LTC Clinical Pearl: ORAL IRON DOSING

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Ironing out daily versus alternate day/every other day oral iron dosing in PCH residents with iron deficiency anemia

Key Takeaways:

- First line treatment of iron deficiency anemia should be with oral iron salts (e.g. ferrous fumarate, sulfate, or gluconate) at dosages of 1 tablet daily or every other day if daily is not tolerated.[6]
- There is no advantage to giving oral iron supplements more than one dose per day.[2]
- When choosing between daily or every other day regimens, daily dosing may provide better iron absorption, overall, due to the greater amount of iron administered per time period whereas every other day regimens are better tolerated. [2]
- Older adults are more likely to experience GI toxicity and constipation from oral iron so lower doses may be preferred.[2]
- Dosing iron in the morning may maximize absorption due to hepcidin hormone levels being at the lowest.[16]
- Avoid controlled release or modified release iron preparations. They do not enhance absorption or reduce side effects.[6]
- Polysaccharide formulations are not more effective than iron salts, are expensive, and are not covered for PCH residents.[2]
- Heme iron polypeptide formulations are not commonly used as they have not been evaluated clinically, their cost is greater, and they are not covered for PCH residents.[2]
- In older adults, low dose oral iron (using liquid preparations) has been reported to be successful and associated with less adverse effects (e.g., daily dose of 15 mg of elemental iron was as effective as 50 mg or 150 mg of elemental iron in terms of the hemoglobin response). This may be considered in elderly residents experiencing adverse effects.[13]
- Appropriate monitoring should always be implemented when adjusting oral iron regimens.
- It is important to recognize most of the oral iron studies supporting this data were performed on average adults, which may limit the applicability of the findings to geriatrics and patients with advanced chronic kidney disease.

Introduction

- Iron deficiency anemia is the second most common cause of anemia in the elderly population, affecting 15-30% of cases and has a significant impact on quality of life, functional decline and mortality.[1,2]
- Iron deficiency anemia usually results from chronic gastrointestinal (GI) blood loss from nonsteroidal anti-inflammatory drug (NSAID) induced gastritis, ulcers, colon cancer, angiodysplasia, as well as bleeding disorders.[1] Table 1 outlines the common causes of anemia in the elderly.[1]
- Anemia in the elderly can be easily overlooked as signs and symptoms (e.g., fatigue, weakness and dyspnea) are often insidious and tend to be attributed to advancing age and frailty and/or other conditions such as worsening chronic heart failure.[1]

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- Optimally treating iron deficiency anemia in the elderly is particularly relevant as anemia is associated with numerous serious consequences including higher incidence of cardiovascular disease, cognitive impairment, reduced quality of life, reduced physical performance, increased risk of falls and fractures, longer hospital stays, and increased risk of mortality.[3] It may also worsen other conditions such as congestive heart failure and chronic obstructive pulmonary disease. Prompt identification and appropriate treatment may provide considerable benefit for these residents.

Table 1: Common Causes of Anemia in the Elderly [1]

Cause of anemia	*Percentage of cases*
Anemia of chronic disease	30 to 45
Iron deficiency	15 to 30
Posthemorrhagic	5 to 10
Vitamin B_{12} and folate deficiency	5 to 10
Chronic leukemia or lymphoma	5
Myelodysplastic syndrome	5
No identifiable cause	15 to 25

Smith DL. Anemia in the elderly. Am Fam Physician. 2000 Oct 1;62(7):1565-72. PMID: 11037074.

