Intravenous iron therapy in the pediatric sleep clinic

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Objectives

- Identify and describe common pediatric sleep disorders, including Restless Sleep Disorder (RSD), Restless Legs Syndrome (RLS), and Periodic Limb Movement Disorder (PLMD).
- Discuss the relationship between brain iron deficiency and sleep disorders such as RLS and PLMD.
- Compare the effectiveness and tolerability of oral iron supplements versus intravenous (IV) iron therapy in treating pediatric sleep disorders.
- Identify different formulations of IV iron, their administration protocols, and potential side effects.

Case Vignette

- Sam is a 6-year-old with h/o autism spectrum disorder and ADHD presenting to clinic for sleep challenges
- He is able to fall asleep without trouble and sleeps through the night without prolonged awakenings
- Parents wake him for the day and seems unrefreshed and has concentration problems and behavioral challenges during the day
- Throughout the night tossing and turning and “restless”; PCP checked a ferritin (25) and placed the child on oral supplemental iron at time of referral 9 months ago
- Deny snoring, witnessed apnea, or other breathing symptoms
- The child denies RLS symptoms
- You obtain an overnight sleep study which does not show any sleep apnea or periodic limb movement disorder, but there are frequent large muscle movements during the night that disrupt sleep quality
- You check a ferritin, and it is 25
- What is this? Normal? Abnormal? What do you do next?

Clinical Challenge

- Group of children present without sleep onset delay, without frequent nocturnal awakenings, but have “restless sleep” that doesn’t fit criteria for a sleep disorder
- The parents recognize this as “not normal”, “different from their other children”, and many times they have daytime impairment like school problems, ADHD, etc
- In 2018, Lourdes DelRosso and colleagues studied these children in detail and coined “Restless Sleep Disorder” as a new diagnostic entity in pediatric sleep medicine
- Oral iron is frequently used for SRMDs, but not well tolerating or effective in many cases

SLEEPJ, 2018, Vol. 41, No. 8

Pediatric RLS/PLMD/RSD are common

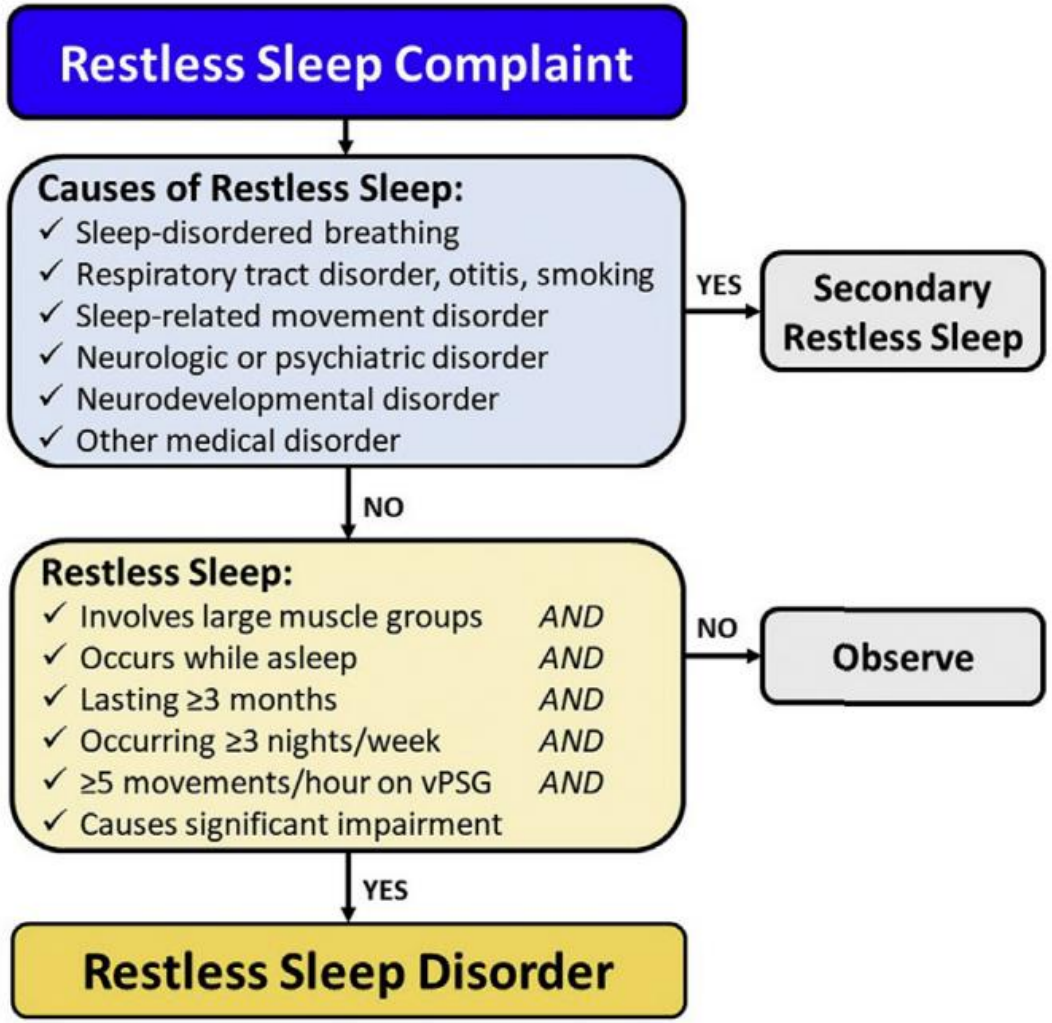
- Pediatric RLS
  - 1-4% all children
  - 0.5-1% moderate/severe RLS
  - 10% of sleep clinic referral population
  - More common than pediatric diabetes and epilepsy
- Pediatric PLMD
  - 9% of sleep clinic referral population
- Pediatric RSD
  - 7% of sleep clinic referral population

TABLE 1 Number of patients with each sleep diagnosis considered and relative prevalence within our sample of 300 participants

Diagnosis	Number	%
OSA	132	44.0
Snoring	75	25.0
Parasomnia	39	13.0
NREM[a]	21	7.0
REM[b]	13	4.3
NREM+REM	5	1.7
RLS	32	10.7
PLMS/PLMD	28	9.3
RSD	23	7.7
Insomnia	22	7.3
Other sleep disorder	19	6.3
Enuresis	15	5.0
Bruxism	10	3.3
Hypersomnia	2	0.7
Narcolepsy	1	0.3

J Sleep Res. 2019 Dec;28(6):e12870.

Evaluation of the “Restless Sleeper”



Sleep Medicine Reviews 56 (2021) 101406

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The Restless Sleeper

	RSD	RLS	PLMD
Clinical presentation	Restless sleep Daytime impairment	Urge to move legs Sleep-onset insomnia Daytime impairment	Periodic leg movements of sleep Daytime impairment
Diagnosis	Clinical + PSG	Clinical	Clinical + PSG
PSG findings	Body movement index > 5 per hour	May or may not have elevated PLMI	PLMI > 5
Pathophysiology	Sleep instability Iron deficiency Sympathetic activation	Dopamine dysfunction Iron deficiency	Unknown (probably shared with RLS)

Abbreviations: PLMI, PLMS index; PSG, polysomnogram; RLS, restless legs syndrome; RSD, restless sleep disorder.

Pediatric Pulmonology. 2021;1–8

Brain Iron Deficiency

- Iron is important in brain dopamine production as well as a variety of other neurotransmitter systems
- Implicated in the pathogenesis of RLS/PLMD from multiple lines of evidence showing low brain iron stores
- Autopsy data
- MRI and other imaging
- Cerebral spinal fluid analysis

Table 1—Age and Iron-Related Measures of Serum and CSF for Subject Groups Defined by Diagnoses and Sex

