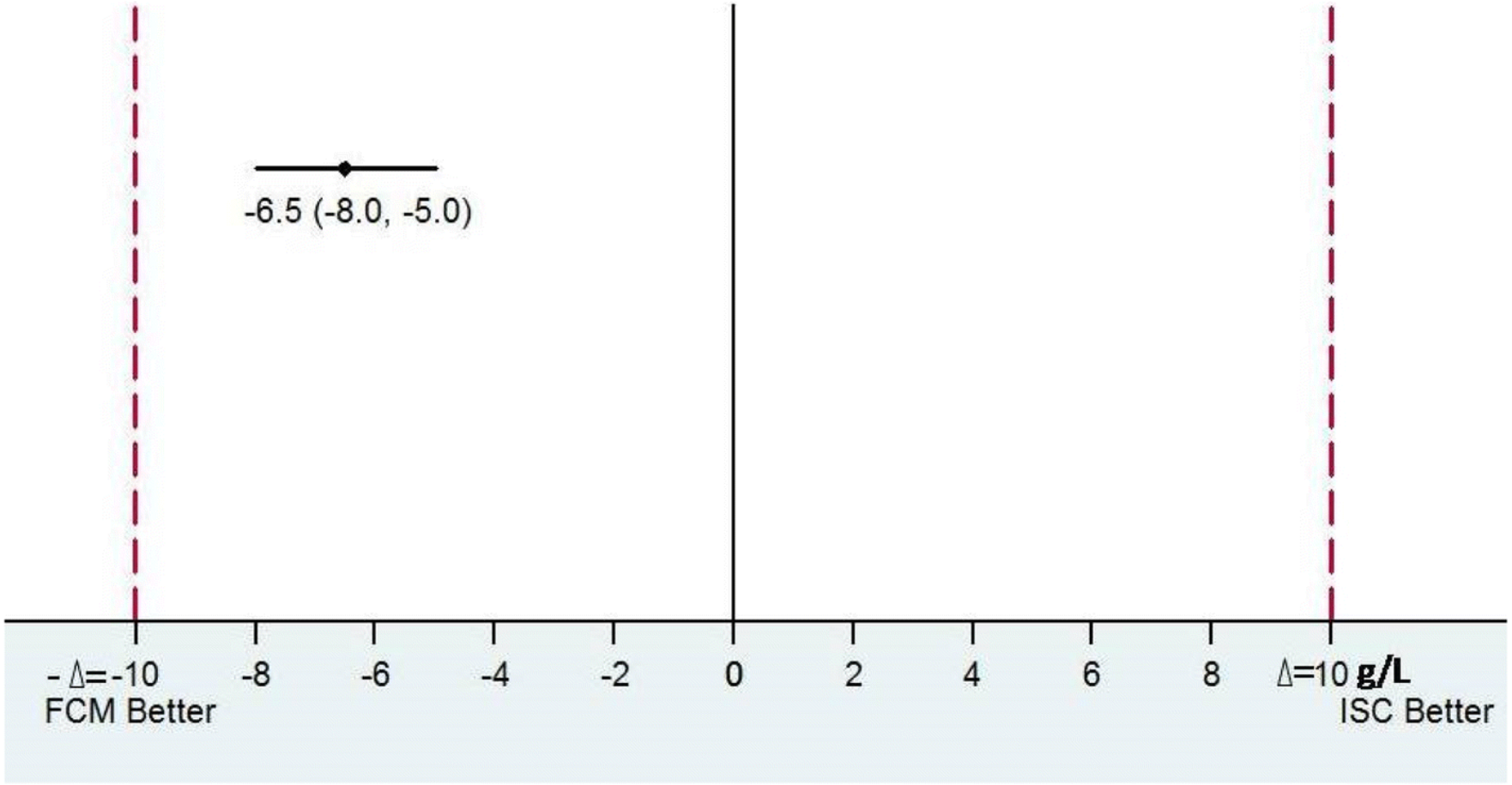


Rogozińska, Ewelina, et al. "Iron preparations for women of reproductive age with iron deficiency anaemia in pregnancy (FRIDA): a systematic review and network meta-analysis." The Lancet Haematology 8.7 (2021): e503-e512.

