A Review of the Appropriate Usage and Efficacy of Iron Replacement Therapy in Gastroenterology Inpatients: Is Intravenous Iron Overutilized?

by

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ABSTRACT

Background:

Iron deficiency anemia (IDA) is highly prevalent in patients with gastrointestinal disease. Therefore, appropriate replacement therapy is an essential component of management. Both intravenous (IV) and oral (PO) iron replacement therapies (IRT) are effective. There are concerns, however, that IV therapy is being overutilized. Given higher medication costs, significant time burdens on patients and nursing staff, and reported similar efficacy to PO therapy in select patients, the use of IV therapy should be judicious. Our study reviewed the use of iron replacement therapy amongst gastroenterology inpatients at a tertiary care center. The objectives of our study were to assess the appropriateness of IV iron use, compare patients' clinical responses to IV and PO therapy, and evaluate predictors of response.

Methods:

This study was a retrospective observational chart review. All consecutive patients admitted to the adult gastroenterology inpatient wards between January 1, 2016, to January 1, 2017, who received iron replacement therapy were included. Demographic information was retrieved for all patients. We reviewed patients' iron therapy details, hemoglobin response and clinical outcomes up to 6 months post-discharge.

Results:

A total of 202 patients who received IV, oral, or combined IV and oral iron replacement during their admission were included. 56% (n=96/172) of patients in whom IV

replacement was prescribed during their admission met the criteria for appropriate use. Overall clinical response was not significantly different between patients receiving IV or PO iron therapy. There were no significant differences between groups in readmission rates within 90 days (p=0.41), emergency department visits within 90 days (p=0.24) and need for blood transfusion within 6 months (p=0.11).

Conclusion:

IV IRT is effective but is overused without appropriate indication. PO and IV IRT had similar efficacy. Appropriate usage of IV iron replacement can be optimized through proper rationalization and quality improvement measures.

PREFACE

This thesis is an original work by Suqing Li. The research project, of which this thesis is part, received research ethics approval from the University of Alberta Research Ethics Board, Project name “A Retrospective Review of Iron Replacement Therapy in Gastroenterology Inpatients”, ID No. Pro00079194, February 8, 2018.

The study idea and design were conceptualized by S. Li and S. Van Zanten in collaboration with H. Rempel and D. Perez from the gastroenterology nursing department at the University of Alberta Hospital (UAH). Data extraction of pharmacy records for intravenous iron and oral iron prescriptions were obtained via collaboration with O. Ghutmey from gastroenterology clinical pharmacy services at the UAH. Literature review, data collection & analysis, concluding analysis and discussion are my original work.

Preliminary results of this thesis were published in abstract form as **Li S**, Ghutmy O, Rempel H, Perez D, Gonzalez-Abraldes J and Van Zanten SV. Sa1089 A Retrospective Review of Intravenous Iron Therapy in Gastroenterology Inpatients: A Single Center Experience. *Gastroenterology*. Volume 156(6) Supplement 1: S-266.

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1 INTRODUCTION & LITERATURE REVIEW

1.1 IRON DEFICIENCY ANEMIA AND IRON REGULATION

Anemia is a condition of low red blood cells (RBCs) and is commonly defined in clinical practice by the World Health Organization (WHO) criteria of a hemoglobin level of <130 g/L in men and <120 g/L in women[1]. Although many mechanisms of anemia exist, iron deficiency anemia (IDA) remains the most common cause worldwide[2]. Iron is a crucial mineral necessary for numerous cellular functions, including DNA synthesis and cellular energy production and is an essential component of erythrocytes[3,4].

The healthy adult human generally has 45-60 mg/kg of total body iron[5]. Individuals typically cycle through 20-25 mg per day of iron in the plasma compartment. Approximately 15-25 mg is derived from the recycling of senescent erythrocytes (average life span of 120 days) via macrophages to maintain erythropoiesis [5,6]. However, small amounts (1-2 mg/day) of iron are lost through various sources such as sweating, urine, skin desquamation, etc[7]. The small amount that is lost can only be replenished via dietary sources[5,7]. IDA thus results when there is an imbalance in iron losses, dietary absorption, and/or liberation of iron from stores[5].

Dietary iron is present in two forms, heme (ferrous [Fe2+] iron) and non-heme (ferric [Fe3+] iron)[7,8]. Heme iron is present in myoglobin and hemoglobin and thus derived from animal food sources, versus non-heme iron is derived from predominantly plant sources[9]. Although heme iron is better absorbed, non-heme iron constitutes most of our

daily dietary iron intake[7]. Most iron is absorbed from the proximal small intestine via enterocytes[9]. The exact mechanisms for the absorption of heme iron are unclear. However, non-heme iron is first reduced to ferrous (Fe2+) iron by duodenal cytochrome B (DCYTB), followed by transport into the enterocyte via the divalent metal transporter (DMT1)[9,10]. Within the enterocyte, the iron is stored as ferritin or released into the plasma compartment through the iron export protein ferroportin 1 (FPN1)[5].

The systemic regulation of iron homeostasis is complex but mainly relies on the liver-derived hormone hepcidin[5,11]. Hepcidin acts via binding to FPN1 and causing its internalization and degradation[6,10]. FPN1 is present on hepatocytes, macrophages, and enterocytes and is responsible for exporting iron from these cells into circulation[5,9]. Thus, degradation of FPN1 mediated by hepcidin results in iron sequestration in these cells, limiting plasma levels that can be utilized for erythropoiesis in the bone marrow[6,7]. Hepcidin expression is regulated by several factors, including (i) iron availability, (ii) inflammation, (iii) erythropoietic demand, (iv) hypoxia, and (v) endocrine signals[5,12]. Hepcidin production is increased in response to high body iron levels and inflammation, whereas it is suppressed in response to iron deficiency, increased erythropoietic demand, hypoxia, and specific endocrine signals[7,12]. In IDA, hepcidin suppression results in increased release of iron from macrophages and increased iron absorption via enterocytes[11].