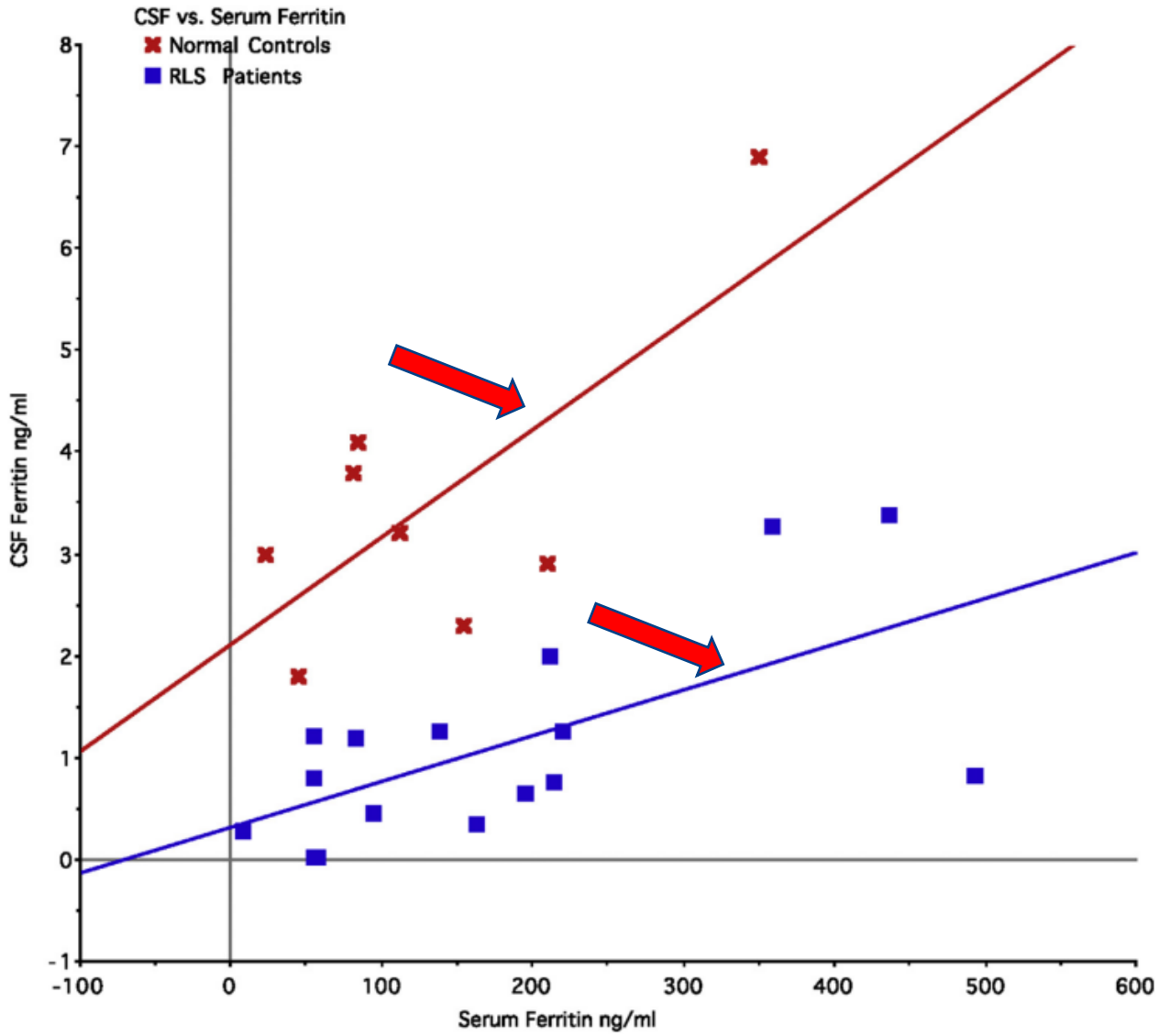
	No.	Age, y	Serum Ferritin, ng/mL	Serum Transferrin, µg/L	Serum Iron, µg/dL	Serum TIBC, µg/dL	Serum TfR, µg/mL	CSF Ferritin, µg/L	CSF Transferrin, mg/dL	CSF Iron, µg/L
Control										
All	22	59.2 ± 8.3	89.9 ± 69.0	34.8 ± 11.5	84.3 ± 28.1	312.9 ± 52.3	3.12 ± 1.21	2.89 ± 0.93	5.17 ± 1.80	26.2 ± 19.1
Male	11	61.2 ± 8.5	123.9 ± 82.9	41.5 ± 11.8	90.6 ± 33.3	309.9 ± 54.3	3.83 ± 1.06	2.85 ± 0.91	5.32 ± 2.01	26.1 ± 15.0
Female	11	57.3 ± 7.9	59.1 ± 33.6	28.1 ± 6.4	77.9 ± 21.4	315.6 ± 52.7	2.41 ± 0.92	2.93 ± 0.99	4.99 ± 1.64	26.4 ± 23.2
RLS										
All	30	62.9 ± 10.1	123.0 ± 119.8	35.6 ± 16.2	81.3 ± 24.1	315.9 ± 60.1	3.31 ± 1.46	2.43 ± 0.73	4.92 ± 1.85	27.4 ± 16.6
Male	14	64.3 ± 10.1	161.7 ± 137.8	39.6 ± 15.4	89.8 ± 29.1	297.9 ± 54.9	3.11 ± 1.21	2.76 ± 0.58	4.23 ± 1.01	27.2 ± 19.3
Female	16	61.7 ± 10.3	91.6 ± 96.2	32.3 ± 16.7	73.8 ± 16.2	331.6 ± 61.7	3.48 ± 1.67	2.14 ± 0.74	5.56 ± 2.23	27.6 ± 14.2

ROIs		Healthy controls	RLS patients
Primary	SN	0.091 ± 0.016	0.088 ± 0.025
	SN_{fs}	0.095 ± 0.026	0.091 ± 0.029
	Thalamus	−0.031 ± 0.0061	−0.034 ± 0.0065 *
Secondary	RN	0.073 ± 0.018	0.072 ± 0.022
	DN	0.064 ± 0.019	0.053 ± 0.022 *
	CN	0.023 ± 0.0064	0.021 ± 0.013
	PUT	0.040 ± 0.010	0.036 ± 0.017
	GP	0.084 ± 0.013	0.087 ± 0.020
	Pulvinar	0.023 ± 0.016	0.023 ± 0.016

SLEEP, Vol. 28, No. 9, 2005
Sleep Med. 2016 June ; 22: 75–82

Brain Iron Deficiency

- CSF vs. serum ferritin for RLS patients and age and gender matched healthy adults without RLS
- Overall increased serum ferritin indicates higher CSF ferritin but wide variability
- The lowest normal CSF ferritin range occurs for those with serum ferritin >200



Sleep Medicine 41 (2018) 27-44

Both RSD and RLS have suboptimal ferritin

Table 2. Comparison between iron parameters obtained in patients with RSD and RLS

	RSD		RLS		Student's *t*-test	
	Mean	*SD*	Mean	*SD*	*t*-value	*p*<
Ferritin, ng/ml	20.8	8.87	30.3	12.03	−2.452	0.021
TIBC, µg/dl	338.9	38.34	345.3	44.36	−0.418	NS
Iron, µg/dl	83.2	36.44	93.7	26.36	−0.901	NS
Transferrin saturation, %	24.3	10.85	26.3	6.58	−0.623	NS

TIBC, Total iron binding capacity.

SLEEPJ, 2018, Vol. 41, No. 8

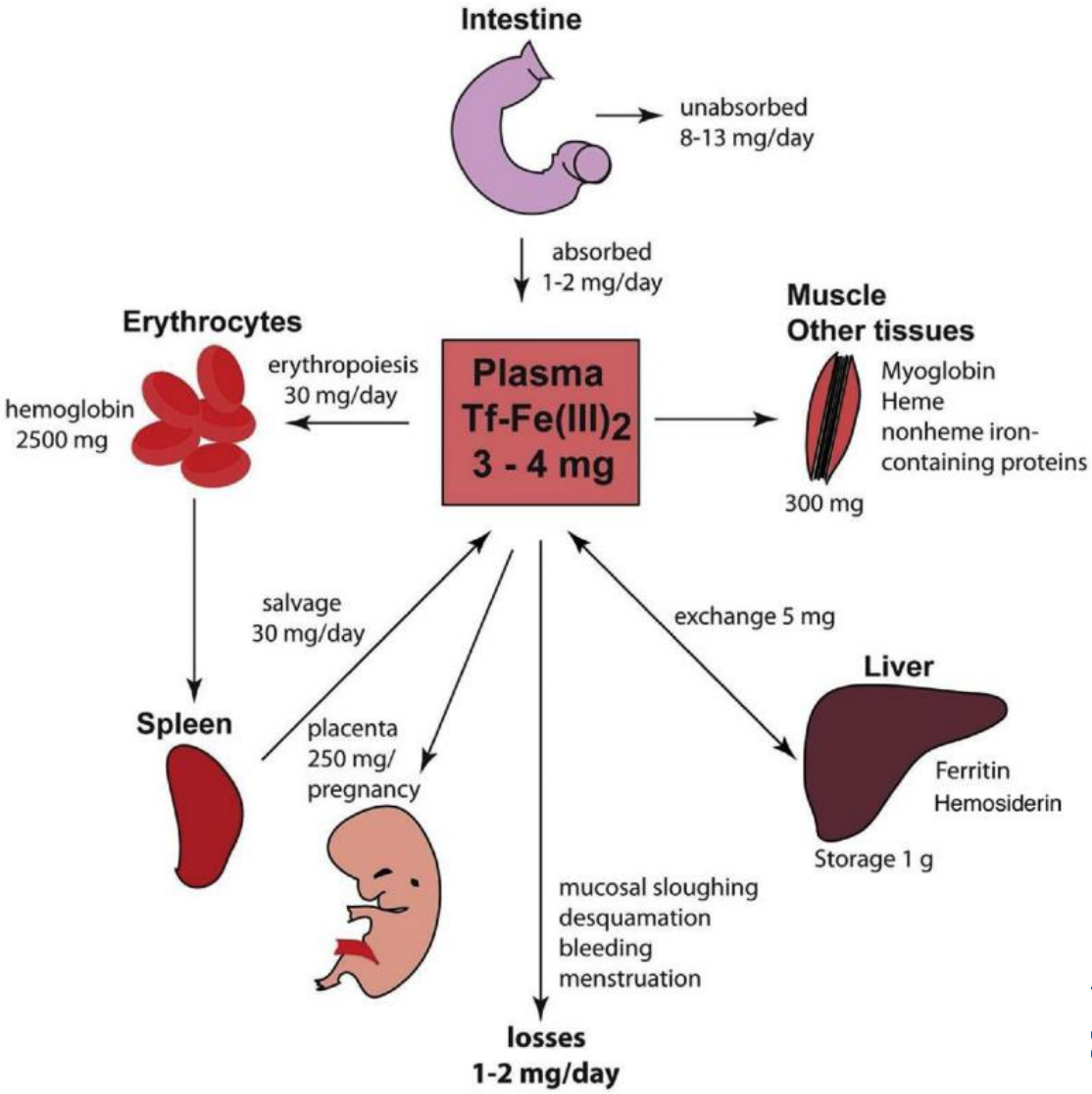
Iron biology

- Iron can exist as ferric (Fe^{3+}) or ferrous (Fe^{2+})
- At physiological pH, iron exists in the oxidized, ferric state
- To be absorbed, iron must be in the ferrous state or bound by a protein such as heme
- Human enterocytes have membrane-bound enzymes (duodenal cytochrome B (Dcytb)) that can reduce insoluble ferric to absorbable ferrous iron in the low pH of gastric acid in the proximal duodenum
- Once reduced to ferrous iron, another membrane protein (divalent metal cation transporter 1 (DMT1)) transports iron across the membrane into the cell
- Iron transported in blood is typically bound to transferrin
- Cellular iron is stored in the protein, ferritin
- Serum ferritin is mostly secreted by monocytic/macrophage cells and provides iron loads to organs independent of transferrin-bound iron
- Serum ferritin is a sensitive/specific marker of iron deficiency, but is also an acute phase reactant

