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Use of oral iron in managing iron deficiency anemia in children with intestinal failure

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ABSTRACT

Background & Objectives: As intestinal failure (IF) inhibits the digestive system from absorbing nutrients, total parenteral nutrition (TPN) is required to provide all of a person's nutritional demands. In children with malabsorptive conditions like IF, iron deficiency anemia (IDA) is common. This study used a quasi-experimental approach to assess the efficacy and safety of oral iron therapy in treating IDA in TPN-dependent children with IF.

Materials and Methods: Sixteen pediatric patients with an ongoing history of IF, TPN dependency, and iron deficiency anemia were enrolled and given an oral iron syrup dose of ferric hydroxide polymaltose complex (6 mg/kg/day in 2–3 separate doses of elemental iron) after receiving ethical approval and parental consent. Blood tests were done to measure serum iron, ferritin, complete iron-binding capacity [TIBC], transferrin saturation [TSAT], and hemoglobin (Hb) level at the time of inclusion (T0), 14 (T14), and 30 days after treatment (T30).

Results: The mean age was 7.13 (±1.99) and female were 12 (75%). No remarkable change in Hb level was noted in the first and second subsequent follow-ups, notwithstanding, the normal estimation of the serum ferritin level significantly increased during the first follow-up (on fourteenth day) which further enhanced by second follow-up (30th day). The aggregate of the total iron binding capacity (TIBC) declined during the course of oral iron therapy with a reduction in transferrin saturation.

Interpretation & Conclusion: The data suggest that oral iron therapy is unsuccessful in the treatment of IDA in children with IF. There is no substantial improvement in hemoglobin level or iron profile aside from serum ferritin. In order to avoid using parenteral iron in IF patients, an additional supportive system is needed to aid in the integration of oral iron therapy.

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1. Introduction

A most common type of anemia in the world is iron deficiency anemia (IDA), which results in microcytic and hypochromic red cells on the peripheral smear (Warner and Kamran, 2020). Due to low iron levels in the body, iron deficiency anemia causes a reduction in red blood cell formation. It is the most common nutritional condition in the world, accounting for over half of all anemia cases (Johnson-Wimbley and Graham, 2011). Inadequate iron intake, poor iron absorption, increased iron demand, and increased iron loss can all contribute to iron deficiency anemia. IDA in children is defined as low iron and serum ferritin levels resulting in an inability to sustain physiological function. Iron has a fundamental role in transporting oxygen to various human tissues, energy metabolism, and DNA synthesis (Wang and Pantopoulos, 2011). It is found in dietary sources and absorbed through the intestine mostly via the duodenum (Wang and Pantopoulos, 2011). Iron absorption is enhanced when the body store is low and decreased when the iron store is high (Saito, 2014). Patients who have impairment in iron absorption will eventually develop IDA.

Intestinal failure (IF) is an orphan disease referred to as impairment of the intestine to absorb nutrients necessitating total parenteral nutrition (TPN) to meet all nutritional requirements (D'Antiga and Goulet, 2013; Ingelfinger et al., 2017). A consensus definition of IF proposed by SJ O'keefe et al. is "Intestinal failure results from obstruction, dysmotility, surgical resection, a congenital defect, or disease-associated loss of absorption and is characterized by the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balance "(Lal et al., 2006). The case is considered to be IF when the need for total parenteral nutrition continues for > 4 weeks or the need for partial PN for >3 months (Salvia et al., 2008). IF has been ascribed to acquired or congenital causes (Allan and Lal, 2018). There are three types of intestinal failure depending on the duration of nutrition support and reversibility (Allan and Lal, 2018). Type I (mild IF) is a short-term and self-limiting disease that commonly occur following abdominal surgery and recover within 28 days. Type II (moderate IF) is intermediate-term of weeks and months that has been arisen during an intra-abdominal catastrophe, intestinal resection, and in severe illness such as sepsis patients. Type III is a long-term disease mandating home parenteral nutrition (Allan and Lal, 2018; O'Keefe et al., 2006; Gardiner, 2011).

