

Efficacy and Tolerability of Intravenous V/s Oral Iron for IDA in IBD Patients: A Systematic Review and Meta-Analysis

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Abstract

Background and Aims: Anemia is the most common extraintestinal complication of inflammatory bowel diseases (IBD). Iron deficiency anemia (IDA) can be treated with oral or intravenous (IV) iron supplementation. The aim of this study is to compare the efficacy and tolerability of oral and IV iron supplementation for treating anemia in adult IBD patients.

Methods: A systematic review and meta-analysis of randomized controlled trials were conducted. Databases including PubMed, Web of Science, Scopus, and Cochrane Central Register of Controlled Trials were searched until December 2022. Trials that included individuals with IBD and compared IV to oral iron for treating IDA were eligible. Two reviewers independently extracted data, and another two reviewers independently graded each trial's risk of bias. The fixed-effect model was used to obtain pooled odds ratio (OR) estimates and their 95% confidence intervals (CI).

Results: Five trials, including 910 IBD patients, were eligible for analysis. The meta-analysis showed that IV iron was more effective than oral iron for raising hemoglobin levels to 2.0 g/dL (OR: 1.44, 95% CI: 1.09 - 1.91, P = 0.01). The IV iron groups had decreased rates of treatment withdrawal prompted by adverse side effects or intolerance (OR: 0.26, 95% CI: 0.13 - 0.51, P < 0.0001). There was no evidence of heterogeneity across all studies.

Conclusion: IV iron appears to be more efficient and well-tolerated than oral iron for treating anemia associated with IBD. The findings suggest that IV iron may be a preferred treatment option for IBD patients with IDA.

Keywords: Crohn's disease; Ulcerative colitis; Iron supplementation; Iron deficiency

1. Introduction

Inflammatory bowel diseases (IBDs), including ulcerative colitis and Crohn's disease, are gastrointestinal disorders caused by an autoimmune response toward the gut mucosa due to an unknown etiology [1]. Being a systemic disease, complications of IBD occur not only in the gastrointestinal tract but also in many organ systems [2]. Among all extra-intestinal manifestations, anemia is the most common, and its prevalence was estimated to vary between 6% and 74% [3,4].

Several mechanisms of anemia have been implicated in IBD. However, the most common causes, according to several previous studies, are either iron deficiency anemia (IDA), anemia of chronic disease (ACD), or combined anemia (IDA

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and ACD simultaneously)[5,6]. Anemia has been associated with worse IBD prognosis, increased hospitalization rates and reduced quality of life (QoL)[7-9]. Therefore, IBD patients must be regularly screened for IDA and adequately treated[10].

Supplementary iron can be administered orally or intravenously (IV). Oral iron is associated with many adverse events. Moreover, it has been shown to exacerbate inflammation by altering the gut microbiome and increasing the permeability of the intestinal epithelium[11-13]. The safety and efficacy of Modern intravenous iron compounds have been demonstrated to provide rapid correction of hemoglobin levels (Hb) in IBD with IDA[14-16]. Subsequently, IV iron was considered first-line therapy for IBD patients with moderate to severe IDA (Hb <10 g/dL) and active disease[10].

However, some aspects of managing IBD patients with IDA have not been clarified [17]. Also, many physicians still need to decide which iron should be supplemented orally or intravenously[14,18]. To help physicians make better evidence-based treatment decisions and enforce their medical decisions on the ideal therapy modality, the current meta-analysis explored the efficacy and tolerability of IV versus oral iron in treating IBD-associated IDA.

2. Material and methods

2.1. Data Sources and Search Strategy

Using the following search query: "(Inflammatory bowel disease OR ulcerative colitis OR Crohn) AND (anemia OR anemia) AND (intravenous iron OR intra-venous iron OR IV iron OR parenteral iron OR oral iron OR PO iron)", we conducted a thorough search of four electronic databases (PubMed, Scopus, web of Science, and Cochrane Central Register of Controlled Trials) until 15 December 2022. Additionally, the listed studies' references were carefully examined for any possible eligible studies.

