

## Observational Study

## Inpatient management of iron deficiency anemia in pediatric patients with inflammatory bowel disease: A single center experience

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## Abstract

## BACKGROUND

Screening for iron deficiency anemia (IDA) is important in managing pediatric patients with inflammatory bowel disease (IBD). Concerns related to adverse reactions may contribute to a reluctance to prescribe intravenous (IV) iron to treat IDA in this population.

## AIM

To track the efficacy and safety of IV iron therapy in treating IDA in pediatric IBD patients admitted to our center.

## METHODS

A longitudinal observational cohort study was performed on 236 consecutive pediatric patients admitted to our tertiary IBD care center between September 2017 and December 2019. 92 patients met study criteria for IDA, of which 57 received IV iron, 17 received oral iron, and 18 were discharged prior to receiving iron therapy.

## RESULTS

Patients treated with IV iron during their hospitalization experienced a significant increase of 1.9 ( $\pm 0.2$ ) g/dL in mean ( $\pm$  SE) hemoglobin (Hb) concentration by the first ambulatory follow-up, compared to patients who received oral iron 0.8 ( $\pm 0.3$ ) g/dL or no iron 0.8 ( $\pm 0.3$ ) g/dL ( $P = 0.03$ ). One out of 57 (1.8%) patients that received IV iron therapy experienced an adverse reaction.

## CONCLUSION

Our findings demonstrate that treatment with IV iron therapy is safe and efficacious in improving Hb and iron levels in pediatric patients with IDA and active IBD.

**Key Words:** Iron deficiency anemia; Pediatric inflammatory bowel disease; Intravenous iron therapy; Inflammatory bowel disease

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**Core Tip:** In summary, in our single center study, we found oral iron generally ineffective in pediatric patients with inflammatory bowel disease and active inflammation. Parenteral iron met the primary clinical goal of the study (a 1g/dL increase in hemoglobin). Addressing inflammation without targeted therapy for iron deficiency is unlikely to correct the anemia associated with iron deficiency.

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## INTRODUCTION

Anemia is one of the most common extraintestinal manifestations observed in patients with inflammatory bowel disease (IBD)[1]. Iron deficiency is the leading cause of anemia in these patients, and it is more prevalent in children and adolescents with IBD than adults[1,2]. Iron deficiency anemia (IDA) in pediatric patients with IBD is likely due to a combination of factors, including inadequate dietary intake, iron malabsorption, gastrointestinal (GI) blood loss, and reduced iron utilization[3]. Persistent IDA increases IBD-related morbidity, and its severity is inversely correlated with patient quality of life[4,5]. The clinical impact of IDA falls disproportionately on pediatric patients with IBD due to the potential for negative impact on physical and cognitive development during childhood[6].

There are published guidelines outlining the need to include IDA screening and treatment in managing pediatric patients with IBD[7-9]. Oral iron has been shown to be cost-effective in managing IDA[7]. However, this approach is limited by poor compliance[10,11], malabsorption, and decreased utilization of orally administered iron in the context of chronic inflammation[12,13]. Data from several comparative studies have demonstrated that intravenous (IV) iron therapy may be a better approach than oral iron to correct IDA, particularly in patients with active disease[14,15]. Nevertheless, there is mixed enthusiasm about the use of IV iron in children[16]. This reluctance likely arises from concerns about adverse reactions associated with IV iron administration and the lack of published data on the clinical efficacy and safety of newer IV iron formulations in this patient population[8].

The primary aim of this observational study was to prospectively evaluate the efficacy and safety of IV iron therapy for managing IDA in pediatric patients admitted to our center to manage clinical exacerbations of their IBD.