The prevalence of intestinal failure is inconstant in each country due to the condition's rarity and is reported to be 13.7 cases per million population, 87 cases per 100,000, and 170 cases per year, in the United Kingdom, Italy, and Germany respectively (Krawinkel et al., 2012). Scott et al. reported the median duration of IF admission was 26 days (range 1–240) and in-hospital mortality by 13% (Scott et al., 1991). IF can be also categorized by pathophysiology as short bowel syndrome (87%), congenital enterocyte defect or extensive parenchymal disease (41%), and severe motility disorders (38%) (Pironi et al., 2016; D'Antiga and Goulet, 2013). Tufting enteropathy (TE) is one of the causes of severe intestinal failure seen as congenital autosomal recessive disease of infancy. Most of the samples included in the study were diagnosed with TE. In western Europe, the prevalence of TE was estimated to be around 1/50000–100,000 per live births (Ko et al., 2010) The prevalence of TE is expected to be significantly higher in areas with a high degree of consanguinity, such as the Arabian Peninsula population; however, data on TE from the Arabian Peninsula countries is limited.

Micronutrient deficiencies, namely vitamin D, vitamin B12, iron, and zinc are frequently encountered in IF patients even if they receive total parenteral nutrition (Ingelfinger et al., 2017). Eventually, regular laboratory monitoring is required with direct management for abnormalities. Basilio et al. reported that iron deficiency is common in children with malabsorptive diseases (de Vizia et al., 1992). Thus, iron supplementation with only parenteral route of administration is initiated in TPN-dependent patients who have intestinal failure to treat IDA. Due to the vulnerability of TPN-dependent patients to serious complications such as catheter-related infection, loss of vascular access with frequent catheter utilization, and increased risk of allergic reaction, it is proven strategy to minimize its need by substitution of intravenous iron therapy to oral iron therapy. Moreover, oral iron therapy is not studied in intestinal failure patients. Therefore, we carried out a study to evaluate the effectiveness and the safety of maximum oral iron therapy for treating IDA in TPN-dependent pediatric patients with intestinal failure.

2. Methods

2.1. Study area/setting

This quasi-experimental trial was conducted in a pediatric gastroenterology clinic in a children's hospital located at King Fahad Medical City (KFMC), Riyadh, Saudi Arabia. The Institutional Review Boards at KFMC (IRB 19-077) approved the study. Informed consent was obtained from all guardians.

2.2. Sample size

Since IF is an orphan disease and only a limited number of patients suffer from such disease, we performed a convenience sampling method. The subjects who visited the gastroenterology clinic after getting diagnosed with IDA were approached to join this study and those whose parents readily gave consent were included.

2.3. Inclusion and exclusion criteria

All patients with a chronic history of IF; TPN dependent; age < 12 years old and diagnosed with iron deficiency anemia were eligible to be included. Besides clinical manifestation assessed by physicians, laboratory parameters were used to diagnose IDA. These were reflected by low hemoglobin ($\leq$11 g/dl) and serum iron level (<30 μmol/l) (Ozdemir, 2015). Exclusion criteria were allergy to oral iron; acute intestinal failure related to intestinal obstruction in which iron stumbles to be given orally; current infection; received proton pump inhibitors, histamine-2 blockers, or antacid; and anemia secondary to folic acid deficiency or vitamin B12 deficiency.

2.4. Enrollment and intervention

The physician in charge in the pediatric gastroenterology clinic enrolled outpatients. They were randomly assigned to receive the maximum oral iron syrup dose of ferric hydroxide polymaltose complex (6 mg/kg/day in 2–3 divided dose of elemental iron, 1 h before meals) recommended by Williams' Hematology textbook and planned to be administered by titration method within 3 days to prevent gastrointestinal (GI) related adverse events (Ozdemir, 2015). To avoid any additional impact of iron content of modified diet/food, parents of participants were asked to keep the same diet/food pattern during the study period as it was prior to enrollment. Daily messaging and smartphone notifications ensured compliance of caregivers to administer oral iron doses on a regular basis.