Diagnosis

- The World Health Organization criteria for anemia is hemoglobin less than 120 g/L in women and less than 130 g/L in men.[1]
- Iron deficiency anemia is often diagnosed if the serum ferritin is less than 30 ug/L or the transferrin saturation (TSAT) is less than 20%. TSAT is often used if the ferritin is thought to be unreliable due to an inflammatory state.[1,2]
- The diagnosis of iron deficiency anemia is challenging in the elderly as mentioned above. Some references suggest higher thresholds for investigation (e.g., serum ferritin below 50 ug/L).[4] Investigation is usually recommended if life expectancy is more than 1 year or the resident has symptomatic anemia.[5]
- Clinical features may also be used to assist diagnosis such as fatigue, headaches, cold intolerance, restless leg syndrome, irritability/depression, ice craving (pica/pagophagia), etc.[6]

Goals of Therapy

- Restore hemoglobin to a range where resident is comfortable, aligning with goals of care (e.g., greater than 100 g/L)
- Optimize iron absorption from the iron supplement
- Minimize adverse effects of iron supplementation
- Maintain resident adherence to iron supplementation
- Minimize cost of iron supplementation
- Improve symptoms of iron deficiency anemia and quality of life

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Treatment

- It is imperative that the cause of iron deficiency anemia be identified and addressed. Treatment of iron deficiency anemia only addresses replacing iron stores and not the root cause of the iron deficiency.
- Oral iron therapy is first line treatment for iron deficiency anemia.[6]
- Side effects of oral iron may include: GI upset, constipation, heartburn, nausea, and even vomiting, which contribute to high discontinuation rates. Unabsorbed iron propagates many of these side effects and thus excessive iron dosing should be avoided as it exacerbates these side effects.[6,7]
- Older adults may have a higher incidence of intolerance to oral iron supplementation (e.g., constipation and GI upset) and may have reduced absorption if they are taking antacids, proton pump inhibitors (PPIs), or other interacting medications.[2] Optimizing dosing regimens in this population is especially important.

Treatment Options

- Traditional oral iron supplementation salts (e.g., ferrous sulfate, ferrous gluconate and ferrous fumarate) are inexpensive, effective, safe and readily available. They are considered the standard therapies for treatment of iron deficiency anemia.[6,4,2]
- Modified release preparations release iron in the more distal small bowel but have not been shown to enhance iron absorption or reduce side effects, so their use is not recommended.[6,2]
- Polysaccharide-iron complexes have similar efficacy but are more expensive and not covered for PCH residents which is why they are not first line. They may have the advantage of no metallic taste, but a small trial showed ferrous sulfate was slightly more effective than polysaccharide-iron complexes.[8]
- Heme iron supplements have not been evaluated clinically.[2]
- Intravenous (IV) iron therapy is reserved for residents who have severe iron deficiency, significant blood loss, malabsorptive syndromes, or are unable to tolerate gastrointestinal side effects of oral iron.[2]
- IV iron has to be given in an acute care setting due to the risk of hypersensitivity reactions (e.g., anaphylaxis/anaphylactoid) during the infusion. IV iron is usually ordered in consultation with a specialist (e.g., hematologist, oncologist, transfusion medicine).
- Intramuscular iron is not recommended due to unpredictable absorption, risk of anaphylaxis, and local complications (e.g., pain, permanent staining of the skin, sarcoma formation).[4]

Dosing Regimens

- Traditionally, oral iron salts were taken as split dose (BID-TID) because it was thought to minimize adverse effects and maximize absorption. However, more recent data suggests lower doses and more infrequent administration is just as effective, while associated with lower rates of adverse effects. In addition, it may be inconvenient for residents and nursing staff to find three periods during the day to administer iron on an empty stomach.[6]
- Currently, there are 2 dosing schedules that are recommended, daily or every other day dosing. Each schedule has small differences in efficacy and adverse effects.
- It is suggested that practitioners choose the dosing regimen that best suits the resident.

  - Daily dosing: May provide more iron absorption, overall, due to the greater amount of iron administered (often recommended initially).
  - Every other day dosing: May be preferred for those who wish to reduce gastrointestinal side effects and/or have experienced an intolerance to daily dosing.
- Based on the available evidence, differences in efficacy appear to be marginal with both regimens and gastrointestinal side effects appear to be greater with daily dosing.[2]
- **There is no advantage to give oral iron supplements more than one dose per day.**
- Coadministration with vitamin C: Vitamin C (greater than 200 mg) along with an iron supplement may cause a modest increase in iron absorption, but is likely not clinically significant.[9,10] A recent large randomized controlled trial has confirmed that it neither enhances the hematological response, iron loading, nor reduces side effects.[9]
- Iron absorption can be decreased by various medications and supplements such as multivitamins, calcium, or antacid tablets. Space administration by at least 2 hours apart. Avoid administration with tea, coffee or milk.[4]