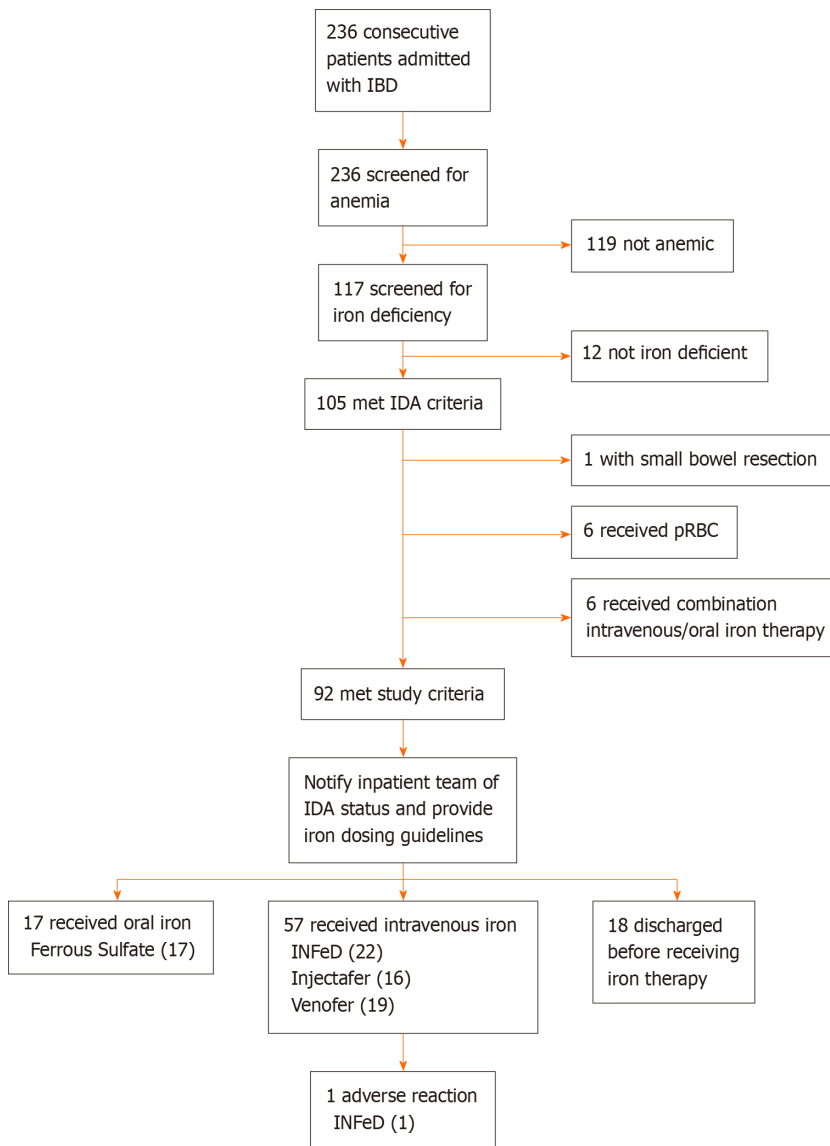
## MATERIALS AND METHODS

### Study design

This prospective, open-label, observational cohort study examined consecutive patients ( $\leq 23$  years of age) admitted to Boston Children's Hospital (BCH) to manage clinically active IBD between September 2017 and December 2019. This study was approved by the Boston Children's Hospital Institutional Review Board (IRB #P00024515).

IDA was based on laboratory values and iron studies [ferritin, serum iron, and total iron-binding capacity (TIBC)] obtained on admission. Patients were screened using the electronic medical record to identify those with an established diagnosis of IBD using the Porto Criteria, including ulcerative colitis (UC), Crohn's disease (CD), and indeterminate colitis (IC). Exclusion criteria included known or suspected concurrent infection, a history of small bowel resection or colectomy requiring packed red blood cell transfusion, or treatment with concurrent IV and oral iron therapy between admission and first follow-up visit (Figure 1).

Anemia was defined according to the World Health Organization criteria as hemoglobin (Hb)  $< 11.5$  g/dL for patients 5-11 years of age,  $< 13$  g/dL in males 12 years and older, and  $< 12$  g/dL in females 12 years and older[17]. Iron deficiency was indicated by one of the following: Serum iron  $< 59$  mg/dL, TIBC  $> 450$  mg/dL, ferritin  $< 100$   $\mu$ g/dL in the presence of an elevated C-reactive protein (CRP) ( $> 1$  mg/dL) or ferritin  $< 30$   $\mu$ g/dL in the presence of a normal CRP (0-1 mg/dL). These standards follow published guidelines for diagnosing and treating IDA in patients with IBD[18,19].



**Figure 1 Study overview.** IBD: Inflammatory bowel disease; IDA: Iron deficiency anemia; pRBC: Packed red blood cell; INFeD: Low-molecular-weight iron dextran.

Research Study Coordinators reviewed the inpatient census daily to assess patient laboratory studies. They notified clinical staff of patients meeting the criteria for iron deficiency and provided them with information about the parenteral IV formulations available on the hospital formulary and dosing guidelines using a standardized electronic template. The inpatient team subsequently made all decisions concerning the preparation and dose of parenteral or oral iron prescribed for individual patients. The recommended repletion dose of IV iron was based on a validated metric that took into account lean body weight (LBW), as well as measured and target Hb levels ( $Hb_0$  and  $Hb_t$  g/dL, respectively) (Equation 1).

$$\text{Dose (mg)} = 0.0442 \times \text{LBW (kg)} \times (Hb_t - Hb_0) + [0.26 \times \text{LBW (kg)}] \times 50 \text{ mg/mL (1)}$$

LBW was determined using each patient's total body mass and height[20]. Target hemoglobin ( $Hb_t$ ) was determined from total body mass: If  $< 15$  kg,  $Hb_t = 12.0$  g/dL; if  $\geq 15$  kg,  $Hb_t = 14.8$  g/dL[21].