2.5. Study procedures and data collection methods

Patients underwent a clinical examination of IDA with the laboratory evaluation of iron study and complete blood count. Blood samples were obtained by nurses at the time of the study inclusion (T0), at 14 days post-therapy (T14), and 30 days post-therapy (T30). All required data were extracted and extrapolated in an MS-Excel sheet. These included patients characteristics (patients age, gender, type of intestinal failure [diagnosis]), iron profile (serum iron, ferritin, total iron-binding capacity [TIBC], transferrin saturation [TSAT], and complete blood count (Hemoglobin level).

2.6. Outcomes and follow-up

The primary endpoint for the effectiveness was an improvement of hemoglobin (Hb) level and iron profile after starting oral iron therapy. Additionally, the adequate response to oral iron therapy was assessed by accounting for the number of patients who had at least 1 g/dl of Hb elevation within four weeks after initiation of treatment. The secondary endpoint was to find the adverse effect of oral iron therapy. All children had follow-up lab testing to evaluate the therapeutic response, safety profile, and adherence to oral iron supplements. Follow-up plans were performed at baseline (T0), at 14 days post-therapy (T14), and 30 days post-therapy (T30) after starting the iron therapy by sending a blood sample to laboratory parameters through complete blood cell (CBC) count and iron study readings.

2.7. Statistical analysis

Mean, median, and standard deviation (±SD) were used for quantitative data, wherever appropriate. Checking of normality assumption was performed to examine data distribution. If the normality assumption was met using normal Q-Q plot, the Shapiro–Wilk test, and Mauchly's sphericity test, we employed the repeated measure ANOVA for pairwise comparisons; if not met, we used Greenhouse–Geisser correction to adjust for lack of sphericity. Pairwise comparisons corrected by Bonferroni test. Categorical variables were compared using the binomial test. All statistical inferences were drawn with 95% confidence intervals with $P < 0.05$. If the confidence interval includes 0, it implies that the treatment effect is not significant. All data were entered and analyzed through statistical package SPSS 25 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patients' characteristics

For the quasi-experimental trial, the study conducted between April 2019 and March 2020 with a total of 16 TPN-dependent children who were identified to have IDA upon the clinic visit. Baseline characteristics of the study patients are shown in Table 1. The mean (±Standard deviation) age was 7.13 (±1.99) and female were 12 (75.0%). The most common diagnosis was tufting enteropathy, also known as intestinal epithelial dysplasia, which represents 13 (81.3%). The median baseline of Hb level, serum ferritin, serum iron, TIBC, and TSAT were 9.85 g/dl, 16.1 ng/ml, 8.2 μmol/l, 44.7 μmol/l, and 44.7%, respectively (Table 1). Just four of the 16 children (25%) had a serum ferritin concentration of <12 ng/l at the time of recruitment; the remainder had a normal baseline ferritin concentration.

Table 2 shows mean value of hemoglobin and other iron parameters during the course of administration of oral iron therapy. No remarkable difference in Hb level was noted in the first and second follow ups, however, the average value of the serum ferritin level was high during the first follow (on 14th day) which further increased by second follow up (30th day) with a median 43.1. The aggregate of the total iron binding capacity (TIBC) also declined during the courses of oral iron therapy with a reduction in transferrin saturation.

Table 1
Demographic and clinical characteristics of patients (n = 16).

Variables	Description
Age (years), Mean ± SD	Median 6.5, Range 5–11
Female, n (%)	12 (75.0%)
Primary Diagnosis, n (%)	
Tufting enteropathy	13 (81.3%)
Short Bowel syndrome[4]	1 (6.3%)
MIVD[1]	1 (6.3%)
Protein convertase 1/3 deficiency	1 (6.3%)
Oral iron dose (Ferric Hydroxide)	6 mg/kg/day in 2–3 divided doses
Baseline Hemoglobin (Hb) g/dl	Mean ± SD 9.7 ± 1.22 Median 9.85, Range 7.3–11
Baseline Ferritin, ng/ml	Mean ± SD 19.11 ± 10.47 Median 16.1, Range 4.8–36.5
Baseline serum iron, μmol/l	Mean ± SD 8.30 ± 4.98 Median 8.2, Range 1.1–18.9
Baseline TIBC[2], μmol/l	Mean ± SD 45.34 ± 16.14 Median 44.7, Range 4–65
Baseline TSAT[3], Percentage	Mean ± SD 16.34 ± 11.32 Median 44.7, Range 4–65

[1] MVID: Microvillus Inclusion Disease; [2]TIBC: Total iron binding capacity [3]TSAT: Transferrin Saturation; [4]Short Bowel syndrome: Smaller size of the small intestine.