1.2 EPIDEMIOLOGY OF IRON DEFICIENCY ANEMIA

Globally, the prevalence of anemia is estimated at 32.9% based on data from the Global Burden of Diseases, Injuries and Risk Factors study in 2010, of which the most common cause was secondary to iron deficiency[2,7]. However, the prevalence of iron deficiency varies depending on region, with estimates as low as 2.9% in North America versus up to 64.7% in central Asia[2]. In general, the burden of IDA is greatest in regions ranking lower on the Human Development Index[13]. Additionally, Gender-related and age differences are generally seen across regions, with women of childbearing age having the highest incidence of IDA[14,15]. Interestingly, in the United States, a recent study based on data from the National Health and Nutrition Examination Survey (NHANES) between 1999 and 2018 has shown rising IDA-associated mortality and prevalence of anemia in addition to lower dietary iron intake[16]. Amongst patients with gastrointestinal (GI) disorders, IDA is highly prevalent, with estimates ranging from 36-72% for those with inflammatory bowel disease (IBD) to as high as 80% for upper gastrointestinal bleeding (UGIB)[17,18].

1.3 SIGNIFICANCE OF IRON DEFICIENCY ANEMIA

The burden of IDA is large and, based on the Global Burden of Disease Study in 2016, was the 5th leading cause globally of years lived with disability (YLDs)[13]. Notably, IDA has been associated with significant morbidity and mortality, particularly in older adults and poor maternal-fetal outcomes[19–23]. IDA may also present with numerous clinical symptoms related to hypoxic functioning, such as fatigue, exertional dyspnea,

headache, etc., which can result in significantly reduced physical performance[7,24]. In turn, numerous studies have established the detrimental impact of IDA on health-related quality of life (QoL)[25–28]. The adverse cognitive and physical productivity effects of IDA can additionally result in significant economic losses[29]. Lastly, IDA is associated with significantly increased healthcare expenditures, hospitalizations, and length of stay, causing a considerable burden on healthcare systems[23,30].

1.4 CAUSES OF IRON DEFICIENCY ANEMIA

Iron deficiency anemia may be caused by an absolute deficiency of iron from low iron stores; or a functional deficiency related to the inability to mobilize iron for erythropoiesis from otherwise adequate stores[7]. The most common aetiologies vary based on age, gender, and geography[7,31]. For example, the most common cause in women of childbearing age is blood loss due to menstruation. In contrast, malabsorption and blood loss related to gastrointestinal disorders are the most common in men and post-menopausal women[31–33]. In many patients with comorbidities and underlying inflammatory conditions, anemia is the result of anemia of chronic disease (ACD), for which functional iron deficiency plays a significant role[34]. However, in most patients with ACD there is generally a combined component of both absolute and functional iron deficiency and IRT has been shown to be effective in these patients[34,35].

The underlying mechanisms for IDA in patients with gastrointestinal diseases are often multifactorial, involving gastrointestinal blood loss, iron malabsorption, or functional

deficiency related to inflammation[3,18,36]. For example, patients with acute GI bleeding develop iron deficiency due to overt blood loss; however, patients with IBD may become deficient due to a combination of malabsorption, systemic inflammation and chronic occult blood losses related to active disease[18]. Ultimately, numerous GI disorders may potentially cause IDA, including and not limited to IBD (Crohn's disease and ulcerative colitis), celiac disease, Helicobacter pylori and autoimmune gastritis, esophagitis and hiatus hernias, GI malignancies, peptic ulcer disease, angiodysplasias, portal hypertensive related bleeding, and diverticular bleeding[18,37]. As such, IDA remains one of the most common reasons for referral to gastroenterologists[38,39].

1.5 DIAGNOSIS AND EVALUATION OF IRON DEFICIENCY ANEMIA

The diagnosis of IDA can be complex and is generally based on the interpretation of laboratory markers[7,11]. Although the gold standard for diagnosis is a direct assessment of the bone marrow via bone marrow aspiration, this is invasive and generally not required in most cases[7]. Some common serum tests utilized in making the diagnosis include the mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), ferritin, serum iron, total iron binding capacity (TIBC), and transferrin saturation (TSAT)[7,33]. Unfortunately, the performance of many of these markers is variable. Ferritin level directly correlates with total iron stores and is the most useful test in the absence of inflammation[11]. The threshold level of ferritin to indicate iron deficiency has been debated, and recent guidelines from the American Gastroenterological Association based on a systematic review of available literature suggest a threshold of <45 ng/ml in establishing a diagnosis of iron deficiency, with the most optimal sensitivity (85%) and

specificity (92%)[39]. However, ferritin levels are independently elevated in inflammatory conditions and thus are unreliable in these settings[7,33]. In these cases, a low TSAT level (<16%) may help establish a state of iron deficiency, although it cannot distinguish between absolute versus functional deficiency[11,33,38,39]. In some cases, a therapeutic trial of oral (PO) IRT (highly sensitive) may be necessary to establish a diagnosis of IDA[40].

After the establishment of a diagnosis of IDA, the patient must undergo a thorough evaluation to determine the etiology. This generally begins with standard clinical history and physical examination to evaluate for clear urogynaecological and GI sources of blood loss or malnutrition[38,39]. However, further evaluation is commonly required, including celiac screening, bi-directional endoscopy and/or small bowel investigations, particularly in men and post-menopausal women[33,38,39].

1.6 MANAGEMENT OF IRON DEFICIENCY ANEMIA

A key aspect in managing IDA involves treating and (if possible) resolving the underlying cause[11]. However, iron replacement therapy (IRT) is indicated in all patients with iron deficiency, including those without anemia[11]. Prior studies have shown providing iron supplementation to non-anemic individuals with iron deficiency still has benefits in subjective measures of fatigue[41]. For patients with GI disorders such as upper GI bleeding and IBD, provision of IRT results in faster correction of anemia and improvement in QoL measures[42–44]. Although the benefits of IRT are established, there

has been significant controversy in the past decade surrounding the optimal use of IRT and when PO or intravenous (IV) IRT is indicated[45–47].