Biochemistry, Iron Absorption. StatPearls Publishing; 2023 Jan.

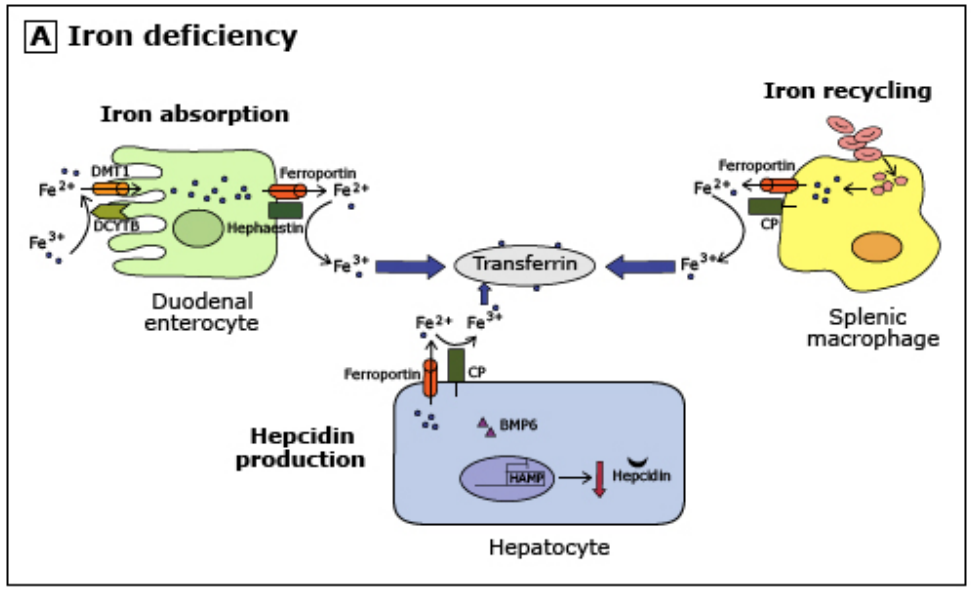
Iron absorption and metabolism

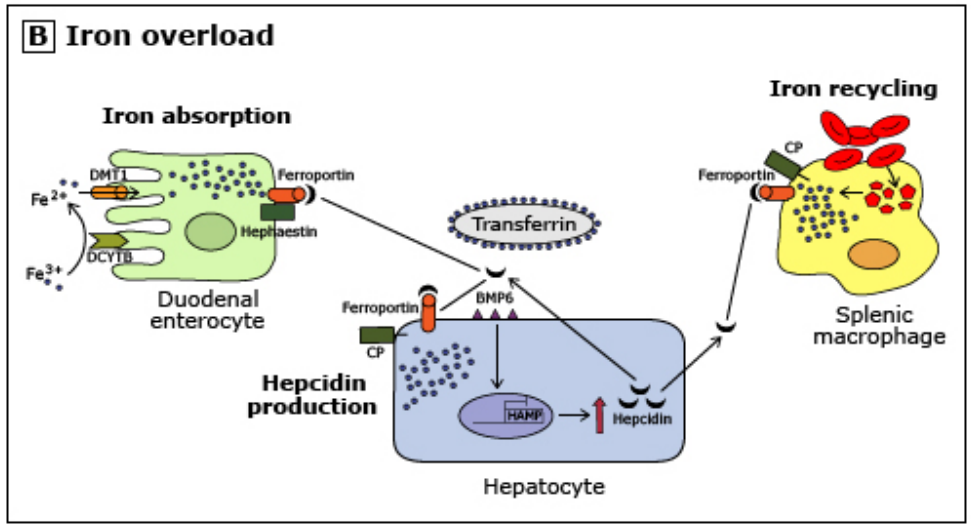
- About 10% of the usual 10-20mg of dietary oral iron is absorbed
- Once in the blood, about 75% goes towards RBC production
- Only 5-15% of newly absorbed iron (0.5-1.5% of iron consumed daily) is available for transport to organs such as brain
- Iron absorption is regulated by hepcidin, which blocks the uptake of iron from GI mucosa, macrophages, and the liver into the blood
- Increases in blood or liver iron stimulate production of hepcidin, reducing GI iron absorption
- Serum tests of iron status are based on iron status in the erythron/macrophage/liver, not of brain iron stores



Iron absorption and metabolism

- Iron deficiency
  - Increased iron absorption and recycling
  - Absorption of iron by enterocytes is facilitated by duodenal cytochrome b (DYCTB), an iron reductase
  - Hepcidin synthesis is suppressed
  - Ferroportin is free to export iron from macrophages and enterocytes, after which iron is bound to transferrin
- Iron overload
  - Reduced iron absorption and recycling
  - Hepcidin production is high; its synthesis is stimulated by BMP6, which is induced by increased liver iron
  - Hepcidin released into the circulation binds ferroportin, and the complex is internalized and degraded, in turn blocking iron export into the circulation.





Oral Iron

- Ferrous sulfate
- NovaFerrum: polysaccharide-iron complex
- Celebrate: ferrous fumarate with vit C; bariatric vitamin
- Lactoferrin: milk-derived iron binding glycoprotein, ?mitigates inflammation
- Heme iron: derived from bovine hemoglobin (as opposed to nonheme from plants)

Oral Iron

Improve absorption

- Avoid enteric coated or timed-release products
- Take separately from foods that may impair absorption
  - Meals
  - Coffee
  - Eggs
  - Oxalates (spinach, kale, beets, nuts, chocolate, tea, wheat bran, rhubarb, strawberries, some herbs)
  - Phytates (soy, fiber, cereals, some nuts, beans, lentils, peas)
  - Tannates (tea, cocoa, some spices, some berries)
  - Calcium (milk, yogurt, cheese, some greens, fish)
- Minimize exposure to medications that decrease gastric acidity
  - Antacids (take iron 2 hours before or 4 hours after the antacid)
  - Histamine receptor blockers (discontinue if no longer needed)
  - Proton pump inhibitors (discontinue if no longer needed)
- Take with foods/supplements that may increase absorption
  - Vitamin C – forms iron chelate with ferric iron that remains soluble in alkaline pH as well as acts as free radical scavenger to reduce iron oxidation
  - Orange juice

Improve tolerability

- Use a titratable (eg, liquid) form
- Change from every-day to every-other-day dosing
- Dietary modifications (eg, take with food)
- Take a product with less elemental iron
- Use a stool softener or laxative

SLEEPJ, 2020, Vol. 40, No. 3

Side effects hinder adherence to oral iron

Table 1. Comparison between the different ferritin and iron parameters obtained at baseline and after follow-up in the two groups of children

	Responders (n = 42)	Nonresponders (n = 35)	Mann-Whitney "U"	$p<$
Baseline ferritin, µg/L	20.0 (16.0/25.0)	14.0 (9.0/23.0)	503.5	0.018
Follow-up ferritin, µg/L	39.5 (35.0/56.0)	16.0 (14.0/25.0)	46.0	0.00001
Treatment duration, days	164.0 (133.0/214.0)	124.0 (82.0/188.0)	524.0	0.031
Ferritin change, µg/L	20.5 (15.0/30.0)	4.0 (2.0/6.0)	0.0	0.00001
Ferritin change rate, µg/L /month	3.6 (2.3/5.1)	0.8 (0.4/1.5)	82.0	0.00001
Iron daily dose, mg/kg	1.7 (1.0/2.0)	1.0 (1.0/2.0)	573.0	NS
			Chi-square	$p<$
Side effects			15.4	0.0005
None	92.9	54.3		
Constipation	7.1	42.9		
Bad taste/nausea	0.0	2.9		
Follow-up outcome			16	0.00035
Resolved	31.0	8.6		
Improved	42.9	20.0		
No change	26.2	71.4		
Adherence			17.9	0.00013
Poor	7.1	40.0		
Fair	4.8	17.1		
Good	88.1	42.9		

Values shown as median (interquartile range). Also, the frequency of side effects reported, outcome at the follow-up visit, and adherence to therapy are reported (values given as percentages).