3.2. Outcomes

Table 3 demonstrates pairwise comparison of primary outcomes. After 4 weeks follow-up, the study showed no difference between baseline and 2nd follow-up (T30) in Hb level (mean difference (MD) −0.28 [95% CI = −1.54 to 0.97] P-value= >0.05). Also, it illustrated non-significant results in iron profile study including serum iron (MD = −1.08 [95% CI = −4.29 to 2.11] P-value= >0.05), TIBC (MD = 6.6 [95% CI = −9.94 to 23.26] P-value = 0.89), and TSAT (MD = −1.61 [95% CI = −9.38 to 6.15] P-value= >0.05) (Table 3). Exceptionally, ferritin level improved after administration of oral iron supplement (MD = −53.19 [95% CI = −100.86 to −5.52] P-value = 0.026). In addition, 87.5% (14 patients) did not achieve at least ≥ 11 g/dl Hb after 4 weeks of oral iron therapy. When considering the safety profile in these subjects following the maximum dose of oral iron, 5 (31.3%) patients developed diarrhea as an adverse drug reaction.

4. Discussion

This study is one of the rare attempt to explore the possibility of using oral iron therapy in managing iron deficiency anemia in pediatric patients suffering of intestinal failure. Thirteen of the sixteen patients in this study had tufting enteropathy (TE), a childhood autosomal recessive condition characterized by severe intestinal failure (IF), electrolyte imbalances, and developmental delays (Barun and Mamata, 2021). Malabsorption and the possibility of micronutrient deficiencies due to IF of TE results in systemic and functional abnormalities (Bielawska and Allard, 2017). Therefore, most of the patients require long-term nutritional support, generally in the form of total parenteral nutrition (TPN). TPN is safe in pediatric patients when given according to protocol, but there are both short and long-term risks associated with its use. Long-term risks include hepatic toxicity and failure, as well as short-term risks including catheter sepsis, moderate reversible liver dysfunction, and cholelithiasis (Farrell and Balistreri, 1986). Pediatric

Table 2
Mean value of hemoglobin and iron profiles during T0, T14, and T30.

Variables	Mean Baseline (T0) [95%CI]	Mean 1st follow up (T14) [95%CI]	Mean 2nd follow up (T30) [95%CI]
Hb[1], g/dl	9.7 [9.19 to 10.49]	10.06[9.34 to 10.79]	10.13 [9.10 to 11.16]
Ferritin, ng/ml	19.11 [13.53 to 24.69]	58.36 [31.52 to 85.21]	72.30 [35.08 to 109.52]
Iron, μmol/l	8.30 [5.6497 to 10.9628]	10.63 [8.2898 to 12.9727]	9.39 [7.3388 to 11.4487]
TIBC[2], μmol/l	45.34 [36.73 to 53.94]	40.15 [33.11 to 47.18]	38.68 [28.28 to 49.07]
TSAT[3], %	16.34 [10.30 to 22.37]	20.85 [14.52 to 27.17]	17.96 [13.67 to 22.25]

[1] Hb: Hemoglobin; [2]TIBC: Total iron binding capacity [3]TSAT: Transferrin Saturation.

Table 3
Pairwise comparisons of primary outcomes of hemoglobin and iron profiles.