Case 2

- I recommend 2 doses of ferric carboxymaltose (FCM) for my patient
- insurance company says no, iron sucrose is preferred

Choice of Iron



Non-inferiority of FCM against ISC in change of Hb at 12 weeks from baseline

Jose, A., Mahey, R., Sharma, J.B. et al. Comparison of ferric Carboxymaltose and iron sucrose complex for treatment of iron deficiency anemia in pregnancy- randomised controlled trial. BMC Pregnancy Childbirth 19, 54 (2019). https://doi.org/10.1186/s12884-019-2200-3

Case 2

- The insurance company relents and she gets 2 doses of FCM

Response to treatment

- Reticulocytosis usually begins within about 1 week
- Hemoglobin should increase by 1g/dL after 2-3 weeks
- Ferritin normalizes within 1 month
- Repeat CBC and iron studies 4-8 weeks after completing iron therapy

Christoph P, Schuller C, Studer H, Irion O, De Tejada BM, Surbek D. Intravenous iron treatment in pregnancy: comparison of high-dose ferric carboxymaltose vs. iron sucrose. J Perinat Med. 2012 May 13;40(5):469-74. doi: 10.1515/jpm-2011-0231. PMID: 22945271.

Case 2

- My patient's hemoglobin normalizes about 6 weeks after completing 2 doses of FCM

Case 3

- 65yo woman with a history of breast cancer s/p right simple mastectomy with sentinel lymph node biopsy now on aromatase inhibitor therapy with anastrozole. She had persistent fatigue and dyspnea post op and is found to be anemic by her PCP.

CBC WITH DIFFERENTIAL AUTO

Component Ref Range & Units	5 mo ago
WBC 4.0 - 11.0 K/uL	5.3
RBC 3.80 - 5.20 M/uL	3.93
HGB 11.7 - 16.0 g/dL	7.4 ↓
HCT 35.1 - 48.0 %	25.9 ↓
MCV 80 - 99 fL	66 ↓
MCH 26 - 34 pg	19 ↓
MCHC 31 - 36 g/dL	29 ↓
RDW 10.0 - 15.5 %	24.2 ↑
Platelet 140 - 440 K/uL	572 ↑

IRON & TIBC

Component Ref Range & Units	5 mo ago
Iron 30 - 160 mcg/dL	<19 ↓
UIBC 110 - 370 mcg/dL	415 ↑

FERRITIN

Component Ref Range & Units	5 mo ago
Ferritin 10 - 291 ng/mL	23

Case 3

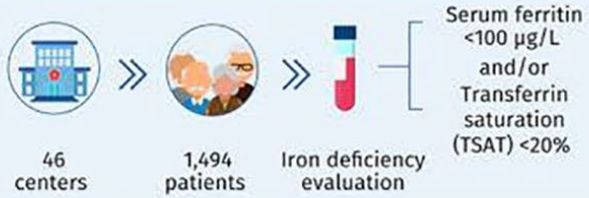
- She is scheduled for breast reconstruction surgery in the next few months.

Prevalence of Iron Deficiency in Patients Undergoing Major Surgeries

Patients scheduled to undergo major surgeries must be screened for perioperative iron deficiency as part of the patient blood management (PBM) program

What is the prevalence of iron deficiency in French patients scheduled for major surgeries?

The CARENFER PBM cross-sectional prospective study



The study found:

	Prevalence of iron deficiency	Patients with iron deficiency + anemia	Patients receiving treatment for anemia and/or iron deficiency
Preoperative Day -1/ Day 0	47%	12.2%	7.7%
Postoperative Day 30	45%	32.4%	21.7%

Iron deficiency continues to be prevalent in French patients scheduled for major surgery, indicating a dire need to improve screening and treatment as part of PBM to improve patient outcomes

Perioperative Iron Deficiency in Patients Scheduled for Major Elective Surgeries: A French Prospective Multicenter Cross-Sectional Study — Capdevila *et al.* (2023)