Traditionally, PO IRT has been the first-line treatment option. However, IV IRT has been increasingly used upfront due to concerns about the tolerance and relative efficacy of PO therapies[48–50]. Although IV IRT is faster in correcting anemia, it has not shown consistent advantages in clinical outcomes compared to PO IRT in all patients, and both are effective in treating IDA[51–53]. Based on available evidence and recommendations, IV IRT should generally be reserved for patients in whom PO therapy is poorly tolerated or ineffective[53]. Even amongst IBD patients, prior reviews and the most recent guideline recommendations from the European Crohn's and Colitis Organization (ECCO) still suggest a trial of oral iron in IBD patients with mild IDA (Hgb >100g/L) and no active flare[54,55]. IV IRT is a reasonable first-line option in select patients where IV IRT has shown particular benefit, including those with end-stage renal disease (ESRD), severe congestive heart failure (CHF), chemotherapy-induced anemia, severe anemia in patients with IBD, or other GI conditions where rapid improvement in anemia is desirable (e.g., severe IDA in new diagnosis of colon cancer for which surgery is planned [54,56]).

1.6.1 ORAL IRON REPLACEMENT THERAPY

PO IRT is widely available, safe, and efficacious in treating IDA. Multiple formulations exist, with iron salts most commonly used, such as ferrous sulfate, ferrous gluconate, and ferrous fumarate[11]. In addition, newer formulations such as liposomal iron and

polysaccharide complexes have been developed that may be better absorbed and tolerated[32,57]. PO iron formulations and costs utilized at our center are noted below in Table 1.

Table 1. Oral Iron Formulations

	Dose per tablet (mg)	Elemental iron per tablet (mg)	Cost per tablet◊
Ferrous Sulfate	325	65	$0.03
Ferrous Gluconate	325	27	$0.03
Ferrous Fumarate	325	106	$0.08
Polysaccharide Iron Complex	150	150	$0.24

*Adapted from Ning, S. and Zeller, M. Management of Iron Deficiency. *Hematology AM Soc Hematol Educ Program (2019).*[57]
◊ Cost per tablet obtained from University of Alberta Hospital Pharmacy records

Although PO IRT has been the mainstay of treatment for IDA, a significant barrier to its use has been a high rate of GI side effects that may result in poor compliance[58]. However, this may be related to traditional PO iron dosing regimens that provide unnecessarily high doses at too frequent intervals[45]. Prior studies have demonstrated equal efficacy and increased tolerability with utilizing PO iron doses as low as 15 mg per day of elemental iron[59]. More recently, studies have shown the increased effectiveness of low-dose iron given on alternating days rather than daily dosing on optimizing absorption and improving side effects[60,61]. Stable isotope studies have demonstrated that higher doses of elemental PO iron raise the concentration of hepcidin for up to 48 hours, thus blocking the absorption of further doses[62]. It has been suggested that the GI side-effects of PO iron may be related to intestinal mucosal toxicity from non-absorbed iron secondary to ROS, thus altering the dosing of PO iron towards a low-dose alternate

day regimen may serve to improve not only efficacy and absorption but also GI side effects and tolerability[58,60].

1.6.2 INTRAVENOUS IRON REPLACEMENT THERAPY

IV IRT has increasingly gained popularity with its rapid effect, improved efficacy in certain disorders, and better patient tolerability[11]. Multiple formulations exist, with the ones available in Canada listed in Table 2.

Table 2. Intravenous Iron Replacement Formulations Available in Canada

	Recommended amount per dose	Infusion Time	Average cost per 1000 mg
Ferrous Gluconate (Ferrlecit)	125 mg	12.5 mg/min	$453.60
Iron Sucrose (Venofer)	200-300 mg	100 mg/30 min	$393.80
Iron Isomaltoside (Monoferric)	1000 mg	≥30 min	$450-900

*Adapted from Ning, S. and Zeller, M. Management of Iron Deficiency. *Hematology AM Soc Hematol Educ Program (2019)*[57] and Pharmacoeconomic Review Report: Iron Isomaltoside 1000 (Monoferric): (Pharmacosmos A/S): Indication: For the treatment of iron deficiency anemia in adult patients who have intolerance or unresponsiveness to oral iron therapy [Internet]. Ottawa (ON): *Canadian Agency for Drugs and Technologies in Health*; (2020). Table 4, CDR Cost Comparison Table for Parenteral Iron Products for IDA. Costs reflect only that of the medication, equipment, nursing, and administrative costs are not included.

Although IV IRT has several advantages, there remain significant concerns regarding its safety[11]. There has been controversy regarding the potential for IV iron to promote infections, given iron is a growth factor for some bacterial pathogens, with conflicting results from prior large meta-analysis[49,50]. In the most recent meta-analysis of over 32,000 patients, IV IRT was associated with increased risks of infection compared to

PO IRT and no therapy[63]. Thus, in general, IV IRT is contraindicated in active infections[11]. Other concerns include infusion reactions, which are generally mild, and more rare adverse events, including the risk of hypophosphatemia with the use of ferricarboxymaltose and anaphylactic reactions[11,64,65]. However, anaphylaxis was more of a concern in older formulations of IV therapy with high molecular weight iron dextran[11,64,65].

1.7 APPROPRIATE USE OF IRON REPLACEMENT THERAPY AND STUDY RATIONALE

The use of IV IRT has seen significant growth in use over the last decade[66,67]. For example, one study in Australia found a five-fold increase in IV iron treatments dispensed for women of reproductive age in 2017 compared to 2013[68]. This has not surprisingly raised concerns regarding whether IV IRT is being utilized appropriately[68]. Notably, concerns about the significantly higher medication costs, availability, and significant time burden on patients and nursing staff, represent major health expenditure concerns that must be considered in the judicious use of IV iron replacement[69,70]. In Canada, the Canadian Agency for Drugs and Technologies in Health (CADTH) has recently raised concerns about the possible overutilization of IV iron and its cost burdens on the healthcare system. Notably, multiple hospitals in Canada were providing IV IRT as an open benefit, particularly in inpatients, and the use of standardized order forms had not decreased costs or utilization[71].