Information provided to clinicians was made in conjunction with BCH Pharmacy staff and product insert guidelines. Iron sucrose (Venofer) was recommended for use in patients requiring a calculated repletion dose of elemental iron  $< 300$  mg (to a maximum dose of 7 mg/kg). Ferric carboxymaltose (Injectafer) was recommended for patients requiring a repletion dose from 300-750 mg. Low-molecular-weight iron dextran (INFeD) was recommended for those patients requiring a repletion dose that was  $> 750$  mg (to a maximum dose of 2000 mg) or in patients unable to receive iron sucrose due to the total dose being greater than 7 mg/kg. Study patients completed repeat iron studies during their first ambulatory follow-up visit after discharge.

This study was uncontrolled, and clinicians treated patients with whichever IV or oral iron supplementation they felt was clinically indicated. Some patients were discharged on no iron treatment at all. This decision was likely related to patient or provider preference or a conscious decision to focus clinical efforts on managing a patient's underlying IBD. Clinicians caring for patients admitted for a shorter duration had less opportunity to screen for iron deficiency, review the results, and initiate inpatient IV iron repletion therapy before discharge. Research Study Coordinators were not available to screen patients on the weekends. Nonetheless, data about these untreated patients were recorded and included for

comparative analysis (Figure 1).

### Efficacy assessment

The efficacy of iron supplementation was defined as a  $\geq 1$  g/dL increase between pre-and post-treatment Hb and an improvement in iron status based on pre- and post-treatment iron studies (ferritin, serum iron, and TIBC).

### Safety assessment

Safety was evaluated by reviewing the electronic medical record for adverse events from the onset of IV iron therapy administration to the first ambulatory follow-up after discharge.

### Statistical analysis

Baseline characteristics, including age at admission, sex, IBD diagnosis and phenotype, and disease duration, are described by frequency count (and percentage) when categorical and by median (interquartile range; IQR) when continuous. Comparisons across iron therapy groups (no iron, oral iron, IV iron) were made by the Fisher exact and Kruskal-Wallis tests, respectively.

Changes in laboratory parameters from baseline assessment until the first follow-up visit were assessed with a repeated-measures linear regression model adjusted for the corresponding baseline lab, age at admission, sex, diagnosis, baseline iron dose, and the number of days between admission follow-up labs. Estimates at admission, first follow-up, and change from admission to follow-up are presented as mean  $\pm$  standard error (SE). Comparison between treatment groups (IV iron, oral iron, no iron) or within-group changes over time are shown as mean [95% confidence interval (CI)], and pairwise comparisons are corrected for multiple comparisons using the Holm's step-down Bonferroni procedure. Assessment of normality was made by the Shapiro-Wilk test. Data for labs that were not normally distributed were transformed using a rank-based inverse normal transformation[22,23]. The results were consistent with the non-transformed data in all cases, and only the latter were reported.

All comparisons were 2-sided, with  $P < 0.05$  indicating statistical significance. Data analysis and figures were accomplished with SAS version 9.4 (Cary, NC).

## RESULTS

### Demographic data

A total of 105 patients (44% of those screened) met the criteria for IDA, of which 92 (40%) met the study criteria. The median age of patients in this cohort was 15 years (range: 1-23), and 41 (45%) were female. All patients included in the study met the criteria for active IBD, of which forty-seven patients (51%) had CD, 41 (45%) had UC, and 4 (4%) had IC. The median disease duration was 1.4 months (IQR: 0.1-31.2). Of the 47 patients with CD, 28 (60%), 10 (21%), and 9 (19%) had an inflammatory, penetrating, and stricturing phenotype, respectively. Of the 41 patients with UC, 34 (83%) had pancolitis, and 7 (17%) had left-sided colitis. Fifty-seven patients (62%) received IV iron therapy, 17 (18%) received oral iron, and 18 (20%) received no iron therapy (Table 1).