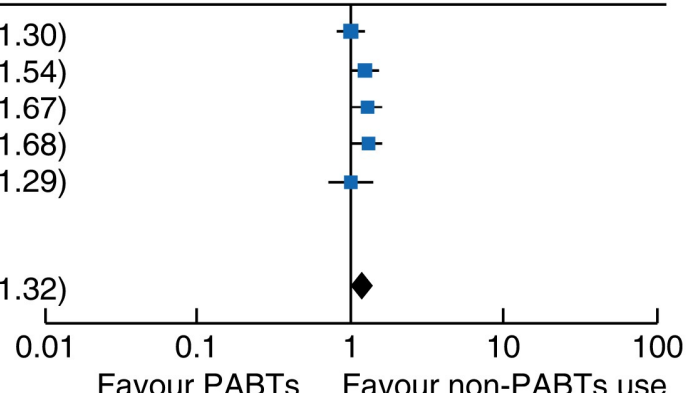
Capdevila, Xavier, et al. "Perioperative iron deficiency in patients scheduled for major elective surgeries: a French prospective multicenter cross-sectional study." *Anesthesia & Analgesia* 137.2 (2023): 322-331.

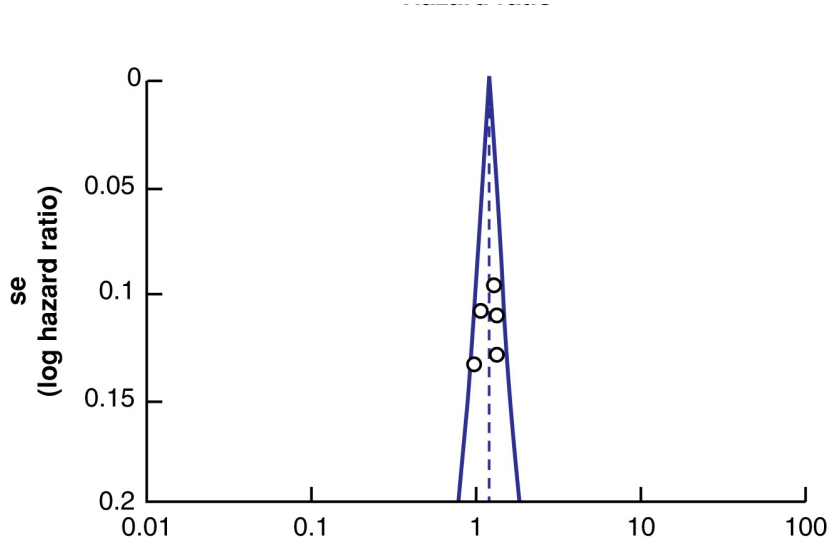
Transfusion in Oncologic Surgery

b OS in GC

Study or subgroup	log (hazard ratio)	s.e.	Weight (%)	Hazard ratio IV, Fixed, 95% c.i.
Cui *et al.*[19]	0.0526	0.1086	21.9	1.05 (0.85, 1.30)
Hsu *et al.*[16]	0.239	0.0971	27.3	1.27 (1.05, 1.54)
Reim *et al.*[20]	0.2624	0.1288	15.5	1.30 (1.01, 1.67)
Song *et al.*[17]	0.3001	0.1106	21.1	1.35 (1.09, 1.68)
Xiao *et al.*[18]	–0.0101	0.1349	14.2	0.99 (0.76, 1.29)
Total (95% c.i.)			100.0	1.20 (1.08, 1.32)

Heterogeneity: $\chi^2 = 5.32$; 4 d.f., $P = 0.26$; $I^2 = 25\%$
Test for overall effect: $Z = 3.53$, $P = 0.0004$