As IDA is a common issue in patients with GI disorders as indicated above and IV iron is commonly utilized in the inpatient setting, we aimed to evaluate the concerns raised by CADTH and our own institution through reviewing the use of IRT in GI inpatients at the University of Alberta Hospital (UAH). The study's primary objective was to assess the appropriateness of IV IRT use, evaluated based on previously established evidence-based criteria and expert recommendations. Other objectives included assessing clinical response to IRT and predictors of response. To our knowledge, our study is the first to directly evaluate the trends and appropriateness of IV versus PO iron replacement therapy among GI inpatients at a tertiary care center.

2 MATERIALS AND METHODS

2.1 STUDY DESIGN

This study was a retrospective observational chart review conducted at the UAH. The UAH in Edmonton provides secondary, tertiary, and quaternary GI and Hepatology care. In addition, our institution operates a large acute gastroenterology inpatient service consisting of two wards with 32 dedicated GI beds.

All consecutive patients admitted to the adult gastroenterology inpatient wards between January 1, 2016, to January 1, 2017, who received IV and/or PO IRT during their admission were included in our study. Patients who did not have a primary GI issue for admission and/or did not receive IRT during admission were excluded.
Patients were identified through the inpatient pharmacy database CERNER, and patient data was extracted utilizing the patient's hospital electronic health record (EHR), e-Clinician.

2.2 STUDY DEFINITIONS

Our study defined ***anemia*** based on the WHO definition of <130 g/L in men and <120 g/L in women[1].

Iron deficiency was defined as serum ferritin <45 ng/mL and/or transferrin saturation <16%, with the caveat of serum ferritin <100 ng/mL defining IDA in individuals with active inflammation (ongoing infection and/or active IBD)[39,72]. The latter aligns with current recommendations on the diagnostic criteria of IDA in IBD and maximizes the ability to detect IDA[72]. Additionally, patients admitted with acute overt GI bleeding requiring hospitalization were considered to meet the definition of iron deficiency.

Appropriate use of IV IRT was defined as having a diagnosis of IDA based on the above criteria and at least one of the following established indications:

1. Documentation of previous intolerance of oral iron[11]
2. Poor response to oral iron and/or use as a substitution for blood transfusions in patients who will not accept blood products for religious reasons[11,73,74]
3. Active IBD Flare (defined as admission CRP >5 with IBD as the main reason for admission) OR IBD patient with Hgb <100 and IDA[54,72]
4. Severe IDA defined by Hemoglobin <70 g/L[38]
5. Comorbidities including Severe CHF, ESRD, active malignancy and/or prior bariatric surgery or bypass surgery

These criteria were derived based on our previously discussed literature review for managing IDA in gastrointestinal patients[11,38,39,54,72–74].

Response to iron replacement was defined as an absolute increase in hemoglobin ≥20 g/L and/or recovery of hemoglobin to normal ranges within 6 weeks, without the

additional use of blood transfusions. Therefore, patients for whom follow-up bloodwork was unavailable up to 6 weeks were excluded from this segment of the analysis. Additionally, patients who received red blood cell transfusions during the follow-up period were excluded from this analysis.

2.3 DATA EXTRACTION & COLLECTION

EHRs were reviewed, and data were systematically extracted into a secure institutional database (REDcap). Demographic information was retrieved for all patients. Details of the patient's iron therapy were reviewed, including pre, peri and post-admission provision of IRT up to 6 weeks post-discharge. The dose of iron therapy and cost data for iron therapy were identified by cross-referencing pharmacy records. Our institution uses iron sucrose as the intravenous iron formulation, generally given at a dose of 200-300 mg per infusion. The PO iron formulations prescribed for patients included: ferrous fumarate, ferrous gluconate, ferrous sulfate, and iron polysaccharide complex, which provide a range of elemental iron doses based on the formulation (35 mg to 150 mg per day).

Admission and discharge hemoglobin and MCV were recorded for all patients, as well as admission ferritin, serum iron, total iron binding capacity (TIBC) and percent transferrin saturation, if available. The number of units administered for patients who received red cell transfusions was also recorded. Post-discharge hemoglobin and MCV were recorded for all patients up to 6 weeks after discharge to assess the response to iron therapy.

The period for follow-up of up to 6 weeks after discharge was chosen as prior literature used this time frame by which patients are expected to have a response to IRT[3,18]. If a patient was re-admitted to the hospital or received a blood transfusion within the 6-week follow-up period after discharge, bloodwork from 48 hours before the re-admission or blood transfusion and onwards was censored to avoid confounders in assessing the responsiveness of patients to iron replacement.

In addition, health records were reviewed for up to 6-months post-discharge from the hospital for clinical outcomes, including hospital re-admission, number of emergency department visits and red blood cell transfusion requirements.
For patients re-admitted to the hospital and/or received blood transfusions during the 6-week follow-up period, their last bloodwork before readmission or transfusion was censored to assess initial responsiveness to iron therapy.

Based on formulation, data for the drug costs of each IV iron dose and PO iron tablet was obtained from our hospital pharmacy database (see Tables 1 and 2). IV iron costs were limited only to the pharmacy cost of the drug and did not consider the nursing time involved in administration. Daily PO iron costs were calculated based on prices per tablet multiplied by the patient's daily dosing regimen as indicated during their admission and discharge. Total PO iron costs were calculated based on the assumption of the patient having continued use of PO iron during admission and through the subsequent 6-week post-discharge follow-up.

2.4 STATISTICAL ANALYSIS

Statistical analysis was conducted with SPSS v24.0. Descriptive categorical data are presented as percentages and continuous data as means and medians as appropriate based on normality distributions via the Shapiro-Wilk test. Fisher's exact test was used to compare categorical data. Response to IV and PO iron were analyzed via Fisher's exact test and one-way ANOVA as appropriate. Predictors of response to PO and IV iron were analyzed via binomial multivariate logistic regression. Co-variates of interest to be examined in the multivariate model were chosen *a priori* and any variables with a p-value of <0.25 in the univariate model were included in the multivariate model. Clinical outcomes were analyzed via Fischer's exact test and students t-test as appropriate.