### Hb and mean corpuscular volume

This was a longitudinal observational study of real-time clinical practice. The first ambulatory follow-up visit after discharge was not protocolized and was scheduled at the discretion of the discharging provider and contingent on physician and patient availability. The median follow-up time was 32 d (IQR: 20-58) following admission. Changes in lab assessments from baseline to first follow-up were examined by repeated-measures regression adjusted for baseline lab, age at admission, sex, diagnosis, baseline iron dose, and the number of days between admission and follow-up labs. There was a significant change in Hb concentration observed in those who received IV iron therapy with a mean  $\pm$  SE increase of  $1.9 \pm 0.2$  mg/dL, compared to  $0.8 \pm 0.3$  mg/dL ( $P = 0.02$ ) and  $0.8 \pm 0.3$  mg/dL ( $P = 0.02$ ) in patients receiving either oral or no iron, respectively (Table 2). The mean Hb change met the study's predetermined criteria for efficacy (Hb increase  $\geq 1$ g/dL) only in patients who received IV iron. Likewise, there was a statistically significant improvement in mean corpuscular volume of  $6.0 \pm 0.6$  fL in patients treated with IV iron compared to those treated with oral iron  $2.8 \pm 1.1$  ( $P = 0.02$ ) or no iron  $1.6 \pm 1.1$  fL ( $P = 0.001$ ), respectively (Table 2).

### Biochemical disease activity

There was no statistically significant difference in baseline erythrocyte sedimentation rate (ESR) ( $P = 0.66$ ) and baseline CRP ( $P = 0.67$ ) in patients subsequently treated with IV, oral, or no iron therapy. This was similarly the case concerning longitudinal changes in ESR and CRP. Although longitudinal changes in ESR were evident within each treatment group (IV:  $-16 \pm 4$  mm/h, oral:  $-20 \pm 8$  mm/h, and no iron therapy:  $-17 \pm 8$  mm/h), the changes were not statistically different from one another when compared across groups ( $P = 0.94$ ). This was similarly the case for CRP (IV:  $-3.2 \pm 0.7$  mm/h, oral:  $-2.4 \pm 1.4$  mm/h, and no iron therapy:  $-1.8 \pm 1.3$  mm/h;  $P = 0.63$ ) (Table 2).

### Iron studies

Paired iron parameters, including TIBC, ferritin, and serum iron, were available in 64/92 (70%), 66/92 (72%), and 65/92 (71%) of patients in the cohort, respectively. IV iron therapy was the only treatment modality associated with an increase in ferritin (from  $79 \pm 15$   $\mu$ g/dL to  $167 \pm 18$   $\mu$ g/dL,  $P = 0.0006$ ). In contrast, ferritin levels decreased in those patients

**Table 1** Subject characteristics (*n* = 92)

	Overall ( <i>n</i> = 92)	Iron therapy			<i>P</i> value
		No iron ( <i>n</i> = 18)	Oral iron ( <i>n</i> = 17)	IV iron ( <i>n</i> = 57)	
Age (years), median (IQR)	15 (11–18)	13 (10–18)	15 (13–17)	15 (11–18)	0.70
Female sex, <i>n</i> (%)	41 (45)	10 (56)	7 (41)	24 (42)	0.63
IBD diagnosis, <i>n</i> (%)					0.008
CD	47 (51)	16 (89)	4 (24)	27 (47)	
UC	41 (45)	2 (11)	11 (65)	28 (49)	
IC	4 (4)	0 (0)	2 (12)	2 (4)	
Disease duration (months), median (IQR)	1.4 (0.1–31.2)	19.6 (0.1–82.3)	1.0 (0.2–16.6)	1.5 (0.1–24.6)	0.58
CD phenotype, <i>n</i> (%)					0.41
Inflammatory	28 (60)	9 (56)	1 (25)	18 (67)	
Fistula	10 (21)	4 (25)	2 (50)	4 (15)	
Stricture	9 (19)	3 (19)	1 (25)	5 (19)	
UC phenotype, <i>n</i> (%)					0.76
Pancolitis	34 (83)	2 (100)	10 (91)	22 (79)	
Left-sided colitis	7 (17)	0 (0)	1 (9)	6 (21)	

IQR: Interquartile range; IBD: Inflammatory bowel disease; IV: Intravenous; UC: Ulcerative colitis; CD: Crohn's disease; IC: Indeterminate colitis.

receiving either oral iron (from  $82 \pm 31$  µg/dL to  $15 \pm 54$  µg/dL,  $P = 0.30$ ) or no iron (from  $117 \pm 30$  µg/dL to  $70 \pm 58$  µg/dL,  $P = 0.45$ ) (Table 2). In addition, only treatment with IV iron increased ferritin levels above 100 µg/dL, thereby raising this parameter above the biochemical threshold supporting a diagnosis of iron deficiency. The mean  $\pm$  SE increase in serum iron was greater in those treated with IV iron ( $30.3 \pm 4.9$  mg/dL) compared to those treated with either oral iron ( $26.8 \pm 12.3$  mg/dL) or no iron ( $10.7 \pm 13.6$  mg/dL). However, this difference did not reach statistical significance ( $P = 0.41$ ) (Table 2). While there was an increase in TIBC among all three treatment groups in the interval between their admission and their first follow-up ambulatory visit, the increase in TIBC was smaller in patients treated with IV iron therapy ( $23 \pm 15$  mg/dL,  $P = 0.15$ ) compared to those who received either oral ( $108 \pm 37$  mg/dL,  $P = 0.006$ ) or no iron ( $101 \pm 39$  mg/dL,  $P = 0.01$ ) (Table 2); however, after adjustment for multiple comparisons, the changes from admission to first follow-up were not statistically different from one another.