Amount of Iron Per Dose

- It recommended that the initial treatment of iron deficiency anemia be with one tablet per day (low dose) of ferrous sulfate, fumarate or gluconate (see Table 2). If not tolerated, a reduced dose of one tablet every other day, alternative oral preparations, or parenteral iron may be considered.[6]
- Uçan et al. (2023) demonstrated that lower iron doses dosed daily or every other day resulted in better absorption compared to higher iron doses dosed similarly, hence one tablet per day is usually sufficient.[11]
- Doses higher than 60–120 mg of elemental iron daily or every other day are unlikely to offer significant benefit and may cause unintended side effects.[11,12]
- 20 to 100 mg elemental iron daily is recommended by some references and if intolerance occurs, changing to every other day dosing regimen is recommended.[2,12]
- In the elderly population specifically, therapy with low dose oral iron has also been reported to be successful and safe. A daily dose of 15 mg of elemental iron was as effective as 50 mg or 150 mg in terms of the hemoglobin response, with a lower incidence of adverse effects.[13]

Table 2: Oral Iron Supplements[10]

Iron Salt		Elemental Iron	Product(s) Covered in Manitoba PCH
Ferrous gluconate 		300 mg tab = 35 mg	Ferrous gluconate 300 mg tablet
Ferrous sulfate	Tablet 	300 mg tab = 60 mg	Ferrous sulfate 300 mg tablet
	Liquid	150 mg/5 mL = 30 mg	Ferrous sulfate 150 mg/5 mL syrup

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Ferrous fumarate	Tablet 	300 mg tab = 100 mg	Ferrous fumarate 300 mg tablet
	Liquid	60 mg/mL = 20 mg/mL	Not covered
Polysaccharide iron complex (e.g., FeraMAX®, Triferexx®, Polyride Fe®)		150 mg	Not covered
Heme iron polypeptide (e.g., Proferrin®)		11 mg heme iron	Not covered

<u>Iron Absorption - Role of Hepcidin</u>

- The new iron dosing recommendation (reduced dose of daily or every other day) is further supported by considering how iron is absorbed.
- Recommendations from the American Society of Hematology and British Society of Gastroenterology guidelines cited many trials which studied iron dosing and the effects on hepcidin levels, a peptide hormone produced in the liver.[6,12]
- Hepcidin is the most important inhibitor of iron absorption. It follows a diurnal and increases after oral iron intake, impairing absorption of subsequent doses by 35-45% pattern (see Figure 1). A 60 mg iron dose is enough to stimulate hepcidin to impair absorption of any subsequent iron supplement doses for the next 24 hours. As a result, twice daily dosing is comparable to once daily dosing because absorption of the second dose is significantly inhibited by hepcidin.[6]

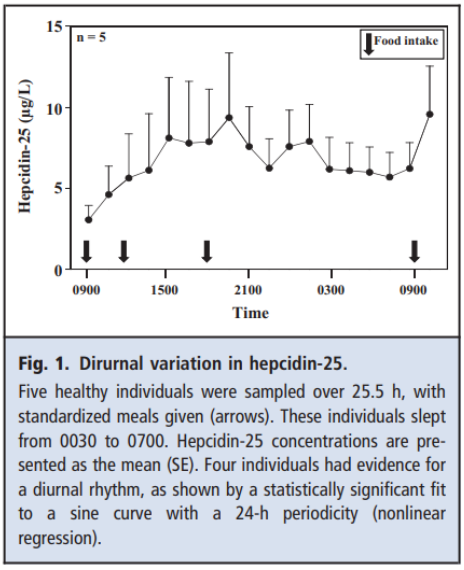

Fig. 1. Dirurnal variation in hepcidin-25.
Five healthy individuals were sampled over 25.5 h, with standardized meals given (arrows). These individuals slept from 0030 to 0700. Hepcidin-25 concentrations are presented as the mean (SE). Four individuals had evidence for a diurnal rhythm, as shown by a statistically significant fit to a sine curve with a 24-h periodicity (nonlinear regression).