3 RESULTS

3.1 PATIENT DEMOGRAPHICS

A total of 202 patients who received IV, oral, or combined IV and oral iron replacement during their admission to the GI service were included. The mean age of all patients was 57 (SD=20) years, with 52% (n=105/202) of patients being male. The Median Charlson comorbidity index (CCI) of all patients was 3.0 (SD=2.7), with a mean of 5.2 (SD=4.3) home medications at admission. Reason for admission of patients included IBD flare/complication in 25% (n=51/202), non-variceal GI bleeding in 43% (n=86/202), variceal bleeding in 3% (n=5/202), cirrhosis in 7% (n=14/202), GI malignancy in 5% (n=9/202) and other reasons in 18% (n=37/202) such as pancreaticobiliary diseases.

The different iron use groups were similar in terms of distribution of gender (p=0.96), discharge hemoglobin (p=0.13), admission CRP (p=0.19) and the average number of inpatient blood transfusions (p=0.83). Additionally, the proportion of patients with an elevated CRP (>5) was similar between groups (p=0.33). However, significant differences were seen in the average age (p=<0.001), CCI (p=<0.001), admission hemoglobin (p=0.002), admission ferritin (p=0.005), and reason for admission (p=<0.001) between patients receiving IV versus PO iron therapy. In general, patients receiving PO therapy only were older and had more significant comorbidities.
The proportion of patients with various admission diagnoses was significantly different between groups (p=<0.001). Patients with non-variceal GI bleeding (40% [n=56/140])

and IBD flares (35% [n=49/140]) were much more common in the IV iron group versus cirrhosis (20% [n=6/30]) and other admission diagnosis (53% [n=16/30]) being more common in the PO iron group, and non-variceal GI bleeding being the predominant admission diagnosis in the combined group (75% [n=24/32]). A greater proportion of patients (42% [n=59/140) and 66% [n=21/32] versus 27% [n=8/30]) required inpatient blood transfusions in the IV iron and combined therapy group compared to the PO iron group (p=0.007). The average length of stay was 7.6 (SD=7.3) days, there was no significant difference in length of stay between treatment groups (p=0.51)

The average total IV iron dose received by patients during their admission was 885 (SD=521) mg. The average daily elemental oral iron dose prescribed to patients was 91 (SD=48) mg per day.

Table 3. Patient Demographics

	All Patients N=202	Intravenous Iron N=140	Oral Iron N=30	Combined IV/PO N=32	P-Value
Age	57 (SD=20)	53 (SD=20)	65 (SD=17)	65 (SD=19)	<0.001*
Male Gender (%)	52% (n=105/202)	52% (n=73/140)	53% (n=16/30)	50% (n=16/32)	0.96
Charlson Co-morbidity Index	3.0 (SD=2.7)	2.3 (SD=2.4)	4.8 (SD=2.9)	3.9 (SD=2.9)	<0.001*
Reason for Admission (%)					
IBD Flare	25% (n=51/202)	35% (n=49/140)	3% (n=1/30)	3% (n=1/32)	<0.001*
Non-Variceal Bleeding	43% (n=86/202)	40% (n=56/140)	20% (n=6/30)	75% (n=24/32)	
Variceal Bleeding	3% (n=5/202)	2% (n=3/140)	3% (n=1/30)	3% (n=1/32)	
Cirrhosis	7% (n=14/202)	4% (n=6/140)	20% (n=6/30)	6% (n=2/32)	
GI Malignancy	5% (n=9/202)	6% (n=9/140)	0% (n=0/30)	0% (n=0/32)	
Other	18% (n=37/202)	12% (n=17/140)	53% (n=16/30)	13% (n=4/32)	
Admission Bloodwork					
Hemoglobin (g/L)	88 (SD=26)	89 (SD=26)	99 (SD=27)	76 (SD=20)	0.002*
MCV (f/L)	85 (SD=10)	85 (SD=10)	87 (SD=11)	82 (SD=11)	0.08
Ferritin (mcg/L)	73 (SD=97)	66 (SD=92)	151 (SD=115)	62 (SD=95)	0.005*
Serum Iron (ug/L)	5.1 (SD=6.8)	5 (SD=7.2)	10 (SD=8.3)	4 (SD=3.0)	0.07
TIBC (umol/L)	60 (SD=18)	59 (SD=17)	46 (SD=14)	70 (SD=19)	<0.001*
Transferrin Sat (%)	10% (SD=10%)	9% (SD=10%)	28% (SD=30%)	6% (SD=10%)	<0.001*
CRP (mg/L)	45 (SD=60)	41 (SD=55)	42 (SD=46)	79 (SD=102)	0.19
Discharge Hemoglobin	96 (SD=17)	97 (SD=17)	98 (SD=20)	91 (SD=10)	0.13
Patients Requiring Inpatient Blood Transfusion	44% (n=88/202)	42% (n=59/140)	27% (n=8/30)	66% (n=21/32)	0.01*
Average Number of Inpatient Blood Transfusions◊ (Units)	3.2 (SD=2.8)	3 (SD=2.6)	3.8 (SD=4.8)	3.3 (SD=2.2)	0.83
Length of Stay (Days)	7.6 (SD=7.3)	8.0 (SD=7.8)	6.3 (SD=4.8)	7.3 (SD=6.8)	0.51

◊Amongst patients receiving blood transfusion (n=88)
*Indicates significance defined as p-value <0.05

3.2 APPROPRIATENESS OF INTRAVENOUS IRON USE

As shown in Table 4, 172 patients received IV iron during their inpatient stay. 56% (n=96/172) of patients in whom IV replacement was prescribed during admission met the criteria for use as defined above. Patients who had appropriate use of IV IRT in our cohort included: previous oral iron intolerance/poor response (13%, n=12/96), active IBD flare or IBD patient with hemoglobin <100 (31%, n=30/96), severe IDA (34%, n=33/96), and indications secondary to medical comorbidities including severe CHF/CKD/bariatric surgery/active cancer treatment (18%, n=17/96). In addition, 14% (n=24/172) of patients received IV iron replacement despite having no evidence of IDA based on the criteria in our study. Of these patients, 11 had normal hemoglobin levels.