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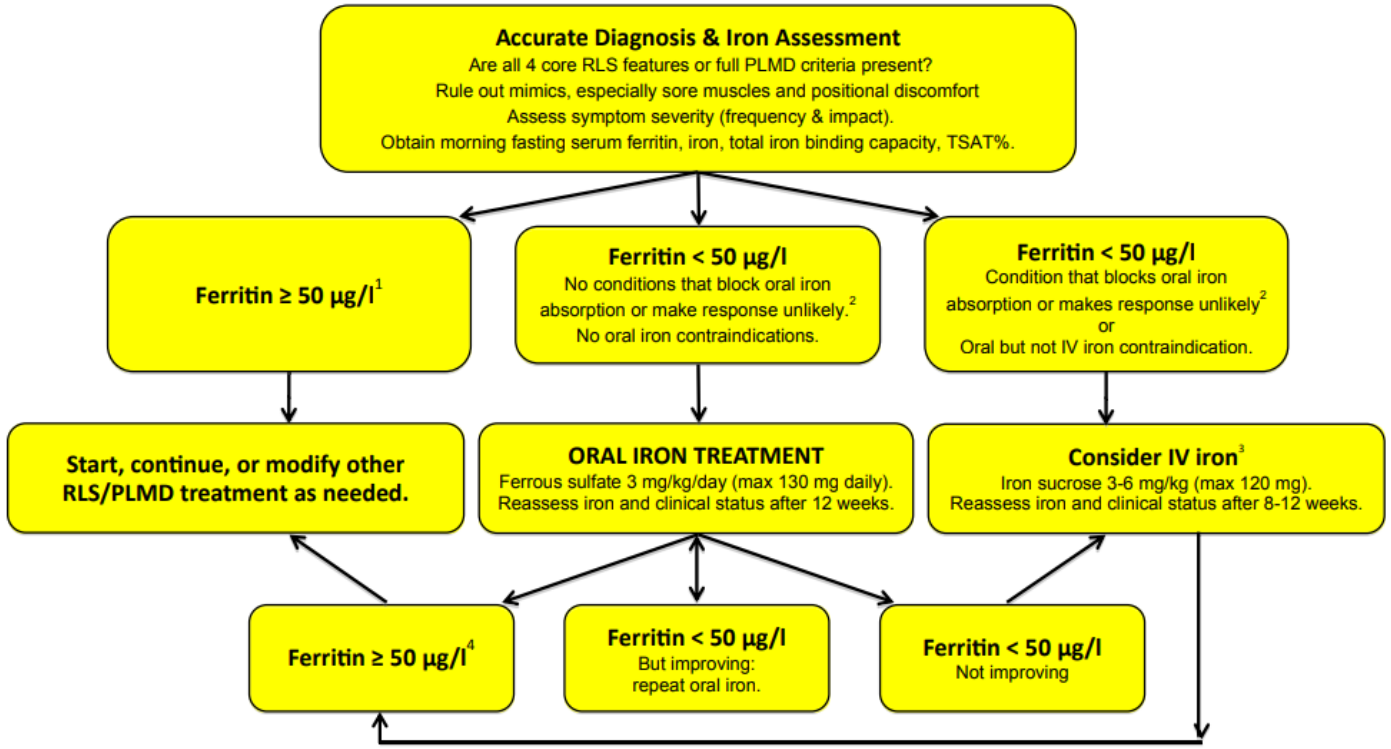
IV Iron as alternative to oral

- Inadequate improved in iron stores with oral iron
- Poor adherence to oral iron
- Gastrointestinal side effects from oral iron
- Desire faster repletion of iron stores in 1 visit compared to several months of oral iron
- Other medical conditions that interfere with oral iron absorption or result in ongoing blood loss

IV Iron for Pediatric RLS/PLMD: Guideline



Therapeutic target of ferritin ≥ 50 mcg/L for iron therapy.

[1]Serum ferritin can be falsely elevated in the presence of acute or chronic inflammation. IV iron treatment can then be considered if transferrin saturation is < 20%

[2]Such as a malabsorption syndrome, inflammatory bowel disease, heavy uterine bleeding, rheumatic diseases, etc.

[3]Administer at an infusion center with pediatric experience and with care taken to avoid IV drug extravasation.

[4]May need to continue oral iron to avoid return of symptoms due to decrease in iron stores with growth.

Abbreviations: IV, intravenous; PLMD, periodic limb movement disorder; RLS, restless legs syndrome; TSAT%, percentage transferrin saturation.

Fig. 6. Algorithm for iron treatment of pediatric RLS/PLMD.

AASM 2024 Updated Clinical Practice Guideline

- Recommendation 27: In children with RLS and a ferritin level of < 50 ng/ml, the AASM suggests the use of 571 ferrous sulfate over no ferrous sulfate (Conditional recommendation, very low certainty of evidence).
- Good Practice Statement (GPS): …In children, supplementation of iron should be instituted for serum ferritin <50 ng/ml with oral or IV formulations. These iron supplementation guidelines are different than for the general population.

- CPG recommendations: These recommendations are based on research evidence and may also consider expert opinion, health care policy, and costs of care. The language used to describe recommendations reflects the strength of the recommendation.
- CPG good practice statements: These statements are used when there is high certainty that the benefits of an intervention outweigh the risks, but the evidence is indirect. The language used to describe good practice points reflects the low quality or absence of evidence.

IV Iron: Contraindications

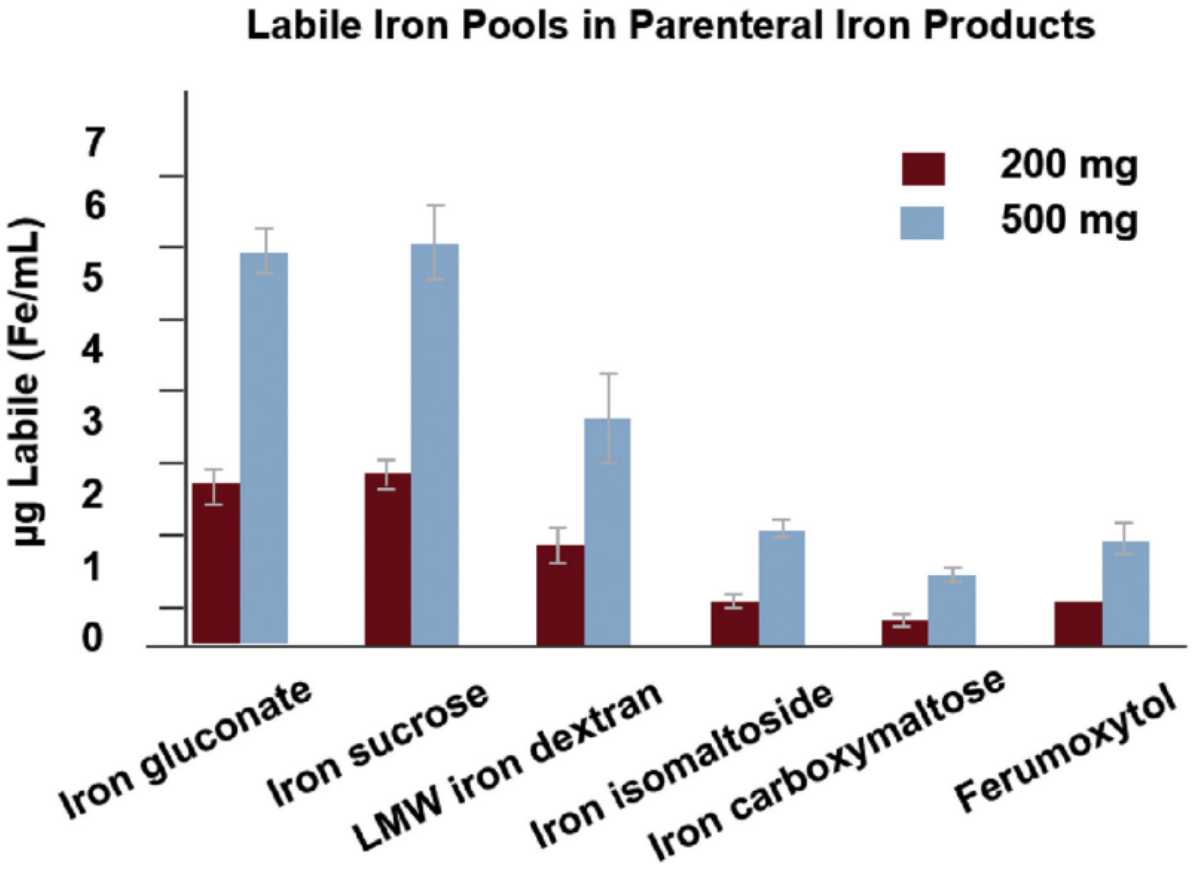
- Can’t sit still for 15 minutes
- Mitochondrial disorders
- Active significant systemic inflammatory process as there are theoretical reasons to be concerned that infections might worsen following iron treatment (?impaired T-cell and neutrophil function)
- Great care should also be taken to prevent the risk of IV drug extravasation
- Hemochromatosis

IV Iron formulations

- Ferric carboxymaltose (Injectafer)
- Iron sucrose (Venofer)
- Ferritic gluconate (Ferrlecit)
- Iron dexran (INFeD)
- Ferumoxytol and ferric derisomaltose are approved for adults with less data in children