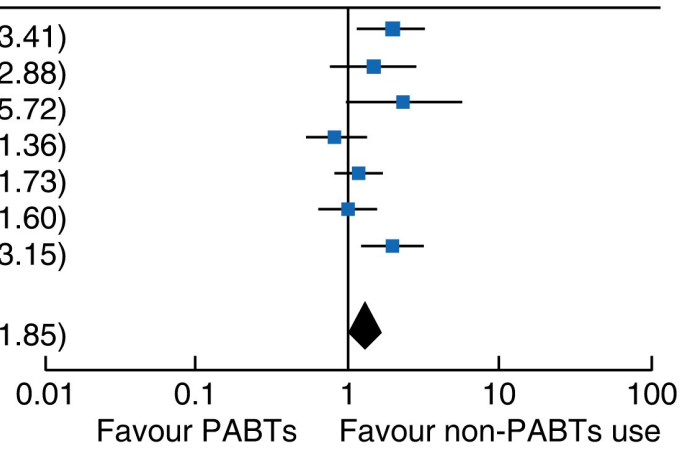


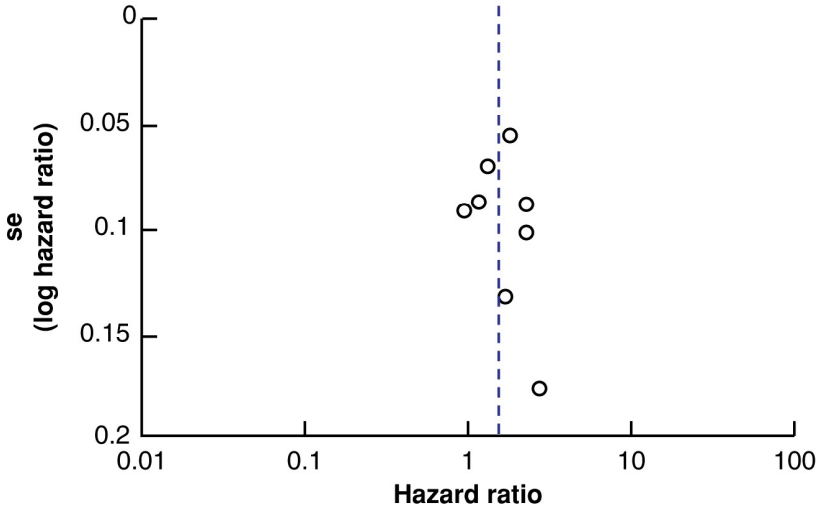


d OS in CRC

Study or subgroup	log (hazard ratio)	s.e.	Weight (%)	Hazard ratio IV, Fixed, 95% c.i.
Hanna *et al.*[24]	0.708	0.264	14.4	2.03 (1.21, 3.41)
Kang *et al.*[25]	0.392	0.34	10.8	1.48 (0.76, 2.88)
McSorley *et al.*[22]	0.8671	0.4475	7.5	2.38 (0.99, 5.72)
Tarantino *et al.*[26]	–0.1625	0.241	15.7	0.85 (0.53, 1.36)
Turri *et al.*[23]	0.1833	0.1881	19.0	1.20 (0.83, 1.73)
Warschkow *et al.*[21]	0.0198	0.2299	16.3	1.02 (0.65, 1.60)
Wu *et al.*[27]	0.6931	0.6931	16.2	2.00 (1.27, 3.15)
Total (95% c.i.)			100.0	1.40 (1.06, 1.85)