Table 4. Appropriateness of Intravenous Iron Use in Patients Receiving Intravenous Iron Replacement Therapy

Meets Study Criteria for Iron Deficiency Anemia	
Yes	86% (n=148/172)
No	14% (n=24/172)
	Normal hemoglobin*: 46% (n=11/24)
	Iron indices not performed: 29% (n=7/24)
	Anemia with iron indices not meeting criteria: 25% (n=6/24)
Patients Meeting Criteria for Use of Intravenous Iron	
Yes	56% (n=96/172)
	Previous PO iron intolerance/poor response: 13% (n=12/96)
	Active IBD flare OR IBD patients with Hgb <100g/L: 31% (n=30/96)
	Severe IDA (Hgb <70 g/L): 34% (n=33/96)
	Indication due to medical comorbidities/Surgery: 18% (n=17/96)
No	44% (n=76/172)

***** Defined as Hemoglobin ≥120 in women or ≥130 in men (note all patients with normal hemoglobin in our cohort did have evidence of iron deficiency based on low iron indices)

3.3 RESPONSE TO IRON REPLACEMENT THERAPY

Of patients who had bloodwork done at 4-6 weeks post-discharge to allow assessment of response, the overall response was seen in 64% of patients with an overall mean hemoglobin change of 23 g/L. The mean change in hemoglobin was 16 g/L for PO, 28 g/L for combined IV/PO, and 23 g/L for IV only (p=0.08). Overall clinical response, defined as an increase in hemoglobin >/= 20 g/L and/or recovery to normal hemoglobin ranges at 4-6 weeks post-discharge, was not significantly different between groups. At 6 weeks post-discharge, clinical response (defined as an absolute increase in hemoglobin >= 20 g/L and/or recovery of hemoglobin to normal ranges) was seen in 64% (n=8/15) of patients receiving PO iron, 75% (n=15/20) receiving combined IV/PO iron, and 64% (n=47/74) receiving only IV iron (Table 5).

Table 5. Response to Iron Replacement Therapy

	Overall Response	**Intravenous Iron Only**	**Combined IV/PO**	**PO Iron Only**	**P-value**
Response to Iron*	64% (n=70/109)	64% (n=47/74)	75% (n=15/20)	53% (n=8/15)	0.41
Change in Hemoglobin g/L	23 (SD=15)	23 (SD=16)	28 (SD=15)	16 (SD=13)	0.08
	Post Hoc Analysis Mean Differences in HB				
IV vs. PO	7.2 (95% CI -3.3 - 17.7)				0.23
Combined vs. IV Only	4.8 (95% CI -4.3 - 13.8)				0.43
Combined vs. PO Only	12.0 (95% CI -0.6 - 24.5)				0.07

* *Response to iron replacement* was defined as an absolute increase in hemoglobin >= 20 g/L and/or recovery of hemoglobin to normal ranges within 6 weeks without the additional use of blood transfusions

Stratification of admission hemoglobin values showed no significant difference in mean change of hemoglobin at 4-6 weeks post-discharge (p=0.39) and overall clinical response to iron therapy (p=0.45) (Table 6).

Table 6. Response to Iron Replacement Therapy Stratified by Admission Hemoglobin

Admission Hemoglobin Range	Mean Change in Hemoglobin at 4-6 weeks post-discharge	P-Value	Clinical Response To Iron Replacement Therapy	P-Value
< 70 g/L	24 (SD=16) g/L	P=0.39	73% (n=30/41)	P=0.45
70 – 89 g/L	21 (SD=18) g/L		61% (n=17/28)	
90 – 109 g/L	26 (SD=13) g/L		61% (n=14/23)	
>110 g/L	19 (SD=12) g/L		53% (n=9/17)	

On univariate analysis (Table 7), only the patient's hemoglobin at discharge was significantly associated with overall clinical response to treatment at 4-6 weeks post-discharge (OR 0.96, 95% CI 0.93-0.99, p=0.01). This finding was also seen in multivariate analysis (OR 0.94, 95% CI 0.89-0.98, p=0.01). No other variables, including the use of IV IRT versus PO IRT, were statistically significant in predicting response on the multivariate model.

Table 7. Predictors of Overall Response to Iron Therapy at 4-6 Weeks Post Discharge

	UNIVARIATE ANALYSIS		MULTIVARIATE ANALYSIS	
	OR (95% CI)	**P-Value**	**OR (95% CI)**	**P-Value**
Age	0.99 (0.97 - 1.01)	0.40		
Male Gender	0.88 (0.40 - 1.92)	0.74		
Charlson Comorbidity Index	0.90 (0.77 - 1.05)	0.18	0.85 (0.70 - 1.02)	0.08
Admission Diagnosis IBD Related	0.87 (0.35 - 2.17)	0.76		
Admission Hemoglobin	0.99 (0.97 - 1.01)	0.23	1.01 (0.98-1.03)	0.67
Hemoglobin at Discharge	0.96 (0.93 – 0.99)	0.01*	0.94 (0.90 - 0.99)	0.02*
Discharged With Home Iron Therapy	1.10 (0.47 - 2.56)	0.82	-	-
Received Intravenous Iron Formulation	1.67 (0.56 - 5.01)	0.34	1.47 (0.41 - 5.25)	0.55

* Indicates significance defined as p-value <0.05

3.4 FOLLOW-UP CLINICAL OUTCOMES

On follow-up (Table 8), there were no significant differences between the three groups in readmission rates within 90 days (p=0.41), emergency department visits within 90 days (p=0.24), need for blood transfusion within 6 months (p=0.11), and total mean number of subsequent blood transfusions (p=0.09) within 6 months. However, there was a significant difference in the total average drug cost of therapy, with the IV iron group being $304 vs. $17 in the oral iron group (p<0.001) at the end of the follow-up period.