IV Iron formulations

- Iron given intravenously is taken up predominately by the erythron, liver and macrophages
- As the macrophages are the primary source of redistributing iron to the other organs, including brain, the amount of iron taken up by the macrophages during the initial iron loading period may be relevant in determining when and/or how much iron reaches the brain
- Different IV formulations have different rates of uptake by macrophages and rates at which the iron is release from the carrier carbohydrate into the blood
- Those with faster release (i.e. iron sucrose) required lower doses to avoid overwhelming available transferrin and increased toxic labile iron; those with slower release (i.e. FCM) allow iron to be taken up by transferrin and less labile iron
- Slow-release formulations have greater increases in macrophage iron concentrations



Sleep Medicine 41 (2018) 27-44

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Iron Sucrose

- The most common form of IV iron utilized in children
- Rates of adverse events including anaphylaxis are very low in this formulation when given in low doses
- No test dose or routine premedication are indicated
- Dosing is typically limited to 200 mg elemental iron per infusion for adolescents and 100 mg per infusion for children
- In pediatric RLS guidelines, a dose of 3-6mg (max 120mg) is recommended
- Infused over 30-90 minutes depending on dose
- Most patients require multiple infusions

Iron sucrose for RLS/PLMD

- Retrospective review of 14 children who underwent IV iron sucrose infusion (3mg/kg) for RLS/PLMD
- Clinical improvement in sleep in 62%
- Minor adverse events in 25% (difficulty with IV placement, transient GI symptoms)
- No episodes of anaphylaxis

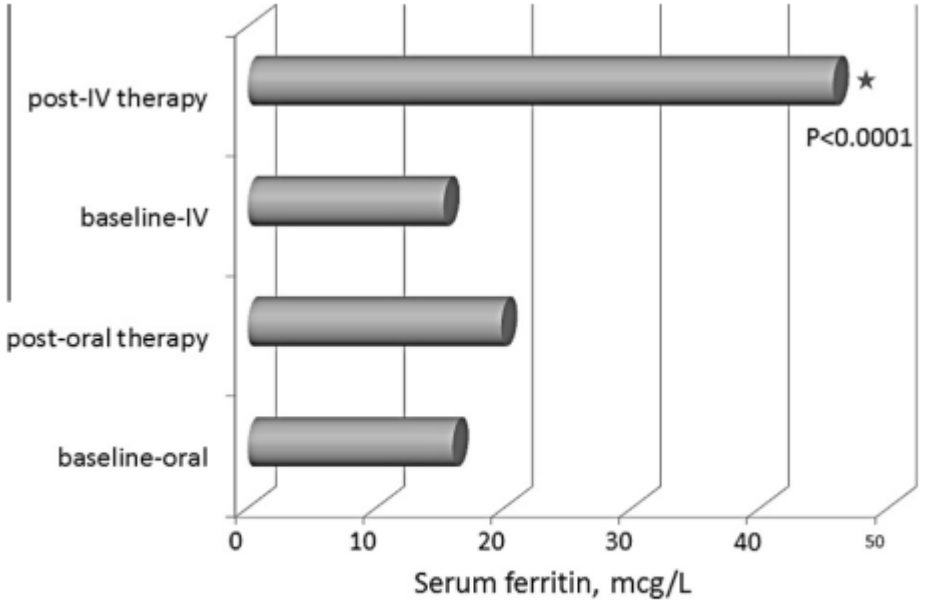


Fig. 1. Serum ferritin levels at baseline and after oral iron supplementation (n = 12; bottom 2 bars) and baseline in comparison with patients after infusion therapy of intravenous iron sucrose (n = 14; top 2 bars).

Sleep Med. 2013 Nov;14(11):1100-4.

Ferric carboxymaltose

- Ferric carboxymaltose is a non-dextran formulation that allows for iron uptake (into reticuloendothelial system) without the release of free iron
- It has tighter binding of elemental iron to the carbohydrate polymer than some other IV iron preparations
- No test dose or routine premedications are indicated
- Dosing is 15mg/kg up to maximum of 750mg
- Infused over 15 minutes

Ferric carboxymaltose: hypophosphatemia

- There is a risk of hypophosphatemia (up to 75% in adult studies), associated with weakness and fatigue or (at more severe levels) bone issues
- Mechanism unclear, but may be due to increased urinary phosphate excretion caused by an increase in serum levels of fibroblast growth factor 23 (FGF-23), a result of decreased degradation after administration of FCM
- Low phosphorus tends to occur within 2 weeks of the infusion
- Can attempt to prevent by eating foods high in phosphorus such as:
  - Dairy products
  - Nuts and seeds
  - Bran and cereals
  - Chicken and turkey

Ferric carboxymaltose: hypophosphatemia

- Study of children undergoing FCM infusion at Texas Children's
- Examined rates of any hypophosphatemia and severe hypophosphatemia (<1); measured within 6 wks infusion
- 313 infusions
- Of the 40 patients who developed hypophosphatemia, none had symptoms documented in the EHR; 7 (18%) were prescribed supplemental phosphorus
- Each 1 mg/dL increase in the pre-infusion phosphorus level was associated with a 70% decrease in the odds of development of hypophosphatemia
- The authors suggest assessing pre- and post-phosphorus levels and:
  - Consider other iron formulations if pre-infusion levels are lower
  - Provide phosphorus supplementation if post-infusion levels <2, regardless of symptoms

Hypophosphatemia	Entire Cohort (N=225)		Total Infusions (N=313)				
Any hypophosphatemia, n (%)	40 (18%)		44 (14%)				
Severe Hypophosphatemia, n (%)	0 (0%)		0 (0%)				
Laboratory Assessment	**All Infusions**						
	Pre-infusion[a] mean (IQR)		**Post-infusion[b] mean (IQR)**		**Mean**	**SD**	**P-value**
Phosphorus, mg/dL (n=281)	4.7	(4.1–5.2)	4.2	(3.5–5.1)	−0.49	1.09	<0.001
Hemoglobin, g/dL (n=243)	9.4	(7.9–10.8)	11.7	(10.5–12.9)	2.37	2.29	<0.001
MCV, fL (n=241)	76.4	(70.7–83.6)	81.9	(77.9–85.9)	5.52	6.74	<0.001

Am J Hematol. 2021 Jun 1; 96(6): E215–E218.

Ferric carboxymaltose: hypophosphatemia

- Review of pediatric studies shows approximately 11% of infusions and 17% of children experience hypophosphatemia

Table 2 Pediatric studies reporting on hypophosphatemia after ferric carboxymaltose infusion

Study	Cause of iron deficiency	Number of patients	Number of infusions	Age range	Hypophosphatemia (%)
Posod et al. (2020) [35]	IBD, other GI diseases, IEM/mitochondrial disease, trauma, unknown	36 F = 22 M = 14	71	8–16.4 years	6 patients (16.7%)
Kirk et al. (2021) [36]	GI diseases, uterine bleeding, nutritional IDA, other	225 F = 139 M = 86	313	2 months to 21 years	40 patients (14%), all asymptomatic, 7 required phosphorus supplementation
Cococcioni et al. (2021) [30]	CD, UC, unclassified IBD	128 F = 60 M = 68	213	3–18 years <6 years: 11 patients	25 patients (19%): low post-infusion serum phosphate 11 patients < 14 years 3 patients < 6 years 2 patients: severe hypophosphatemia
Panagopoulou et al. (current study)	CD, GI diseases, nutritional IDA, other	21 F = 11 M = 10	23	1–16 years	2 patients (9.5%)
Total		410 F = 232 M = 178	620	2 months to 21 years	73 patients 11.8% of infusions 17.8% of patients

CD Crohn's disease, *F* female, *GI* gastrointestinal, *IBD* inflammatory bowel disease, *IDA* iron deficiency anemia, *IEM* inborn error of metabolism, *M* male, *UC* ulcerative colitis