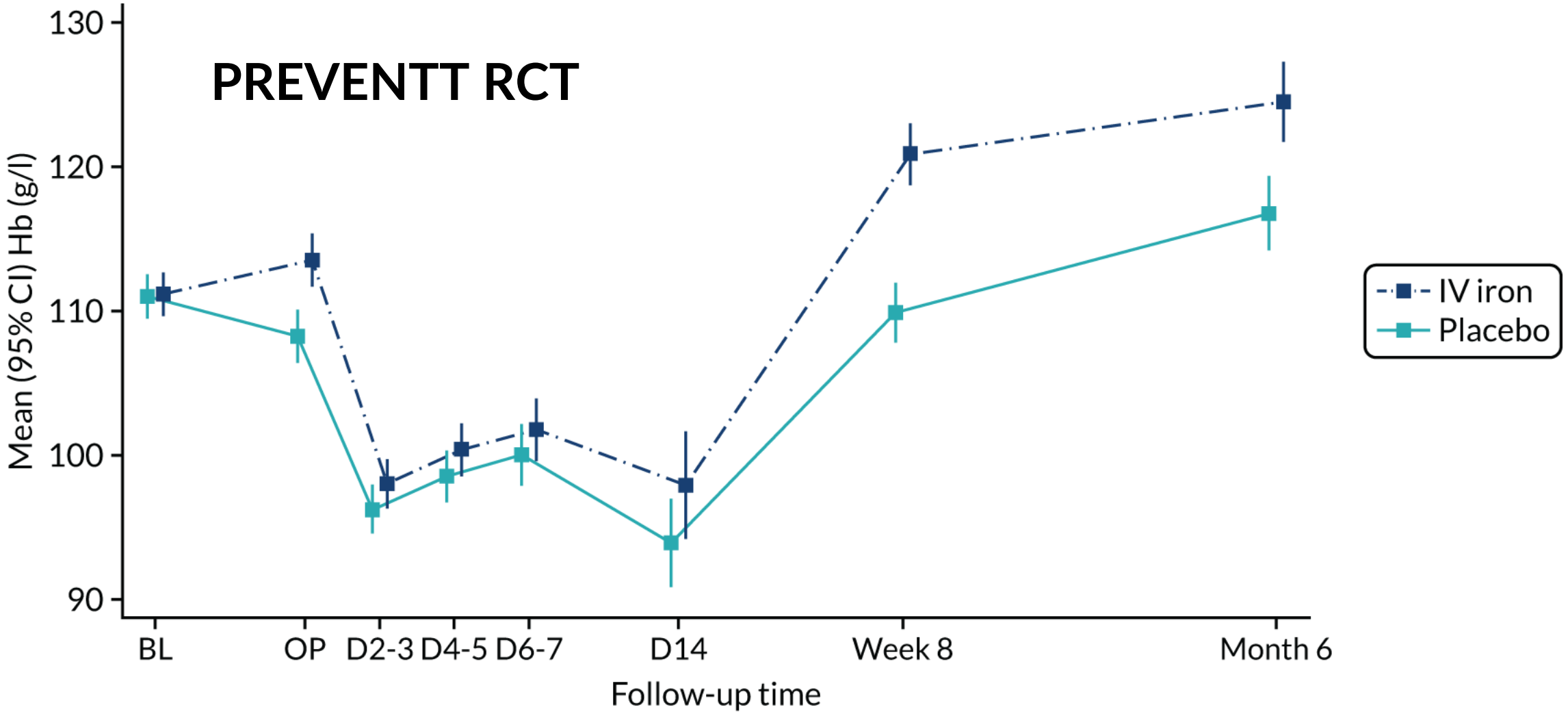
Heterogeneity: $\tau^2 = 0.07$; $\chi^2 = 12.51$, 6 d.f., $P = 0.05$; $I^2 = 52\%$
Test for overall effect: $Z = 2.35$, $P = 0.02$





Zhang, Weilan, et al. "Association of perioperative allogeneic blood transfusions and long-term outcomes following radical surgery for gastric and colorectal cancers: systematic review and meta-analysis of propensity-adjusted observational studies." *BJS open* 7.4 (2023)

PREVENTT RCT



Numbers of patients								
IV iron	238	199	218	181	139	50	157	136
Placebo	234	206	197	158	122	52	155	132

Erythropoietin Supplementation

- anemia of chronic disease/inflammation
  - EBL >500mL
  - All cardiac surgery if Hgb<13
- CKD
- Patients declining blood transfusion

- Start 40,000 units weekly starting 3 weeks prior to surgery
  - Administer with IV iron even in the absence of iron deficiency

Mueller MM, Van Remoortel H, Meybohm P, Aranko K, Aubron C, Burger R, Carson JL, Cichutek K, De Buck E, Devine D, Fergusson D, Folléa G, French C, Frey KP, Gammon R, Levy JH, Murphy MF, Ozier Y, Pavenski K, So-Osman C, Tiberghien P, Volmink J, Waters JH, Wood EM, Seifried E; ICC PBM Frankfurt 2018 Group. Patient Blood Management: Recommendations From the 2018 Frankfurt Consensus Conference. JAMA. 2019 Mar 12;321(10):983-997. doi: 10.1001/jama.2019.0554.