### Comparison of IV iron formulations

Among 57 patients who were treated with IV iron, 22 (39%) received INFeD, 19 (33%) were treated with iron sucrose (Venofer), and 16 (28%) with ferric carboxymaltose (Injectafer). Median (IQR) dose was 1119 (761–1320) mg for INFeD, 234 (120–300) mg for Venofer, and 750 (548–750) mg for Injectafer. After adjusting for baseline lab, age at admission, sex, diagnosis, baseline iron dose, and the number of days between admission and follow-up labs, all three parenteral iron therapies proved efficacious, resulting in an increase in Hb of at least 1 g/dL from pre- to post-treatment. Both Injectafer and INFeD elicited a greater change in mean  $\pm$  SE Hb concentration ( $2.4 \pm 0.3$  mg/dL and  $2.2 \pm 0.3$  mg/dL, respectively) compared to that observed in patients receiving Venofer ( $1.0 \pm 0.3$  mg/dL) ( $P = 0.02$  for each comparison) (Table 3). Likewise, changes in serum iron levels were significantly higher in response to treatment with Injectafer ( $57.7 \pm 9.7$  mg/dL,  $P = 0.001$ ) and INFeD ( $41.7 \pm 7.3$  mg/dL,  $P = 0.006$ ) compared to those treated with Venofer ( $8.3 \pm 7.1$  mg/dL) (Table 3). Changes in ferritin levels observed in patients receiving the three different IV iron formulations resulted in a non-significant  $P$  value ( $P = 0.30$ ) (Table 3). There were no significant differences in the change in Hb, serum iron, and ferritin between patients treated with Injectafer and those treated with INFeD.

### Adverse events

Only 1/57 (1.8%; 95%CI: 0.04%–9.4%) of patients who received IV iron therapy had an adverse reaction noted in their electronic medical record. This patient was a three-year-old with very early onset IBD and no prior history of atopy. He was administered INFeD and developed an anaphylactoid reaction (Figure 1). There was no prior history of allergies noted in the patient's medical record, and he had not received any IV iron in the past. The patient was stabilized and required one additional day of inpatient observation prior to discharge.

Table 2 Iron studies (*n* = 92)

		Iron therapy			P value
		No iron ( <i>n</i> = 18)	Oral iron ( <i>n</i> = 17)	IV iron ( <i>n</i> = 57)	
Hb (g/dL) ( <i>n</i> = 92)	Admission	10.4 ± 0.2	10.0 ± 0.2	9.7 ± 0.1	0.003
	Follow-up	11.2 ± 0.2	10.8 ± 0.2	11.6 ± 0.1	
	Change	0.8 ± 0.3 <sup>a</sup>	0.8 ± 0.3 <sup>a</sup>	1.9 ± 0.2 <sup>b</sup>	
MCV (fL) ( <i>n</i> = 92)	Admission	78.8 ± 0.8	78.6 ± 0.7	78.2 ± 0.4	0.0004
	Follow-up	80.4 ± 0.8	81.4 ± 0.8	84.2 ± 0.4	
	Change	1.6 ± 1.1 <sup>a</sup>	2.8 ± 1.1 <sup>a</sup>	6.0 ± 0.6 <sup>b</sup>	
CRP (mg/dL) ( <i>n</i> = 85)	Admission	3.8 ± 0.8	3.2 ± 0.8	4.0 ± 0.4	0.63
	Follow-up	1.9 ± 0.9	0.8 ± 0.9	0.8 ± 0.4	
	Change	-1.8 ± 1.3	-2.4 ± 1.4	-3.2 ± 0.7	
ESR (mm/1h) ( <i>n</i> = 80)	Admission	48 ± 5	42 ± 5	44 ± 3	0.94
	Follow-up	31 ± 6	23 ± 6	27 ± 3	
	Change	-17 ± 8	-20 ± 8	-16 ± 4	
TIBC (μg/dL) ( <i>n</i> = 64)	Admission	284 ± 19	296 ± 19	301 ± 9.1	0.04
	Follow-up	385 ± 35	404 ± 29	323 ± 10.7	
	Change	101 ± 39 <sup>a</sup>	108 ± 37 <sup>a</sup>	23 ± 15 <sup>a</sup>	
Ferritin(μg/dL) ( <i>n</i> = 66)	Admission	117 ± 30	82 ± 31	79 ± 15	0.02
	Follow-up	70 ± 58	15 ± 54	167 ± 18	
	Change	-46 ± 61 <sup>a</sup>	-67 ± 61 <sup>a</sup>	88 ± 23 <sup>b</sup>	
Iron (μg/dL) ( <i>n</i> = 65)	Admission	34.5 ± 6.9	26.6 ± 6.7	23.7 ± 3.2	0.41
	Follow-up	45.3 ± 12.8	53.4 ± 10.6	54.0 ± 3.8	
	Change	10.7 ± 13.6	26.8 ± 12.3	30.3 ± 4.9	

<sup>a</sup>*P* < 0.05.<sup>b</sup>*P* < 0.01.