Pediatric Drugs (2022) 24:137–146

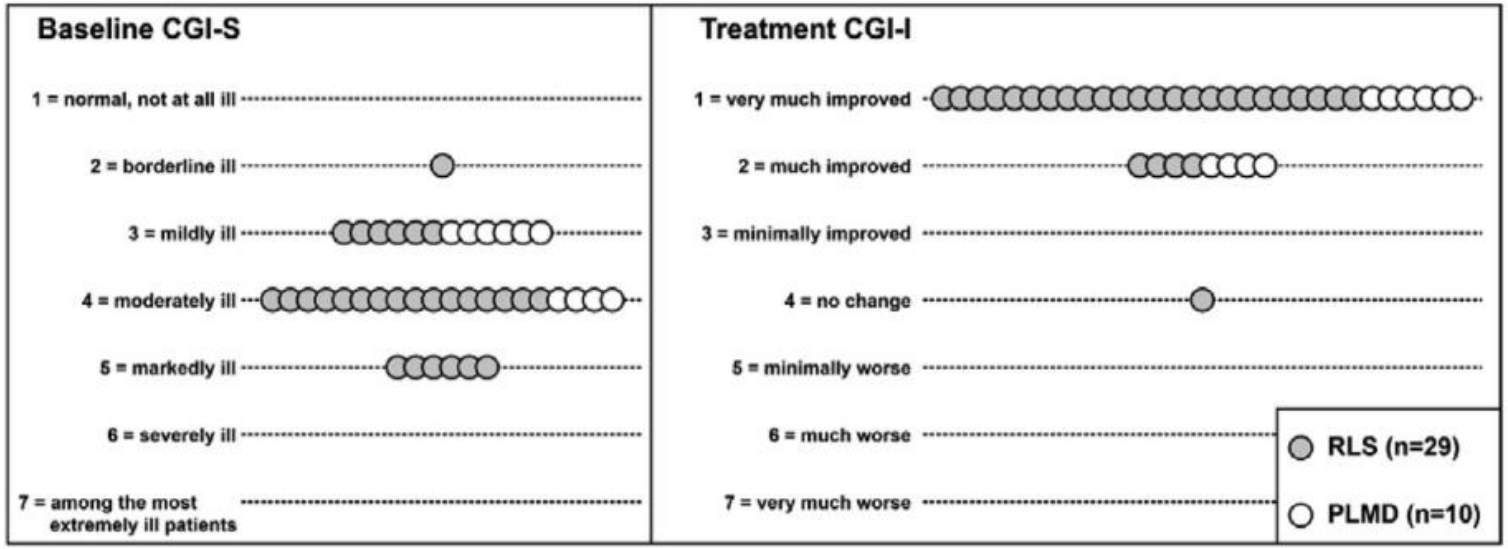
Ferric carboxymaltose: other AE

- 6% patients developed AE that included skin rashes, pruritus, mild urticaria, dizziness, mild fever, headache, and extravasation injury (grades I–III)
- Hypersensitivity reactions were rare with only 2% of patients (18/901) reporting mild urticarial rashes, one grade III anaphylactic reaction with transient drop in oxygen saturation, and no severe grade IV anaphylactic reactions requiring resuscitation
- No SAE were noted among patients belonging to the younger age group (< 6 years old)
- In the Greek cohort where all FCM-related AE were prospectively captured, no hypersensitivity reactions were noted during the FCM intravenous administration or within 24 h after the end of it, highlighting that a short post-infusion observation period is sufficient without need for hospital admission and/or overnight stay

Pediatric Drugs (2022) 24:137–146

FCM for RLS/PLMD

- 39 children with RLS/PLMD underwent IV iron infusion with FCM
- Ferritin increased from 14 to 112
- Clinical improvement noted
- 14% experienced an adverse event, which were mild



Sleep Med. 2021 Nov:87:114-118.

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Oral vs IV iron for RSD

- Children with RSD were offered oral ferrous sulfate (FS) or IV ferric carboxymaltose (FCM) as therapy
- Those who underwent IV iron infusion had greater clinical improvement as rated by families, as well as greater improvement in ferritin levels
- FS resulted in constipation and noncompliance
- IV FCM resulted in 1 case of syncope and no cases of hypophosphatemia

Table 2. Comparison of outcome variables between the two treatment groups after iron supplementation

	Oral iron		Intravenous iron		Mann–Whitney	
	Median	Interquartile range	Median	Interquartile range	*U*	*P*<
CGI-Improvement	3.0	2–4	2.0	1–2	57.0	0.023
Ferritin, µg/L	34.0	25–44	124.0	90–143	0.0	0.00003
Iron, µg/dL	77.0	61–89	103.0	87–121	24.5	0.0084
TIBC, µg/dL	333.0	312–359	298.0	284–302	30.0	0.02
Transferrin, mg/dL	22.5	17–25	31.0	28–36	20.5	0.004

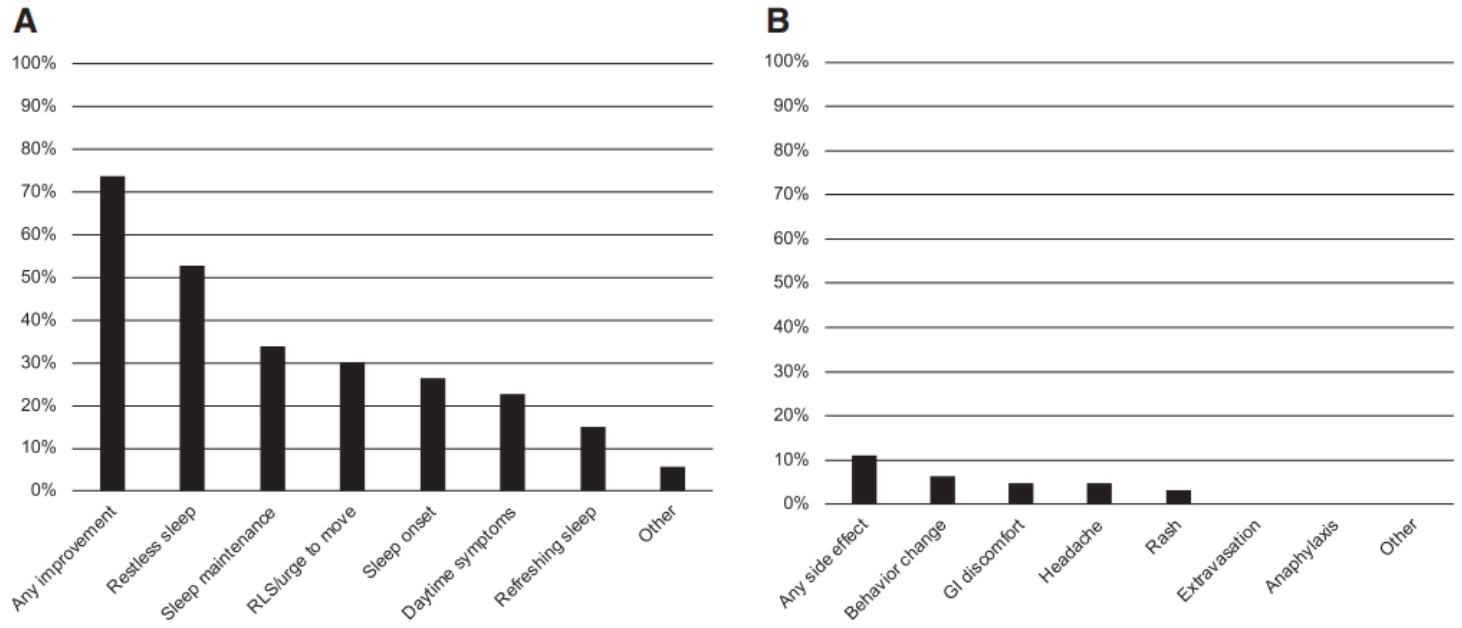
CGI, Clinical Global Impression Scale (3 = minimally improved; 2 = much improved); TIBC, total iron binding capacity.

SLEEPJ, 2021, Vol. 44, No. 2

IV Iron for RLS/PLMD/RSD: Our Experience

- Our institutional experience
- 63 children underwent infusion (60 with FCM)
- 73% noted clinical improvement
- 11% had side effect, the most common being behavior change and GI discomfort
- No anaphylaxis or extravasation

Figure 1—Overall improvement in response to IV iron therapy.



Overall improvement in clinical symptoms **(A)** and side effects **(B)** in response to IV iron therapy. IV = intravenous.

J Clin Sleep Med. 2022 Nov 1;18(11):2545-2551

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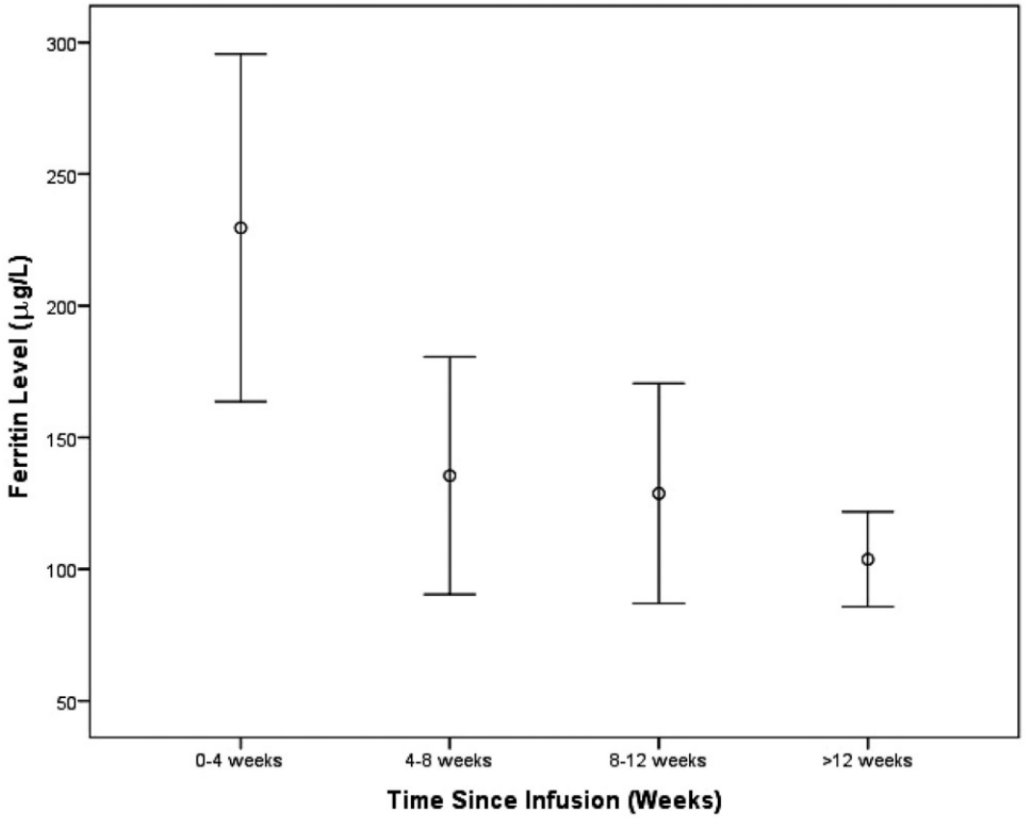
IV Iron for RLS/PLMD/RSD: Our Experience