Perioperative Anemia

- Target hemoglobin 13 g/dL to minimize transfusion needs
- Non-urgent surgery should be postponed
- Give IV iron if if surgery is planned for < 6 weeks

Muñoz, M., Acheson, A.G., Auerbach, M., Besser, M., Habler, O., Kehlet, H., Liumbruno, G.M., Lasocki, S., Meybohm, P., Rao Baikady, R., Richards, T., Shander, A., So-Osman, C., Spahn, D.R. and Klein, A.A. (2017), International consensus statement on the peri-operative management of anaemia and iron deficiency. Anaesthesia, 72: 233-247

Case 3

My patient receives 1g iron dextran administered over 1 hour

- 25mg test dose over 5 minutes
- 975mg over 1 hour
- Observe 30 minutes post infusion

Component	1 d ago
Ref Range & Units	
Ferritin 5 - 200 NG/ML	673 ^

Component Ref Range & Units	1 d ago (4/9/24)
Iron 50 - 170 ug/dL	63
Transferrin 140 - 330 mg/dL	252
Percent Saturation 16 - 48 %	18

Component Ref Range & Units	1 d ago (4/9/24)
WBC 4.00 - 11.00 K/UL	5.28
RBC 4.20 - 5.20 M/UL	4.59
Hemoglobin 12.0 - 16.0 G/DL	13.0
Hematocrit 35.0 - 47.0 %	39.9
MCV 83.0 - 95.0 FL	86.9
MCH 28.0 - 32.0 PG	28.3
MCHC 32.0 - 36.0 G/DL	32.6
RDW 11.0 - 14.0 %	16.1 ^
MPV 9.0 - 12.0 FL	8.8 v
Platelets 150 - 450 K/UL	360

Case 4

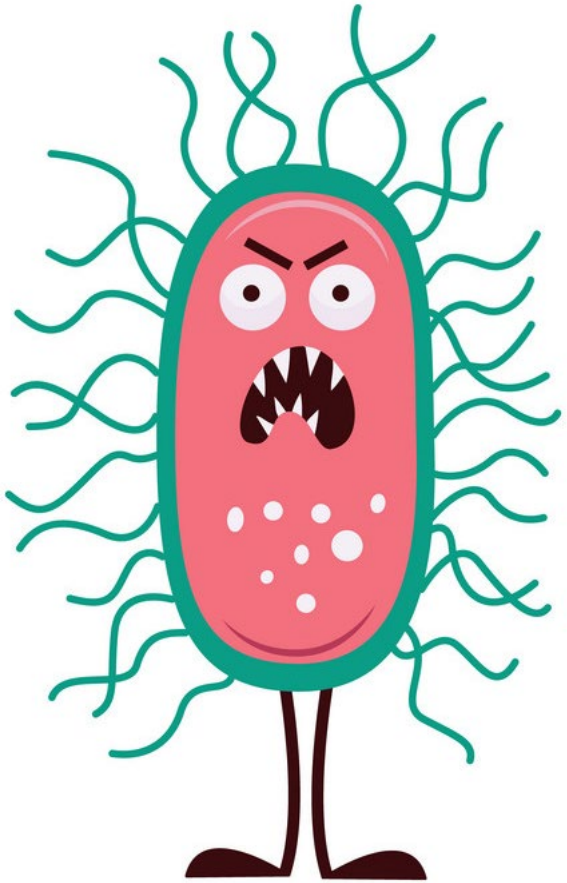
- 75yo man on iron supplementation with iron sucrose due to chronic GI bleeding. He comes in for his scheduled infusion. He reports recent diagnosis of pneumonia now on double antibiotic therapy.
  - Infusion calls to question safety of iron in setting of active infection

Component	Ref Range & Units	1 mo ago (3/5/24)
Ferritin	20 - 275 NG/ML	15 ⌄

Component	Ref Range & Units	1 mo ago (3/5/24)
WBC	4.00 - 11.00 K/UL	7.81
RBC	4.60 - 6.20 M/UL	4.25 ⌄
Hemoglobin	14.0 - 18.0 G/DL	11.8 ⌄
Hematocrit	40.0 - 52.0 %	37.0 ⌄
MCV	83.0 - 95.0 FL	87.1
MCH	28.0 - 32.0 PG	27.8 ⌄
MCHC	32.0 - 36.0 G/DL	31.9 ⌄
RDW	11.0 - 14.0 %	14.0
MPV	9.0 - 12.0 FL	9.8
Platelets		257