Effects with different superscripts are statistically significant, mean ± standard error at admission, follow-up encounter, and change over time are shown. Results are from a repeated measures linear model adjusted for baseline outcome, age at admission, sex, diagnosis, baseline iron dose, and the number of days between admission and follow-up labs. After adjustment for multiple comparisons, the differences between total iron binding capacity and ferritin are not significant. Hb: Hemoglobin; MCV: Mean corpuscular volume; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; TIBC: Total iron binding capacity.

## DISCUSSION

Data collected from our single-center study demonstrate the safety and efficacy of parenteral iron administration in a population of children and young adults with IBD and IDA. Patients who received IV iron experienced a significant rise (greater than 1g/dL) in their Hb level in the interval between their admission and first post-discharge ambulatory follow-up visit. Only one adverse event was recorded during the study period.

The prevalence of IDA (44%) observed in this study is consistent with previous reports of IDA in pediatric patients with IBD[9,24-26]. After controlling for baseline Hb levels and the number of days between admission and the first ambulatory follow-up, we observed that the subset of patients with IDA who were not treated with iron or who were treated with oral iron experienced a minimal change in their Hb level. In contrast, patients receiving IV iron experienced significant increases in Hb levels by their first ambulatory follow-up visit, which occurred at a median duration of 32 d following discharge.

IV iron therapy was the only treatment modality that increased serum ferritin levels, whereas ferritin levels declined in patients receiving oral iron or no iron therapy. Serum ferritin is a non-specific acute-phase reactant that is elevated during periods of active inflammation[7]. The rise in ferritin levels observed in patients treated with IV iron and not with oral iron has been previously reported in a randomized controlled trial assessing these two treatment modalities in managing IDA in adults with IBD[14]. This suggests that tracking serum ferritin levels in the context of inflammation may be a misleading metric for assessing the response to oral or parenteral iron administration.



Table 3 Comparison of intravenous iron types (*n* = 57)

		Iron therapy			P value	Difference (95%CI)		
		Venofer ( <i>n</i> = 19)	Injectafer ( <i>n</i> = 16)	INFeD ( <i>n</i> = 22)		Injectafer-Venofer	INFeD-Venofer	Injectafer-INFeD
Hb (g/dL) ( <i>n</i> = 57)	Admission	9.4 ± 0.3	9.5 ± 0.2	9.4 ± 0.2				
	Follow-up	10.5 ± 0.3	11.9 ± 0.2	11.7 ± 0.2				
	Change	1.0 ± 0.3 <sup>a</sup>	2.4 ± 0.3 <sup>b</sup>	2.2 ± 0.3 <sup>b</sup>	0.009	1.3 (0.2, 2.5) <sup>a</sup>	1.2 (0.1, 2.3) <sup>a</sup>	0.1 (-1.0, 1.2)
Ferritin (µg/dL) ( <i>n</i> = 43)	Admission	117 ± 36	82 ± 33	73 ± 36				
	Follow-up	153 ± 39	183 ± 45	206 ± 42				
	Change	37 ± 43	101 ± 57	133 ± 44	0.3	64 (-118, 247)	96 (-61, 254)	-32 (-215, 151)
Iron (µg/dL) ( <i>n</i> = 43)	Admission	19.2 ± 6.5	23.0 ± 5.8	25.3 ± 6.5				
	Follow-up	27.5 ± 7.0	80.7 ± 8.0	67.1 ± 7.4				
	Change	8.3 ± 7.1 <sup>a</sup>	57.7 ± 9.7 <sup>b</sup>	41.7 ± 7.3 <sup>b</sup>	0.0006	49.4 (18.5, 80.2) <sup>c</sup>	33.5 (7.4, 59.6) <sup>b</sup>	15.9 (-15.0, 46.8)

<sup>a</sup>*P* < 0.05.<sup>b</sup>*P* < 0.01.<sup>c</sup>*P* < 0.001.