Comparison			Results		
Parameter	comparison	Mean difference	Standard Error	95% CI	P-value[1]
Baseline-Hb2 (T0)	1st follow up-Hb (T14)	−0.22	0.30	−1.04 to 0.59	0.700
	2nd follow up-Hb (T30)	−0.28	0.46	−1.54 to 0.97	0.610
1st follow up-Hb (T14)	2nd follow up-Hb (T30)	−0.062	0.26	−0.76 to 0.63	0.621
Baseline –Ferritin (T0)	1st follow up-ferritin (T14)	−39.2	13.28	−75.04 to −3.46	0.029
	2nd follow up-ferritin (T30)	−53.19	17.69	−100.86 to −5.52	0.026
1st follow up-ferritin (T14)	2nd follow up-ferritin (T30)	−13.93	21.44	−71.71 to 43.83	0.426
Baseline –Iron (T0)	1st follow up- Iron (T14)	−2.32	1.03	−5.10 to 0.45	0.119
	2nd follow up- Iron (T30)	−1.08	1.19	−4.29 to 2.11	0.375
1st follow up- Iron (T14)	2nd follow up- Iron (T30)	1.23	1.13	−1.82 to 4.29	0.88
Baseline -TIBC3 (T0)	1st follow up-TIBC (T14)	5.19	4.16	−6.03 to 16.42	0.690
	2nd follow up-TIBC (T30)	6.66	6.16	−9.94 to 23.26	0.891
1st follow up-TIBC (T14)	2nd follow up-TIBC (T30)	1.46	5.19	−12.51 to 15.45	0.297
Baseline - TSAT 4 (T0)	1st follow up-TSAT (T14)	−4.50	2.16	−10.33 to 1.32	0.164
	2nd follow up-TSAT (T30)	−1.61	2.88	−9.38 to 6.15	0.583
1st follow up-TSAT (T14)	2nd follow up-TSAT (T30)	2.88	2.93	−5.02 to 10.80	0.104

[1] Benferroni corrected; [2]Hb: Hemoglobin; [3]TIBC: Total iron binding capacity [4]TSAT: Transferrin Saturation.

patients are more vulnerable due to immaturity. Therefore, there are recommendations to look for alternative system of supply of micronutrients to the growing children.

Despite several guidelines for oral nutrient intake in iron deficiency diseases, oral nutritional therapy is difficult to implement (Vanek et al., 2012), especially in pediatric patients with intestinal failure. The study aimed to identify the effectiveness and safety of maximum oral iron therapy for the treatment of IDA among TPN-dependent patients. The outcomes discussed here show that oral iron treatment isn't successful for treating IDA in this populace. Aside from serum ferritin, pre and post hemoglobin and iron profile have no critical improvement.

Similar to earlier reports (Khalafallah and Dennis, 2012; Breymann et al., 2010), we found an increased incidence of diarrhea following maximum oral iron therapy. Patients with diarrhea have a background marked by tufting enteropathy. There is a possible role of ferric hydroxide polymaltose complex used in this study in developing diarrhea. The disaccharide (maltose) used requires the action of mucosal enzymes (maltase & *iso*-maltase) to release the iron molecule that should then be absorbed to treat the iron deficiency anemia, which patients with intestinal failure lacks that might result in increased incidence of diarrhea.

Ferritin is an iron storage protein and presence of IDA hinders the serum ferritin expression, yet by virtue of being an acute-phase protein, serum concentration of ferritin are expanded in number of pathological conditions, for example, infection, cancer, obesity, inflammatory conditions, and liver disease (Dignass et al., 2018). Despite the fact that at the time of recruitment, just 25% of children had serum ferritin <12 ng/ml, there was a critical rise in serum ferritin level across all examination subjects when contrasted with their baseline values. Despite this, there was no simultaneous increase in serum iron with an increase in serum ferritin, implying that serum ferritin is not a reliable indicator of the response and efficacy of oral iron therapy. Worwood (1980) recorded that only 20% of their clinic patients with absent bone marrow hemosiderin had serum ferritin concentrations below 10 ng/ml, despite the fact that all patients with values below 10 ng/ml were iron deficient. Cook et al. (1976) found that serum ferritin alone isn't adequate to foresee the serum iron profile. Subsequently the rise of serum ferritin isn't a pointer to introduce the viability of persistent oral iron treatment. Different parameters are needed to show the adequacy of oral iron treatment in IDA patients (Madanat et al., 1984). It is additionally intriguing to take note of that the most of the subjects included for this investigation were diagnosed to have intestinal failure dependent on introduction of tufting enteropathy. As referenced above, since ferritin is an acute phase protein, and inflammatory components are accounted for in tufting enteropathy (Elin et al., 1977), it is conceivable that the rise is the serum ferritin is somewhat because of inflammation (Gerada et al., 2013). The ferritin in the serum was likely derived from macrophages (Cohen et al., 2010), and although it does not reflect the effect of administered oral iron, it does reflect iron and ferritin concentrations in the liver and other tissues (Garcia-Casal et al., 2015).