Iron and Infection

- Bacteria compete with their host to obtain iron which they need for DNA synthesis
- Hepcidin is increased during infection/inflammation to decrease iron availability to infectious organisms
- preexisting iron deficiency can impair T-cell, B-cell, and neutralizing antibody responses to infection



Shah AA, Donovan K, Seeley C, Dickson EA, Palmer AJR, Doree C, Brunskill S, Reid J, Acheson AG, Sugavanam A, Litton E, Stanworth SJ. Risk of Infection Associated With Administration of Intravenous Iron: A Systematic Review and Meta-analysis. JAMA Netw Open. 2021 Nov 1;4(11):e2133935.

Iron and Infection

Outcome	No. of studies	No. of participants[a]		Treatment effect	*P* value	I^2, %
		Intravenous iron	Oral iron or no iron			
Primary outcome						
Infection	64	1101/10 010	955/9312	RR (95% CI): 1.16 (1.03 to 1.29)	.003	36
Continuous outcomes						
Hemoglobin	110	10 816	9720	MD (95% CI): 0.57 (0.50 to 0.64) g/dL	<.001	94
RBCs transfused	11	998	956	MD (95% CI): −0.20 (−0.32 to −0.08) cells	<.001	81
Hospital LOS	8	807	883	MD (95% CI): −0.43 (−1.10 to 0.24) d	.05	50
Dichotomous outcomes						
Treatment response[b]	60	4336/7137	2611/6165	RR (95% CI): 1.46 (1.32 to 1.60)	<.001	92
Mortality						
Short term (≤30 d)	15	40/1298	40/1292	RR (95% CI): 0.99 (0.69 to 1.42)	.73	0
Long term (>30 d)	12	165/2752	161/2258	RR (95% CI): 0.94 (0.75 to 1.18)	.63	0
Requirement for RBC transfusion	54	802/6256	989/6040	0.83 (0.76 to 0.89)	<.001	15

Shah AA, Donovan K, Seeley C, Dickson EA, Palmer AJR, Doree C, Brunskill S, Reid J, Acheson AG, Sugavanam A, Litton E, Stanworth SJ. Risk of Infection Associated With Administration of Intravenous Iron: A Systematic Review and Meta-analysis. JAMA Netw Open. 2021 Nov 1;4(11):e2133935.

Iron and Infection

Table 2. Associations between receipt of intravenous iron and adverse outcomes

Outcome	Estimated Adjusted Association or Length of Stay	*P* Value
All-cause mortality within 30 d of admission[a]	0.86 (0.74 to 1.00)	0.04
All-cause 2010 mortality[b]	0.92 (0.85 to 1.00)	0.04
Mean length of stay, d	10.1 (9.7 to 10.5) versus 10.5 (10.3 to 10.7)	0.05
Readmission for infection or all-cause mortality within 30 d of discharge[a]	1.08 (0.96 to 1.22)	0.19

Estimated adjusted association and length of stay data are presented with 95% confidence intervals. Results show the comparison of receipt versus no receipt of intravenous iron adjusted for age, duration of ESRD, sex, race, geographic location of ESRD network, coronary artery disease, other cardiac disease, congestive heart failure, hypertension, peripheral vascular disease, diabetes mellitus, cerebrovascular disease, cancer, chronic obstructive pulmonary disease, alcohol dependence, drug dependence, tobacco use, and the infected organ system.

a Odds ratio.

b Hazard ratio.

Ishida, Julie H., et al. "Receipt of intravenous iron and clinical outcomes among hemodialysis patients hospitalized for infection." *Clinical Journal of the American Society of Nephrology* 10.10 (2015): 1799-1805.

Case 4

- My patient is afebrile, vitals are normal and reports feeling well so we proceed with his iron infusion.

Thank You