Effects with different superscripts are statistically significant at *P* < 0.05, mean ± standard error at admission, follow-up encounter, and change over time are shown. Results are from a repeated measures linear model adjusted for baseline outcome, age at admission, sex, diagnosis, baseline iron dose, and the number of days between admission and follow-up labs. The 95% confidence interval is adjusted for multiple comparisons using the Bonferroni step-down procedure. Hb: Hemoglobin; CI: Confidence interval; INFeD: Low-molecular-weight iron dextran.

The marginal improvement in hematologic and iron parameters observed in patients treated with oral iron therapy in this study may be explained by a combination of factors. Inflammatory cytokines released during chronic active inflammation can decrease iron absorption and utilization. Interleukin-6, in particular, upregulates hepatic production and release of hepcidin[27]. This signaling molecule impedes iron transport by inhibiting ferroportin channels in the enterocytes lining the small intestine[28,29]. It is also plausible that the blunted response to oral iron therapy could be related to ongoing GI blood loss. Furthermore, adverse GI side effects negatively impact long-term compliance with oral iron therapy, including nausea, diarrhea, abdominal pain, and pill fatigue[10]. Thus, the increased bioavailability of IV iron, combined with its lack of reliance on patient adherence, makes parenteral iron a more reliable alternative to addressing IDA in this vulnerable pediatric patient population and has been recommended as first-line treatment in patients with active IBD, severe anemia (Hb < 10g/dL), or previous intolerance to oral iron by the European Crohn's and Colitis Organization in 2015[18].

The reluctance to use IV iron in pediatric patients with IBD and IDA may be rooted in concern for serious adverse events, including anaphylaxis, which had been previously reported with the use of high-molecular-weight iron dextran [30]. However, newer low-molecular-weight and polysaccharide-based IV iron formulations, including those employed in the present study, have a much better safety profile in the pediatric IBD population[30-33]. We observed only one adverse event in this study, which coincided with administering INFeD.

Patients receiving INFeD and ferric carboxymaltose (Injectafer) experienced a greater increase in their Hb levels than those receiving iron sucrose (Venofer) in this study. This is likely related to the higher dose of infused iron permissible with INFeD and Injectafer. Of the IV iron formulations used in this study, we found INFeD and Injectafer more effective than Venofer for improving mean Hb and iron status by the time of a patient's first ambulatory follow-up visit. This is not surprising, as INFeD can be administered in doses as high as 2 g during a single infusion, while ferric carboxymaltose and iron sucrose are limited to 750 mg and 300 mg, respectively[34]. As such, patients receiving Venofer may require multiple infusions to achieve iron repletion. Injectafer allows for a more rapid IV iron infusion, taking only fifteen minutes to deliver a maximum dose[35]. There are reports of ferric carboxymaltose being associated with a higher incidence of hypophosphatemia than other IV iron preparations[36-39]. Previous meta-analysis revealed that patients receiving ferric carboxymaltose were at a significantly higher risk of hypophosphatemia related to those treated with iron sucrose [risk ratio (RR): 9.40, 95%CI: 2.30-33.0], iron isomaltose (RR: 7.90, 95%CI: 2.10-28.0), INFeD (RR: 6.60, 95%CI: 1.91-220.0), and ferumoxytol (RR: 24.0, 95%CI: 2.50-220.0)[38]. As such, phosphate monitoring may be warranted in patients receiving ferric carboxymaltose therapy to identify and address hypophosphatemia and its associated sequelae[39].

Our data demonstrate that patients with IBD and IDA who were not treated with IV iron therapy did not experience a significant change in their mean Hb level between their baseline and their first ambulatory follow-up visit. Of relevance, IDA did not resolve in patients who had otherwise responded favorably (comparable decreases in ESR and CRP levels) to medical therapy. In contrast to previous tenets suggesting that iron deficiency would resolve when the underlying inflammation was corrected, our data suggest that in the absence of targeted iron therapy, correction of the underlying inflammatory response is insufficient to resolve iron homeostasis in patients with IBD. Instead, many of these patients will likely experience a clinical or biochemical improvement (ESR and CRP) in the context of ongoing IDA. This

observation underscores the need for early recognition and active management of IDA in pediatric IBD care.

Our previous retrospective study found that only 32% of patients with UC and IDA admitted to our Center between 2003 and 2014 were treated with oral iron, and none had been treated with IV iron by discharge<sup>[40-43]</sup>. In contrast, 81% of patients with IBD and IDA admitted during the study period between 2017 and 2019 were identified and treated (77% with IV iron) during their hospitalization. It's likely that the engagement with Research Study Coordinators raised awareness of IDA in patients with IBD, educated providers about dosage calculations and the availability of parenteral iron preparations, and increased the level of provider comfort with respect to ordering parenteral iron therapy. Together, these factors likely contributed to a greater percentage of patients being identified and treated for IDA.