2.1.1. Selection Criteria

Studies were eligible for inclusion if they were randomized controlled clinical trials comparing IV versus oral iron replacement therapy in adult IBD patients with IDA. According to World Health Organization, anemia was defined as Hb <12 g/dL in women and <13 g/dL in men. Studies with concurrent use of erythropoietin and those published in non-English or that employed a cross-over study design were excluded.

2.2. Outcome measure and Data Extraction

Our primary (efficacy) outcome was the effect of treatments on the hemoglobin response, defined as the rate of patients who achieved an increase of at least 2.0 g/dL in hemoglobin concentration at the end of the follow-up. As secondary (safety) outcomes, we studied the rates of discontinuation of the intervention due to adverse events or intolerance. A pre-established Excel form was applied independently by two authors to gather information on the following study aspects: study name, publication year, study design, number of patients, follow-up, dose, age, gender, and outcome indicators. A third researcher checked and reviewed the collected data and discussed any discrepancies with the researcher who entered the data to arrive at a solution.

2.3. Risk of Bias Assessment

Using the Cochrane Risk Bias Assessment Tool, two trained reviewers independently scored the quality of the included literature, which included selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential biases.

2.4. Data Analysis

Data synthesis and statistical analysis were conducted using Review Manager 5.4 software. Risk ratios (RRs) with corresponding 95% confidence intervals (95% CIs) were calculated using a fixed-effect model for each outcome. Heterogeneity between studies was measured using an I^2 value, with $I^2 \geq 50\%$ indicating substantial heterogeneity. The relative risk (RR) and its 95% confidence intervals were used for the dichotomous variables. A p-value of less than 0.05 was considered significant.

3. Results

3.1. Study Selection

Our literature search retrieved 1479 results. After being subjected to title and abstract screening, 21 articles were qualified for full-text screening, and five studies were included in the meta-analysis. No further publications were included despite manually searching the references of the included studies. The PRISMA flowchart for the study selection procedure is displayed in Figure 1.