- Ferritin increased from 21 to 147 on average
- Effect durable, 3 months or more
- No association between clinical improvement, baseline ferritin, follow-up ferritin, change in ferritin level, or other examined variables



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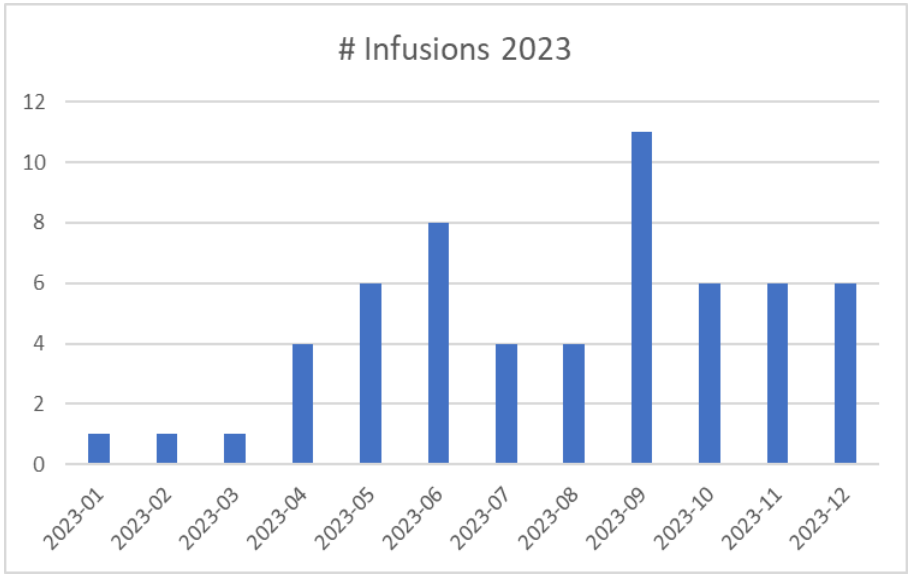
Children's Mercy KANSAS CITY

Our Institution: FCM vs Iron sucrose

- A retrospective study
- All children who underwent either IV FCM or iron sucrose infusion at CMH outpatient infusion center between 1/2023 and 12/2023
- FCM was initially requested for all children
- Iron sucrose was ordered instead if dictated by insurance coverage:
  - FCM: $6,229 per encounter (with infusion center charge)
  - Iron Sucrose: $882 per encounter (with infusion center charge)
- Children were included if:
  - The infusion was ordered by a peds sleep physician for treatment of a confirmed SRMD
  - There were baseline and follow-up ferritin levels available, and
  - There was follow-up clinical information regarding sleep symptoms

Our Institution: FCM vs Iron sucrose

- Participants:
  - Total of 60 iron infusions
  - N=40 (18 FCM and 22 Iron sucrose) had complete clinical and laboratory follow-up data
  - Mean age was 8.1 years
  - 60% male
  - No baseline differences by group, except dose

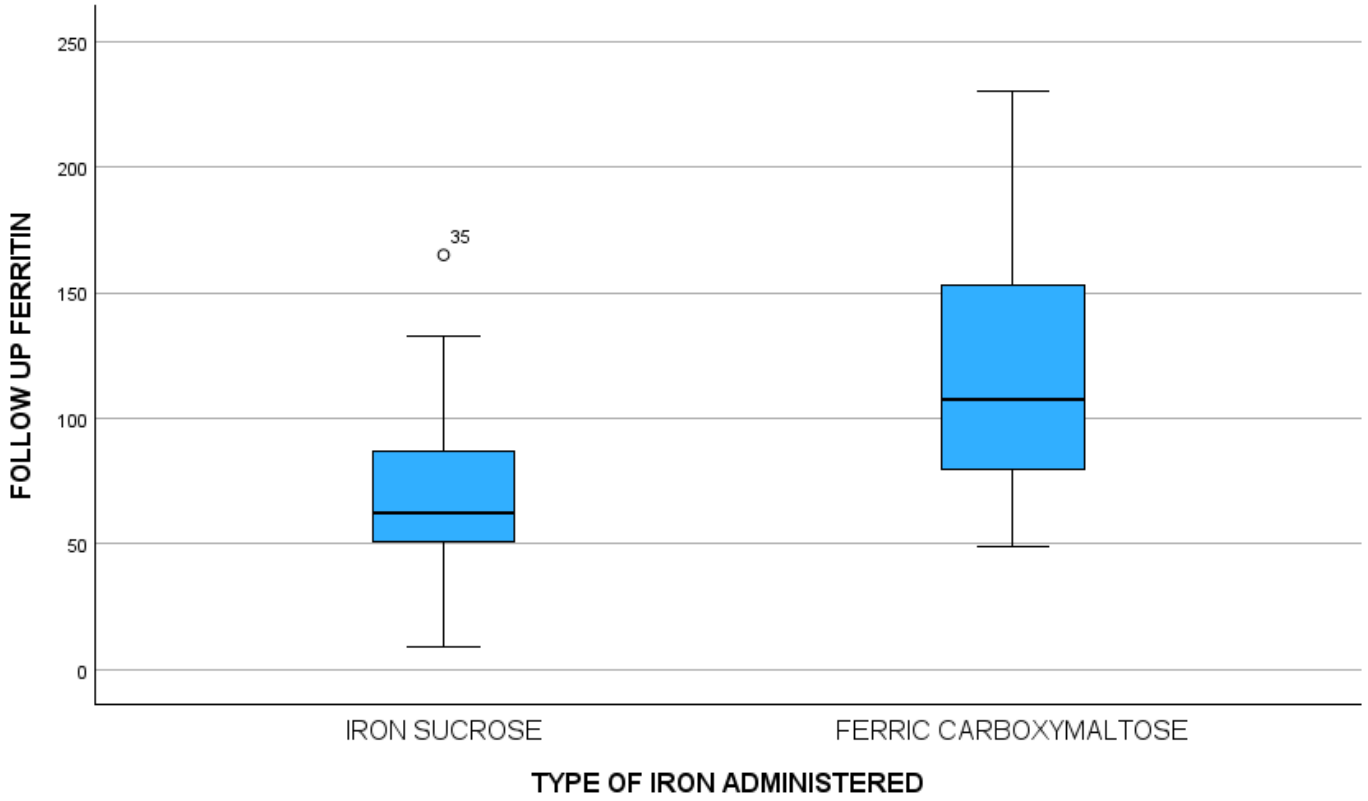


Group Statistics

	TYPE OF IRON ADMINISTERED	N	Mean	Std. Deviation	Std. Error Mean
WEIGHT	IRON S	22	28.36	17.201	3.667
	FERRIC	18	42.17	31.294	7.376
AGE	IRON S	22	7.27	4.188	.893
	FERRIC	18	9.17	5.159	1.216
BASELINE FERRITIN	IRON S	22	32.00	17.221	3.672
	FERRIC	18	26.28	14.942	3.522
DOSEKG	IRON S	22	6.4244	4.66308	.99417
	FERRIC	18	12.8217	2.73729	.64519