Table 8. Post-Discharge Clinical Outcomes of Iron Replacement Therapy

	All Patients	IV Iron	PO Iron	Combined IV/PO	P-Value
Average Length of Stay (Days)	8 (SD=7.3)	8 (SD=7.8)	6 (SD=4.8)	7 (SD=6.8)	0.51
Readmission within 90 days	28% (n=57/202)	27% (n=36/140)	30% (n=9/30)	39% (n=12/32)	0.41
ED Visit within 90 days	35% (n=70/202)	32% (n=43/140)	43% (n=13/30)	45% (n=14/32)	0.24
Need for Blood Transfusion within 6 months post-Discharge	16% (n=32/202)	13% (n=17/140)	23% (n=7/30)	26% (n=8/32)	0.11
Average number of Blood Transfusions within 6 months post-Discharge (Units)	4.5 (SD=4.4)	2.9 (SD=2.9)	6.4 (SD=4.3)	6.3 (SD=6.3)	0.09
Average Total Cost of Therapy ($ CAD)	$261.03 (SD=160.93)	$310 (SD=137)	$17 (SD=13.9)	$277 (SD=125)	<0.001*

* Indicates significance defined as p-value <0.05

4 DISCUSSION AND CONCLUSION

4.1 SUMMARY AND INTERPRETATION OF RESULTS

We have noted several significant findings in our study of the usage and outcomes of IRT amongst GI inpatients at an academic center. The rate of use for IV iron therapy and blood transfusions is high in our inpatient population. Most notably, based on published criteria, many patients inappropriately received IV IRT as first-line therapy. Surprisingly 14% (n=24/172) of patients receiving IV IRT did not meet the criteria for IDA in our study. This is an important finding that needs to be addressed by quality improvement initiatives. Our results also support the efficacy of PO and IV iron replacement for patients with IDA-related GI disorders. Although it is established that IV iron corrects iron deficiency and anemia faster, our data suggest that a proportion of patients can be effectively treated by PO iron alone. We also noted that readmission rates were relatively high at 28% overall; this is likely because our hospital is a tertiary care center that looks after a large population of decompensated cirrhosis patients and patients with complex IBD, recurrent GI bleeding and GI cancers.

4.1.1 APPROPRIATENESS OF IRON REPLACEMENT THERAPY

Appropriate and judicious use of IV iron therapy is an essential consideration in patients with IDA secondary to GI disorders, given the significant cost differences, burden of increased nursing time, and the rare but serious adverse events of IV therapy, such as anaphylaxis. Although all patients with IDA should receive IRT, direction on the preferred route and type of therapy has been limited[17]. In our study, we used generally

agreed-upon indications for IRT based on a review of the literature[11,38,39,54,72–74]. Amongst the gastroenterology population, the use of IV iron has been increasingly promoted, particularly in patients with IBD[45]. Our study showed very high preferential use of IV iron amongst GI inpatients, despite a significant proportion (44% [n=76/172]) not meeting appropriate criteria for use. Most indications of those who met the criteria were related to IBD and severe anemia at admission. Amongst patients receiving PO iron monotherapy, only two patients met the criteria for IV therapy, suggesting that inappropriate avoidance of IRT was infrequent.

The reasons for our findings are likely multifactorial, relating to the ease of access to IV iron for inpatients, lack of practitioner knowledge on appropriate usage of IRT, and concerns regarding tolerability and adherence to PO iron. In many Canadian hospitals, there are no to minimal restrictions placed on the use of IRT for inpatients and outpatients; however other countries with universal pharmacare programs, such as Australia and France, have placed clinical and reimbursement restrictions for the use of IV iron[71]. Additionally, knowledge surrounding the appropriate use of IV iron appears lacking, with a significant proportion (46%) of gastroenterologists surveyed reporting poor knowledge of the proper use of IV iron in IBD patients[75].

Although PO iron has previously been noted to have significant rates of intolerance related to GI side effects, recent studies have shown that lower alternate day dosing may significantly reduce side effects and increase efficacy[60,76]. Additionally, new formulations, such as ferric maltol, have shown a similar rate of tolerability and

adherence to placebo[77]. Although newer formulations are more expensive, they remain significantly cheaper than IV iron[38].

Expectedly, we found a substantial difference in the overall cost of iron replacement therapy of over 17-fold ($304 vs. $17, p<0.001) for the IV route. However, it is also important to note that these costs reflect only the cost of the medication and do not factor in additional costs associated with administering IV iron, including nursing support, clinic infrastructure and miscellaneous materials needed to deliver intravenous therapy safely. Registered nurses in our hospital must monitor patients closely up to every 15 minutes for up to three hours if a patient receives IV iron for the first time, given the aforementioned rare but serious risks.

4.1.2 RESPONSE AND OUTCOMES OF IRON REPLACEMENT THERAPY

Our study has shown both PO and IV IRT were effective in treating IDA, with the proportion of complete responders being similar (p=0.41) by 4-6 weeks. Notably, the only significant predictor of response was the hemoglobin level at discharge on multivariate analysis, with no significant impact of the type of IRT. The significance of lower hemoglobin levels being associated with response to IRT is likely explained by greater physiologic suppression of hepcidin and higher erythropoietin levels, resulting in a greater drive for erythropoiesis[78,79]. Our overall response rate of 64% was consistent with findings from prior studies on the use of IRT in patients with GI disorders such as IBD[47]. The reasons for lack of response are multiple and may include ongoing losses, poor compliance, as well as relative iron deficiency from ACD. Patients with ACD have

multiple pathologic mechanisms resulting in anemia, including iron dysregulation, reduced erythropoiesis, diminished erythropoietin response, and decreased erythrocyte survival[34]. Given these pathophysiologic mechanisms, patients with a component of ACD likely have a diminished response to IRT[34]. However, as previously noted, most patients with ACD have a significant element of absolute iron deficiency, which is likely more pronounced in GI disorders given bleeding and malabsorption are seen in most luminal GI disorders[35].