Our study's strength is derived from its sample size and observational longitudinal cohort design, which allowed us to evaluate changes in Hb and iron levels over time in individuals and groups of patients. This study has limitations, including the fact that this was a single-center, non-randomized design. As such, we could not actively control which patients received each treatment option nor the dosage of iron administered. Also, the ultimate choice of IV iron preparation used may have been affected by provider bias. As such, a more complete evaluation of the association between changes in Hb and iron levels in response to IDA therapy is clearly warranted.

## CONCLUSION

In conclusion, our findings demonstrate that treatment with parenteral iron therapy is most likely to result in a significant improvement in Hb levels in pediatric patients admitted with IBD and IDA. Conversely, we found no significant changes in Hb levels in patients receiving oral or no iron therapy. Correction of IDA appears to occur independent of other biochemical responses to therapy, including changes in inflammatory (ESR and CRP) markers. As such, IDA may persist without directed therapy, even in patients who otherwise respond to effective corticosteroid, biologic, or other immunosuppressive therapies. IV iron therapy was safe and effective for managing IDA in our pediatric patients with IBD hospitalized for worsening disease activity. More extensive prospective studies are needed to investigate further the efficacy and safety of IV iron therapy in IDA in children with IBD.

## ARTICLE HIGHLIGHTS

### Research background

Screening for iron deficiency anemia (IDA) is uniformly recommended but may not always occur in the management of pediatric patients with acute exacerbation of their inflammatory bowel disease (IBD). In addition, clinicians may be hesitant to use intravenous (IV) iron in practice in the active IBD population due to concerns about adverse reactions reported in prior IV formulations. Our study sought to evaluate the efficacy and safety profile of IV iron therapy in pediatric patients with IDA admitted to our tertiary care center for their active IBD.

### Research motivation

The significance of this research is that it provides additional data on the efficacy and safety profile of the newer IV iron preparations in pediatric patients with active IBD. This research will provide data in directing management of pediatric patients with IDA and active IBD.

### Research objectives

The primary aim of this observational study was to prospectively evaluate the efficacy and safety of IV iron therapy for managing IDA in pediatric patients admitted to our center to manage clinical exacerbation of their IBD. The significance of achieving these objectives will allow providers caring for such patients to know the efficacy and safety profile of the newer iron preparations and possible expected outcomes.

### Research methods

We performed a prospective, open-label, observational cohort study to evaluate our study aims. Research Study Coordinators reviewed the inpatient census daily to assess patient laboratory studies. They notified clinical staff of patients meeting the criteria for iron deficiency and provided them with information about the IV iron formulations available on the hospital formulary and dosing guidelines using a standardized electronic template. The inpatient team subsequently made all decisions concerning the preparation and dose of IV or oral iron prescribed for individual patients. The observational longitudinal cohort design allows us to evaluate changes in hemoglobin (Hb) and iron levels over time in individuals and groups of patients.

### Research results

First, we found that IV iron is more efficacious than oral or no iron therapy in increasing Hb levels by their first ambulatory follow-up after receipt of iron therapy. This suggests that IV iron therapy is a more efficacious option in elevating Hb levels by the time of first ambulatory follow-up. Second, we found that IV iron was overall a safe option in the repletion of IDA in this pediatric IBD population with only 1/57 adverse events reported. This suggests that IV iron is a safe option in this patient population. Third, IDA did not resolve in patients who had otherwise responded favorably



(comparable decreases in erythrocyte sedimentation rate and C-reactive protein levels) to medical therapy. In contrast to previous tenets suggesting that iron deficiency would resolve when the underlying inflammation was corrected, our data suggest that in the absence of targeted iron therapy, correction of the underlying inflammatory response is insufficient to resolve iron homeostasis in patients with IBD.

### Research conclusions

Our single-center study shows that IV iron is safe and efficacious in treating IDA in children with active IBD. Our data further demonstrate that addressing inflammation is insufficient to correct iron deficiency and that successful treatment of iron deficiency in pediatric patients with IBD warrants active management.

### Research perspectives

More extensive prospective studies are needed to investigate further the efficacy and safety of IV iron therapy in IDA in children with IBD.

## FOOTNOTES

**Co-first authors:** Krishanth Manokaran and Jonathan Spaan.

**Author contributions:** Manokaran K and Spaan J contributed equally to this work; Rufo PA conceptualized the study; Rufo PA, Manokaran K, and Spaan J conceived methodology; Mitchell PD performed formal statistical analysis; Manokaran K, Spaan J, Cataldo G, and Lyons C performed data collection; Manokaran K, and Spaan J prepared original draft; Rufo PA, Mitchell PD, and Zimmerman LA helped review and edit manuscript; Rufo PA and Sare T provided resources and project administration; All authors have read and agree to the published version of the manuscript.

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