There are conflicting studies on the relationship between serum ferritin and hemoglobin levels in adult males. Franchini et al. (2007) defined a positive relationship between serum ferritin and Hb, whereas another study (Ton and Lopez, 1980) found no such connection. In addition, a study of pregnant women found no correlation between Hb levels and serum ferritin levels (Rasmussen et al., 2005). Khan and Shah (2005), on the other hand, found a correlation between serum ferritin and Hb levels in children. While serum iron is an important component in the formation of hemoglobin, increased ferritin does not indicate increased Hb synthesis in the bone marrow. Ferritin is not an iron molecule, but it is an iron storage protein, and the signaling mechanism for erythropoiesis promotes iron transmission. Without iron retention, such as in the case of intestinal failure, increased ferritin has little effect on Hb formation.

To our knowledge, this was one of the rare efforts to perform a prospective quasi-experimental trial testing oral iron treatment in TPN-dependent patients. Despite the fact that we made our point, the findings of this study indicate that oral iron therapy has no role in treating iron deficiency anemia in children with intestinal failure. Total parenteral nutrition is the most direct way to maintain adequate calorie intake as well as liquid, electrolyte, and micronutrient balance. Parenteral iron was recommended over oral iron for effective treatment of iron deficiency anemia in a systematic study of the use of iron therapy in patients with another intestinal condition, inflammatory bowel disease (Nielsen et al., 2015). Also, number of practitioners believe that intravenous iron should be the preferred route of administration when oral iron intolerance exists, and should be used in all gastrointestinal conditions where oral iron is ineffective (Auerbach et al., 2020). Nonetheless, there is a need to search for an alternative because its use could be linked to potentially severe metabolic and catheter complications, as well as decreased personal satisfaction.

With accessible arising information on the job of teduglutide, an analog of glucagon-like peptide-2 (GLP-2), in streamlining nutritional absorption (Kocoshis et al., 2020), we accept that combined administration of oral iron and teduglutide may diminish the need of parenteral iron treatment and consequently limit PN needs and the related cost (Canovai et al., 2019a; Canovai et al., 2019b).

The research has some limitations, such as a limited sample size and a convenience sampling process. Some confidence intervals are large, indicating a less accurate estimation of the outcome, due to subject variability and limited sample size. Furthermore, it is possible that four weeks of oral iron therapy is not sufficient to anticipate a significant rise in Hb levels.