We did note a trend towards improved response in patients who received combined therapy with both IV iron and maintenance PO iron, highlighting the importance of providing maintenance iron replacement therapy, which unfortunately was only done in 19% (n=32/172) of patients. This is in line with prior studies where only 16% of patients with anemia after UGIB were prescribed maintenance PO IRT[80]. Similarly, a survey of Canadian gastroenterologists showed wide variation in prescribing practices of maintenance IRT for patients with UGIB who remain anemic at discharge, with only <15% consistently prescribing maintenance IRT[81]. This is a crucial care quality gap, particularly as prior evidence has shown the importance and efficacy of prescribing maintenance IRT after UGIB to correct anemia[43]. Additionally, we found no significant difference in length of stay, blood transfusion requirements at 6 months, readmission within 90 days, and representation to the emergency department within 90 days between PO and IV IRT.

Although it is accepted that IV iron is superior in more rapidly replenishing iron stores, data have not conclusively shown that this translates into significant differences in the overall degree of hemoglobin recovery after standard treatment periods[45,82,83]. PO iron is effective and comparable to IV in patients with UGIB and IBD in prior studies, consistent with our findings[43–45]. Randomized trials of patients with IBD, UGIB, and bariatric surgery have not consistently shown significant differences in hemoglobin response between patients receiving IV iron replacement formulations and PO iron[43,51,52,82,83].

Apprehension surrounding the use of PO iron in patients with IBD has been highlighted in the literature due to concerns with poor intestinal absorption and potential worsening of disease activity. However, the evidence for this is weak, and prior studies from Gisbert *et al.* and Rampton *et al.* demonstrated that PO iron was efficacious and did not exacerbate disease activity [44,84]. In addition, a previous study utilizing radiolabeled oral $^{59}FeCl_3$ showed preserved oral iron absorption in those with IBD, even in severe disease[85]. Ultimately the optimal method for IRT in IBD patients remains controversial and should be decided based on the specific clinical situation[86].

Lastly, although not evaluated in our study, recent data suggests that the current standard dose of PO iron is too high and may negatively impact the absorption, side effect profile and overall clinical efficacy of PO iron replacement[59]. As previously indicated, alternate day low-dose PO iron may optimize effectiveness and improve side effects based on tests in iron deficient, non-anemic women mediated via hepcidin[60,62].

Stoffel *et al.* recently demonstrated that anemic women with iron deficiency still see a significant increase in iron absorption with alternate day dosing compared to daily dosing despite the baseline physiologic hepcidin suppression from IDA[61]. Thus, future studies comparing efficacy between low-dose alternate day PO regimens and IV iron formulations across a range of disorders are necessary to guide clinician decisions on which route of therapy is best for patient outcomes and healthcare economics.

4.2 STRENGTHS AND LIMITATIONS

Our study has several notable strengths and weaknesses. The relatively small sample size in patients receiving PO iron replacement significantly limits the power of our findings in comparing the outcomes and effectiveness of PO versus IV iron replacement. However, the relatively small number of patients given PO IRT is an important finding, indicating the suspected underuse of PO IRT amongst GI inpatients. The retrospective design of our study also brings inherent issues with potential confounders that we were unable to control for, such as the distribution of types of admission diagnoses between groups and comorbidity burden. Most patients receiving IV iron had fewer comorbidities and were admitted for IBD or GI bleeding, versus those receiving PO therapy had more comorbidities and were admitted for issues such as cirrhosis and pancreaticobiliary disorders. It would be assumed, however, that given the higher chronic disease burden in the PO therapy population, this would negatively impact the hemoglobin response to iron therapy.

Our review of the literature was extensive to establish acceptable criteria for the use of IV iron. We were mindful that decisions to use IV therapy are nuanced in clinical practice, and we thus provided relatively broad criteria on what is considered acceptable use. Lastly, our results were obtained from inpatients in a single tertiary center in Canada, limiting its generalizability to the ambulatory setting and across other countries. Selection bias, however, was reduced in our study as all consecutive patients were reviewed, and our cohort of patients receiving IV iron was large, allowing for an accurate assessment of usage trends.

Future prospective studies with larger sample sizes are necessary to confirm our comparative findings. However, our study brought to light a significant problem with the excessive use of IV iron replacement. It highlights the need for new policy measures to be put in place to ensure judicious use.

4.3 STUDY SIGNIFICANCE AND FUTURE STEPS

The findings from our study provide real-world evidence of the overuse of IV IRT despite the implementation of relatively broad use criteria. Notably, our results may reassure providers that PO IRT is comparably effective to IV IRT in the correct settings. Ultimately, we hope our study will highlight the issue of inappropriate IV IRT use by healthcare providers and institutions and translate to the development of quality improvement initiatives and health policy changes surrounding the optimal and judicious use of IRT. Several key areas that could be targeted include:

1. Education to prescribers on best practice use of IRT

2. Implementation of hard-stop functions for ordering IV IRT in computerized provider order entry systems
3. Creation of standardized order sets with prescribing criteria
4. Imposing limitations on open benefit prescribing of IV IRT
5. Implementation of standard follow-up care pathways for anemic patients at discharge

Further research is additionally required in the optimal management of IDA in GI disorders, particularly as IDA remains highly prevalent globally. Potential questions to be examined include:

1. What is the efficacy and tolerability of low-dose alternate day PO IRT compared to IV IRT in patients with IDA across disorders?
2. What is the real-world cost-effectiveness of PO IRT and IV IRT across GI disorders in inpatient and outpatient settings?
3. What are the utilization trends of PO IRT and IV IRT in ambulatory settings?

4.4 CONCLUSION

In our study, IV iron replacement therapy was effective but overused as a substantial proportion received IRT with an appropriate indication. Although commonly considered inferior, PO IRT is efficacious in patients with gastrointestinal illness and is a valuable option in patients with IDA when IV iron replacement is not indicated. Judicious use of IV iron replacement is necessary to ensure optimal care and resource management in hospitals.

Measures to educate prescribers on appropriate indications for the use of IV iron replacement are necessary. Future quality improvement studies implementing the measures mentioned earlier and cost-effectiveness analyses are essential to further guide prescribing practices.

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