Our Institution: FCM vs Iron sucrose

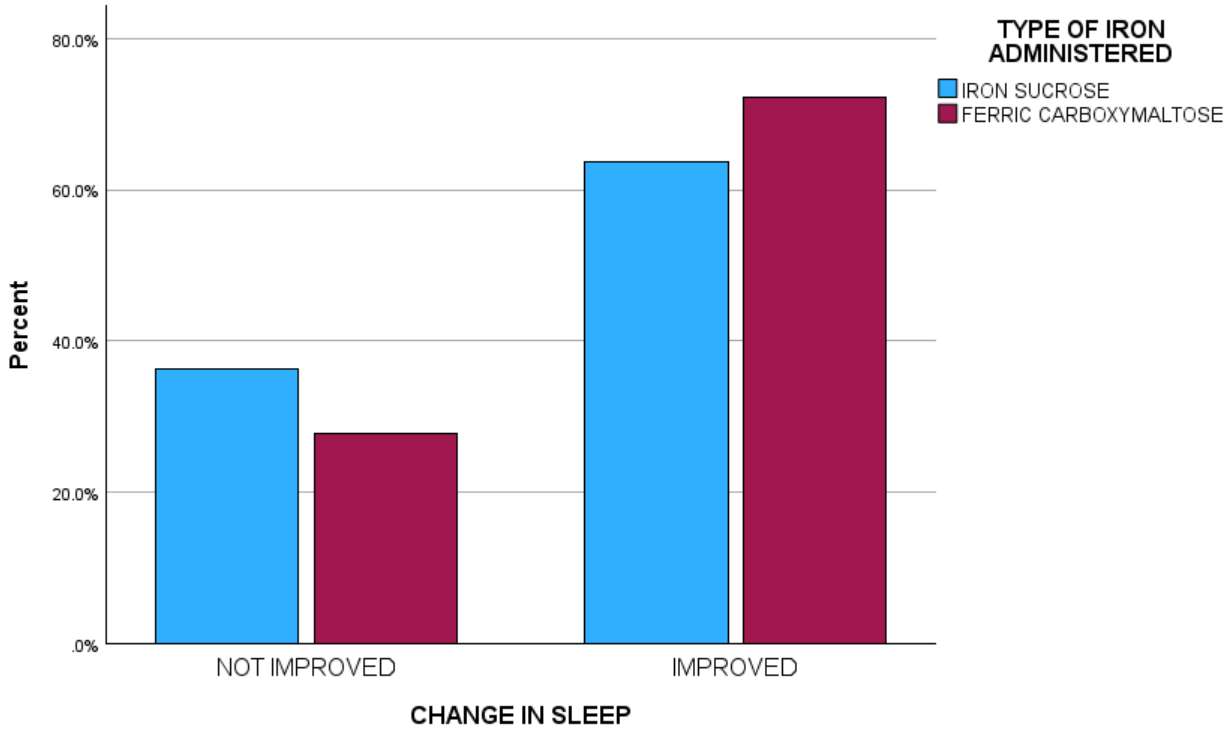
Children who underwent FCM infusion had significantly higher follow-up ferritin levels compared with iron sucrose (117.9 +/-52.2 vs 69.7+/-38.9 ng/mL, p=0.002), even with longer time to follow-up lab draw (71.4+/- 40.6 vs 38.1+/-37.1 days, p=0.010) .



Our Institution: FCM vs Iron sucrose

- Clinical improvement in sleep was noted in children underwent FCM and iron sucrose (72.2% vs 63.6%, p=0.564)

- No predictors of symptom improvement were noted



Our Institution: FCM vs Iron sucrose

Repeated infusions were needed significantly more often with iron sucrose compared with FCM (27.3% vs 0.0%, p=0.024).

REPEAT * TYPE OF IRON ADMINISTERED Crosstabulation

		TYPE OF IRON ADMINISTERED					
		FERRIC		IRON S		Total	
		N	%	N	%	N	%
REPEAT	NO	18	100.0%	16	72.7%	34	85.0%
	YES	0	0.0%	6	27.3%	6	15.0%
Total		18	100.0%	22	100.0%	40	100.0%

Our Institution: FCM vs Iron sucrose

- Each group had 1 case of mild gastrointestinal symptoms during infusion, otherwise no significant infusion reactions were noted.

- There were no cases of significant hypophosphatemia noted following FCM infusion (mean=4.4+/-0.7, none < 2.0 mg/dL).

SIDE EFFECTS * TYPE OF IRON ADMINISTERED Crosstabulation

		TYPE OF IRON ADMINISTERED				Total	
		FERRIC		IRON S			
		N	%	N	%	N	%
SIDE EFFECTS	GI DISCOMFORT	1	5.6%	1	4.5%	2	5.0%
	NONE	17	94.4%	21	95.5%	38	95.0%
Total		18	100.0%	22	100.0%	40	100.0%

Infusion Reactions

- Monitoring/vitals every 15 minutes during infusion and for 30-60 minutes after infusion is complete
- Minor adverse effects include discomfort at the injection site, non-specific headache, nausea, dizziness, and transient elevation of blood pressure
- A minor infusion reaction due to labile free iron can occur in about 1% of infusions and is characterized by facial flushing, chest or back myalgias, and/or throat tickling (but not wheezing, stridor, periorbital edema, or hypotension) – this resolves spontaneously
- More serious adverse effects include iron extravasation, hypophosphatemia, and hypersensitivity reaction
- Hypersensitivity reaction is extremely rare, occurring in less than 1:250,000 IV iron administrations

Managing Infusion Reactions: Our protocol

- **Mild HSR** *(itching, flushing, urticaria, sensation of heat, slight chest tightness, hypertension, back/joint pains)*
  - Stop iron infusion for ≥ 15 minutes
  - Inform provider
  - Monitor pulse, BP, resp. rate, O_2 saturation
  - Resolved in 5-10 minutes→ restart iron infusion at reduced rate (50%)
  - No better in 5-10 minutes/deteriorating → treat as a ***moderate HSR***
  - Make note to run subsequent infusions at ≤ 50% rate
- **Moderate HSR** *(Mild reaction + transient cough, nausea, chest tightness, shortness of breath, tachycardia, hypotension)*
  - Stop iron infusion
  - Call provider
  - Monitor pulse, BP, resp. rate, O_2 saturation
  - Consider isotonic fluid bolus (i.e. NS 10 mL/kg)
  - Consider IV hydrocortisone or methylprednisolone
  - Observe for 1-4 hours
  - Consider future treatment strategy
  - Patient deteriorating → treat as ***severe HSR***
  - Document as an ADR in Cerner
  - May consider alternate iron formulation in future
- **Severe/Life-Threatening HSR** *(sudden onset/rapid aggravation of symptoms + wheezing/stridor, periorbital edema, cyanosis, loss of consciousness, cardiac/respiratory arrest)*
  - Stop iron infusion
  - Call rapid response team
  - Monitor pulse, BP, resp. rate, O_2 saturation
  - Additional fluid bolus (i.e. NS 10 mL/kg)
  - EPINEPHrine (EpiPen Auto-Injector)
  - IV hydrocortisone or methylprednisolone
  - Albuterol MDI or nebulizer
  - O_2 face mask, ACLS or PICU transfer if necessary
  - Not recommended to re-challenge with any iron product

Preparing the child/family for infusion success

- Education in the clinic
- Child life
- Comfort dog
- Infusion nurses
- Monitor afterward
- Check in with family

IV Iron insurance coverage

CMH Payor Poll Prior Authorization: Iron Medication							
Payor	**J1756 Venofer/Iron Sucrose**	**J1750 Iron Dextran/**	**J2916 Sodium Ferric Cluconate/ Ferrlecit**	**J1439 (FCM) Ferric Carboxymaltose/Injectafer**	**Q0139 Ferumoxytol**	**Medical Policy**	**Route to Auth/Auth notes (for FC only)**
Commercial							
Aetna	Not Reqd	Not Reqd	Not Reqd	Yes (PA/Pre-D)		Aetna Iron Policy	Availity > Novologix Aetna Auth Form
BCBS KC	Not Reqd	Not Reqd	Not Reqd	No Auth Required, however must meet medical necessity. IF medical necessity isn't met, request Pre-D		B for Peds	BC KC portal
BCBS KS	Not Reqd	Not Reqd	Not Reqd	Yes (Pre-D)		BCBS KS Iron Policy no updates as of 1.3.23	Availity > BCBS KS portal
BCBS Out of State	Not Reqd	Not Reqd	Not Reqd	Maybe (PA/Pre-D		Anthem Iron Policy	
Cigna CMH	Not Reqd	Not Reqd	Not Reqd	Yes, preferred is Venofer			Fax Cigna auth form & clinicals to 855-840-1678. Phone: 800-851-3713, appeals fax: 877-815-4827.
Cigna	Not Reqd	Not Reqd	Not Reqd	YES (must have tried and failed 2 of the 3 preferred iron products before FCM will be approved)		Cigna Iron Policy	Fax Cigna auth form & clinicals to 855-840-1678. Phone for Medical Injectable Group: 800-244-6224.
UHC	Not Reqd	Yes, PA required	Not Reqd	*YES (must have tried and failed 2 of the 3 preferred iron products before FCM will be approved)		UHC Iron Policy	UHC portal
Missouri Medicaid							
MO Medicaid (ALL, including PCNs)	Not Reqd	Not Reqd	Not Reqd	YES (must have tried and failed 2 of the 3 preferred iron products in the past 90 days before FCM will be considered)		Mo Medicaid Iron Policy	Pre-D Form
Kansas Medicaid							
Aetna Better Health / PCN	Not Reqd	Not Reqd	Not Reqd	No- must meet medical necessity. If medical necessity isn't met submit PA		ABH Iron Policy (same as commercial)	Availity portal
Sunflower	Not Reqd	Yes, PA required	Not Reqd	Yes, PA required (must try and fail both preferred products)		https://www.kdhe.ks.gov/DocumentCenter/View/420/Preferred-Drug-List-PDF?bidId= page 22	Sunflower portal (takes forever) Fax form w/clinicals
UHCCP KS	Not Reqd	Yes, PA required	Not Reqd	Check UHC Auth Tool		UHCCP KS Iron Policy	UHC portal/check auth tool
Government Other							
Tricare West PRIME	No Auth Required, however active referral to CMH Clinic or ordering provider should be on file					Tricare follows approved FDA guidelines. See J codes on left for hyperlinked policies detailing indications.	Prime – FCM doesn't require, verified 9.2.22 (Hunter C. ref # 32495056)
Tricare West SELECT	Referral is not req to CMH Clinic or ordering provider, No Auth Required						

Aetna Iron Auth Form

Future areas of investigation

- Direct comparison of different IV iron formulations
- Characterize durability of effect
- Better tools for characterizing sleep-related movements and response to therapy
- Better tools for characterizing brain iron stores
- Predicting those children who will be responders to IV therapy vs oral iron or other medications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