Figure 1: Hepcidin Diurnal Pattern[14]

- This finding is further supported by two small open-label trials which confirmed that divided doses of iron increased hepcidin compared with once daily dosing and failed to improve absorption.[15] In some studies, every other day dosing also resulted in slightly greater iron

absorption than once daily dosing, with a statistically nonsignificant trend toward reduced nausea, in some studies.[14,7]

- Furthermore, hepcidin is naturally at its lowest in the morning. Consideration of morning dosing of iron is recommended to further reduce the impact hepcidin has on absorption.[14,16]

Management of Oral Iron Adverse Effects[2]

- Modifying the interval to every other day dosing if currently at once daily.
- Making dietary modifications (e.g., taking the iron supplement with food), although this may reduce absorption.
- Switching to a formulation with a lower amount of elemental iron (e.g., ferrous sulfate to ferrous gluconate).
- Switching from a tablet to a liquid, so that it may be easier to titrate the dose to achieve improved tolerability.
- Use of a laxative to manage constipation (e.g., sennosides, PEG, lactulose).

Monitoring

- When oral iron therapy is initiated, or when there is a change in dose or regimen, monitoring for hematological response is recommended.
- The frequency of monitoring depends upon the severity of the anemia, the cause of the iron deficiency, and the clinical status of the resident.
- A suggested monitoring plan is outlined in Table 3 below:

Table 3: Oral Iron Monitoring[10,4]

Parameter	Desired Outcome and Threshold for Concern	Frequency of Monitoring	Comments
Hemoglobin (HgB)	• Optimal: Males 130-180 g/L Females 120-160 g/L • Target: greater than 100 g/L and absence of anemia symptoms	• Depends on resident's clinical status, response to iron (e.g., change in HgB), or change in erythropoietin stimulating agent dose. • Suggest check HgB 2-4 weeks after initiating iron and after dose changes. • HgB should increase 10-20 g/L in 4 weeks. HgB should be corrected in 2-4 months, but it may take up to 6 months.	• Continue iron therapy for an additional 4 to 6 months after correction of anemia to replenish the iron stores. • If ongoing need for iron supplementation (e.g., bleeding), continue maintenance dose. • Poor/no response to oral iron after 3 weeks, consider adherence, ongoing bleeding, malabsorption, alternate diagnosis, or IV therapy. • If the resident's clinical status is compromised by moderate to severe
Ferritin	• Greater than 30 g/L in young healthy adults • Greater than 50 g/L in older adults	• Check every 1-3 months • Ferritin should be re-checked 3 to 6 months after normalization of HgB in anemic patients.	

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	• Greater than 100 g/L in non-dialysis CKD • Greater than 200 g/L in dialysis CKD		anemia, consider hospitalization and/or blood transfusion.
TSAT	• Greater than 16-20%	• Check every 1-3 months	
Adverse Effects	• Minimal or tolerable adverse effects (e.g., nausea, vomiting, or constipation)	• Nausea/vomiting: 1-3 days after initiating iron supplement • Constipation: 5-7 days after initiating iron supplement	• If iron supplement not tolerated, consider administration with food, changing to every other day dosing, or changing to a formulation with lower elemental iron. • For treatment of constipation, consider laxatives (e.g., sennosides, PEG, lactulose etc.). • If oral iron is intolerable, consider if IV iron administration is required and within goals of care.