5. Conclusions

In TPN-dependent patients with intestinal failure, four weeks of oral iron therapy was not effective in treating iron deficiency anemia. In addition, patients who received the treatment experienced a high incidence of diarrhea as an adverse drug reaction.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Dignass, A., Farrag, K., Stein, J., 2018. Limitations of serum ferritin in diagnosing iron deficiency in inflammatory conditions. Int. J. chronic Dis. 2018, 1–11.
Auerbach, M., Behm, B.W., Sankineni, A., 2020. Treatment of iron deficiency in gastroenterology: a new paradigm. Pract. Gastroenterol.
de Vizia, B., Poggi, V., Conenna, R., Fiorillo, A., Scippa, L., 1992. Iron absorption and iron deficiency in infants and children with gastrointestinal diseases. J. Pediatr. Gastroenterol. Nutr. 14 (1), 21–26.
Bielawska, B., Allard, J.P., 2017. Parenteral Nutrition and Intestinal Failure. Nutrients 9, 466. https://doi.org/10.3390/nu9050466.
Breymann, C., Honegger, C., Holzgreve, W., Surbek, D., 2010. Diagnosis and treatment of iron-deficiency anaemia during pregnancy and postpartum. Arch. Gynecol. Obstet. 282 (5), 577–580.
Ingelfinger, J.R., Duggan, C.P., Jaksic, T., 2017. Pediatric intestinal failure. N. Engl. J. Med. 377 (7), 666–675.
Canovai, E., Ceulemans, L.J., Peers, G., De Pourcq, L., Pijpops, M., De Hertogh, G., Hiele, M., Pirenne, J., Vanuytsel, T., 2019a. Cost analysis of chronic intestinal failure. Clin. Nutr. 38 (4), 1729–1736.
Cohen, L.A., Gutierrez, L., Weiss, A., Leichtmann-Bardoogo, Y., Zhang, D.L., Crooks, D. R., Sougrat, R., Morgenstern, A., Galy, B., Hentze, M.W., et al., 2010. Serum ferritin is derived primarily from macrophages through a nonclassical secretory pathway. Blood 116, 1574–1584 [PubMed] [Google Scholar].
Cook, J.D., Finch, C.A., Smith, N.J., 1976. Evaluation of the iron status of a population. Blood 48 (3), 449–455. PMID: 953365.
Das, B., Sivagnanam, M., 2021. Congenital Tufting Enteropathy: Biology, Pathogenesis and Mechanisms. J. Clin. Med. 10 (1), 19. https://doi.org/10.3390/jcm10010019.
Canovai, E. et al., 2019b. Cost analysis of chronic intestinal failure. Clin. Nutr. 38 (4), 1729–1736.
Elin, R.J., Wolff, S.M., Finch, C.A., 1977. Effect of induced fever on serum iron and ferritin concentrations in man. Blood 49, 147–153.
Madanat, F., El-Khateeb, M., Tarawaneh, M., Hijazi, S., 1984. Serum ferritin in evaluation of iron status in children. Acta Haematol. 71 (2), 111–115.
Farrell, M.K., Balistreri, W.F., 1986. Parenteral nutrition and hepatobiliary dysfunction. Clin. Perinatol. 13 (1), 197–212.
Franchini, M., Salvagno, G.L., Montagnana, M., Lippi, G., 2007. Serum ferritin levels correlate with haemoglobin concentration: a report on 589 outpatients from a single centre. Blood Transfus. 5 (4), 244–245. https://doi.org/10.2450/2007.0021-07. PMID: 19204781; PMCID: PMC2581914.
Salvia, G., Guarino, A., Terrin, G., Cascioli, C., Paludetto, R., Indrio, F., Lega, L., Fanaro, S., Stronati, M., Corvaglia, L., Tagliabue, P., De Curtis, M., 2008. Neonatal onset intestinal failure: an Italian Multicenter Study. J. Pediatr. 153 (5), 674–676.e2.
Garcia-Casal, M.N., Pasricha, S.-R., Martinez, R.X., Lopez-Perez, L., Peña-Rosas, J.P., 2015. Serum or plasma ferritin concentration as an index of iron deficiency and overload (Protocol). Cochrane Database Syst. Rev. 7, CD011817 [Google Scholar].
Gerada, J., DeGaetano, J., Sebire, N.J., Hill, S., Vassallo, M., Attard, T.M., 2013. Mucosal inflammation as a component of tufting enteropathy. Immunogastroenterology 2 (1), 62–67.
Saito, H., 2014. Metabolism of iron stores. Nagoya J. Med. Sci. 76 (3–4), 235.
Wang, J., Pantopoulos, K., 2011. Regulation of cellular iron metabolism. Biochem. J. 434 (3), 365–381.
Johnson-Wimbley, T.D., Graham, D.Y., 2011. Diagnosis and management of iron deficiency anemia in the 21st century. Therap. Adv. Gastroenterol. 4 (3), 177–184.
Gardiner, K.R., 2011. Management of acute intestinal failure. Proc. Nutr. Soc. 70 (3), 321–328.
Khalafallah, A.A., Dennis, A.E., 2012. Iron deficiency anaemia in pregnancy and postpartum: pathophysiology and effect of oral versus intravenous iron therapy. J. Pregnancy 2012, 630519.
Khan, A.S., Shah, S.A., 2005. Iron deficient children and significance of serum ferritin. J. Pak. Med. Assoc. 55 (10), 420–423. PMID: 16304848.
Ko, J.S., Seo, J.K., Shim, J.O., Hwang, S.H., Park†, H.S., Kang†, G.H., 2010. Tufting enteropathy with EpCAM mutations in two siblings. Gut. Liver 4 (3), 407–410.
Kocoshis, S.A., Merritt, R.J., Hill, S., Protheroe, S., Carter, B.A., Horslen, S., Hu, S., Kaufman, S.S., Mercer, D.F., Pakarinen, M.P., Venick, R.S., Wales, P.W., Grimm, A. A., 2020. Safety and efficacy of teduglutide in pediatric patients with intestinal failure due to short bowel syndrome: a 24-week, phase III study. J. Parenteral Enteral Nutr. 44 (4), 621–631.
D'Antiga, L., Goulet, O., 2013. Intestinal failure in children: the European view. J. Pediatr. Gastroenterol. Nutr. 56 (2), 118–126.
Pironi, L., Arends, J., Bozzetti, F., Cuerda, C., Gillanders, L., Jeppesen, P.B., Joly, F., Kelly, D., Lal, S., Staun, M., Szczepanek, K., Van Gossum, A., Wanten, G., Schneider, S.M., 2016. ESPEN guidelines on chronic intestinal failure in adults. Clin. Nutr. 35 (2), 247–307.
Krawinkel, M.B., Scholz, D., Busch, A., Kohl, M., Wessel, L.M., Zimmer, K.-P., 2012. Chronic intestinal failure in children. Dtsch. Arztebl. Int. 109 (22–23), 409.
Scott, N.A., Leinhardt, D.J., O'Hanrahan, T., Finnegan, S., Irving, M., Shaffer, J., 1991. Spectrum of intestinal failure in a specialised unit. Lancet 337 (8739), 471–473.
Ozdemir, N., 2015. Iron deficiency anemia from diagnosis to treatment in children. Turkish Arch. Pediatr. Pediatr. Ar{c{s}}ivi 50 (1), 11–19.
Nielsen, Ole Haagen, Ainsworth, Mark, Coskun, Mehmet, Weiss, Günter, 2015. Management of iron-deficiency anemia in inflammatory bowel disease. Medicine 94 (23). https://doi.org/10.1097/MD.0000000000000963.
Allan, P., Lal, S., 2018. Intestinal failure: a review. F1000Research 7.
Rasmussen, S., Bergsjø, P., Jacobsen, G., Haram, K., Bakketeig, L.S., 2005. Haemoglobin and serum ferritin in pregnancy–correlation with smoking and body mass index. Eur. J. Obstet. Gynecol. Reprod. Biol. 123 (1), 27–34. https://doi.org/10.1016/j.ejogrb.2005.02.012. PMID: 16260337.
O'Keefe, S.J.D., Buchman, A.L., Fishbein, T.M., Jeejeebhoy, K.N., Jeppesen, P.B., Shaffer, J., 2006. Short bowel syndrome and intestinal failure: consensus definitions and overview. Clin. Gastroenterol. Hepatol. 4 (1), 6–10.
Lal, S., Teubner, A., Shaffer, J.L., 2006. intestinal failure. Aliment. Pharmacol. Ther. 24 (1), 19–31.

Ton, S.H., Lopez, C.G., 1980 Mar. Serum ferritin concentrations in male Malaysian blood donors. Southeast Asian J. Trop. Med. Public Health 11 (1), 87–90. PMID: 7403958.

Vanek, V.W., Borum, P., Buchman, A., Fessler, T.A., Howard, L., Jeejeebhoy, K., Kochevar, M., Shenkin, A., Valentine, C.J., 2012. A.S.P.E.N. position paper: recommendations for changes in commercially available parenteral multivitamin and multi–trace element products. Nutr. Clin. Pract. 27 (4), 440–491.

Warner, M.J., Kamran, M.T., 2021 Jan. Iron Deficiency Anemia. [Updated 2020 Aug 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. Available from: https://www.ncbi.nlm.nih.gov/books/NBK448065/

Worwood, M., 1980 Feb 16. Serum ferritin and iron deficiency anaemia in hospital patients. Lancet 1 (8164), 375–376. https://doi.org/10.1016/s0140-6736(80)90929-0. PMID: 6101836.