References:

1. Smith DL. Anemia in the elderly. Am Fam Physician. 2000 Oct 1;62(7):1565-72. PMID: 11037074.
2. Auerbach, M et al. Causes and diagnosis of iron deficiency and iron deficiency anemia in adults. In: UpToDate, Connor RF (Ed), Wolters Kluwer. (Accessed on July 2, 2024.)
3. Stauder R, Thein SL. Anemia in the elderly: clinical implications and new therapeutic concepts. Haematologica. 2014 Jul;99(7):1127-30. doi: 10.3324/haematol.2014.109967. PMID: 24986873; PMCID: PMC4077071.
4. Government of British Columbia. (2023). Iron Deficiency – Diagnosis and Management. Iron Deficiency – Diagnosis and Management - Province of British Columbia (gov.bc.ca)
5. Balducci L. Epidemiology of anemia in the elderly: information on diagnostic evaluation. J Am Geriatr Soc. 2003 Mar;51(3 Suppl): S2-9.
6. Snook J, Bhala N, Beales ILP, Cannings D, Kightley C, Logan RP, Pritchard DM, Sidhu R, Surgenor S, Thomas W, Verma AM, Goddard AF. British Society of Gastroenterology guidelines for the management of iron deficiency anaemia in adults. Gut. 2021
7. Kaynar LA, Gökçen S, Can F, Yeğin ZA, Özkurt ZN, Yağcı M. Comparison of daily oral iron replacement therapy with every other day treatment in female reproductive age patients with iron-deficiency anemia. Ann Hematol. 2022 Jul;101(7):1459-1464. doi: 10.1007/s00277-022-04835-6. Epub 2022 Apr 23. PMID: 35460388.
8. Powers JM, Buchanan GR, Adix L, Zhang S, Gao A, McCavit TL. Effect of Low-Dose Ferrous Sulfate vs Iron Polysaccharide Complex on Hemoglobin Concentration in Young Children with Nutritional Iron-Deficiency Anemia: A Randomized Clinical Trial. JAMA. 2017 Jun 13;317(22):2297-2304. doi: 10.1001/jama.2017.6846. PMID: 28609534; PMCID: PMC5815003.
9. Li N, Zhao G, Wu W, et al. The efficacy and safety of vitamin C for iron supplementation in adult patients with iron deficiency anemia: a randomized clinical trial. JAMA Netw Open 2020;3: e2023644.
10. RxFiles. *RxFiles Drug Comparison Charts*. Iron Management: Iron Deficiency Anemia (IDA). Saskatoon: RxFiles, 2021.
11. Uçan A, Kaya ZI, Yilmaz EÖ, Vasi İ, Özgeyik MO. Comparing therapeutic effects of alternate day versus daily oral iron in women with iron deficiency anemia: A retrospective cohort study. Medicine (Baltimore). 2023 Jul 28;102(30): e34421. doi: 10.1097/MD.0000000000034421. PMID: 37505179; PMCID: PMC10378732.
12. Lo JO, Benson AE, Martens KL, et al. The role of oral iron in the treatment of adults with iron deficiency. Eur J Haematol. 2023;110(2):123-130. doi:10. 1111/ejh.13892

13. Rimon E, Kagansky N, Kagansky M, et al. Are we giving too much iron? Low-dose iron therapy is effective in octogenarians. Am J Med 2005; 118:1142–7.
14. Troutt, J.S., Rudling, M., Persson, L., Ståhle, L., Angelin, B., Butterfield, A.M., Schade, A.E., Cao, G., & Konrad, R.J. (2012). Circulating human hepcidin-25 concentrations display a diurnal rhythm, increase with prolonged fasting, and are reduced by growth hormone administration. *Clinical chemistry, 58 8*, 1225-32.
15. 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(11):e524-e533.
16. Alberta Health Services. Oral Iron Optimization. Drugs and Therapeutic Backgrounder: Optimizing the use of oral iron supplementation in the treatment of iron deficiency anemia. https://www.albertahealthservices.ca/assets/info/phm/info-phm-ds-pub-dtb-iron-optimizing-oral-supplementation-treatment-iron-deficiency-anemia.pdf (Accessed Aug 15 2024).
17. Düzen Oflas, N., Demircioğlu, S., Yıldırım Doğan, N., Eker, E., Kutlucan, A., Doğan, A., Aslan, M. and Demir, C. (2020), Comparison of the effects of oral iron treatment every day and every other day in female patients with iron deficiency anaemia. Intern Med J, 50: 854-858. https://doi-org.login.ezproxy.library.ualberta.ca/10.1111/imj.14766