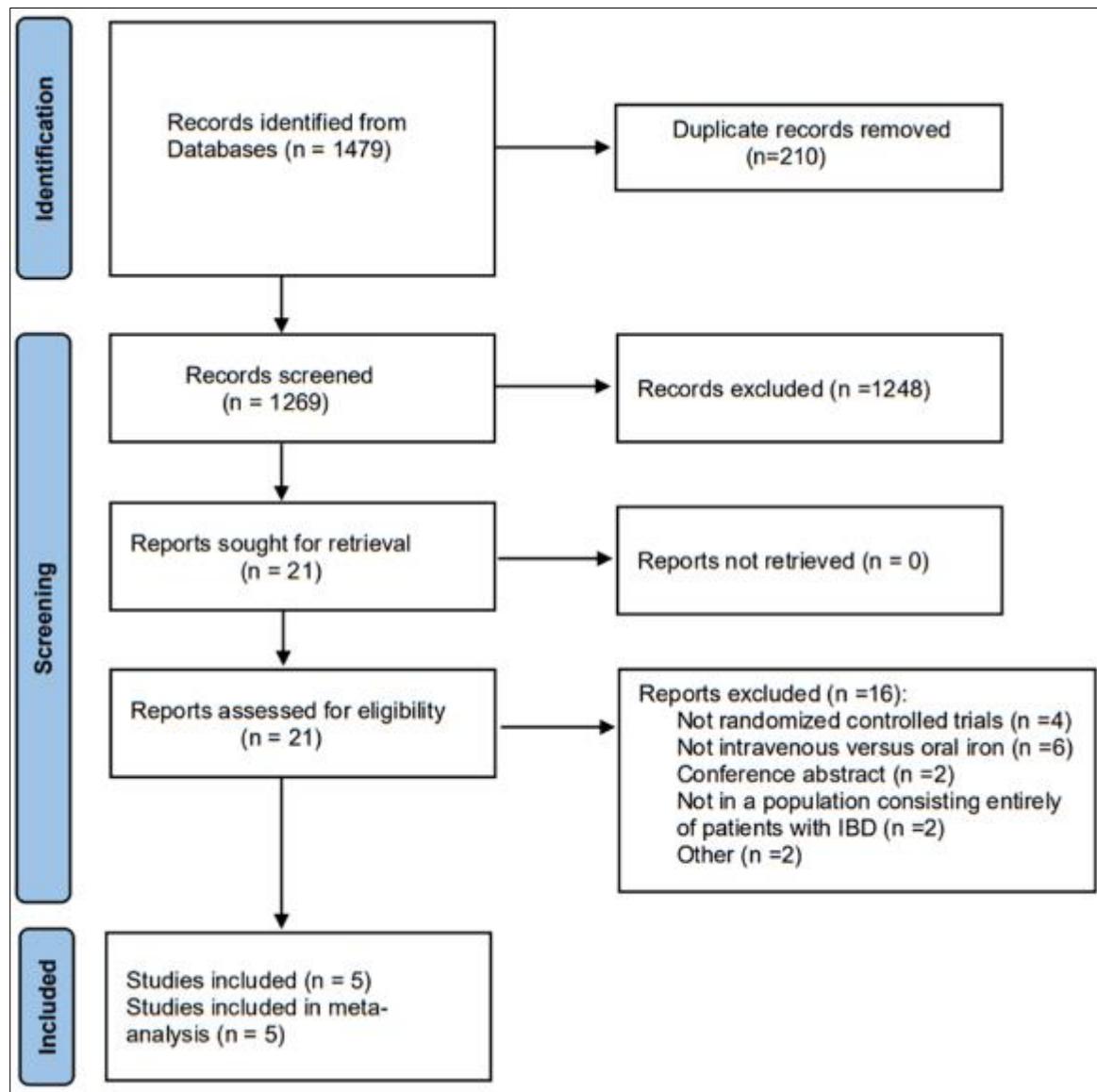


Figure 1 PRISMA flowchart of selection of studies, PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis

There were 910 IBD patients with IDA in the five studies that comprised the meta-analysis¹⁹⁻²³. Patients were allocated to receive either IV iron or oral in all studies, 547 patients in the IV iron group and 363 patients in the oral iron group, 390 patients were Crohn's disease, and 520 were Ulcerative colitis. Features of the included studies are outlined in summary form in Table 1.

Table 1 Characteristics of included studies

Study (year)	Study design	Intervention; route, type, and dosage (mg)	Number of patients (CD/UC)	Age	Follow up (weeks)	Hematological inclusion criteria;	TSAT (%)	Ferritin (µg/L)	Hb: ♀/♂ (g/dL)
Schroder et al. (2005)[19]	RCT, parallel	IV, iron sucrose in a single dose of 7 mg/kg followed by five 200 mg doses in 5 weeks.	22 (17/5)	35 (median)	6		≤20	≤20	≤10.5 / ≤11.5
		Oral, iron sulfate, 100–200 mg/d in 5 weeks.	24 (12/12)	33 (median)			≤20	<100	≤11
Kulnigg et al. (2008)[23]	RCT, parallel	IV, ferric carboxymaltose, A maximum dose of 1,000 mg, or for patients with body weight (BW) below 66 kg, 15 mg/kg BW. Split across visits.	136 (40/96)	44 (mean)	12		NS	≤300	<11.5
		Oral, Ferrous sulfate, 200 mg. Patients received one capsule(100 mg) b.i.d.	60 (16/44)	47 (mean)			NS	≤20	<12
Lindgren et al. (2009)[20]	RCT, parallel	IV, Iron sucrose, Total dose individually determined. Based on Ganzoni formula, drug was given either in a single weekly dose of 200 mg or every 2nd week until the cumulative dose was reached. 1000 mg was given to replenish iron stores. Mean dose: 1708 ± 331 mg.	45 (20/25)	42.1 (mean)	20		<20	<30	8 - 11 / 8 - 12
		Oral, Iron sulfate, 100 mg, two tablets twice daily. Mean dose: $38\,387 \pm 19\,955$ mg.	46 (24/22)	42.8 (mean)			<20	<30	8 - 11 / 8 - 12
Reinisch et al. (2013)[21]	RCT, parallel	IV, Iron isomaltoside (ISM), Ganzoni formula was used, Patients were randomized to either a single once weekly infusion of ≤ 1000 mg ISM 1000 over 15 min until reaching cumulative dosage or to single once weekly 500 mg bolus injections over 2 min until reaching cumulative dosage. Mean dose: 885 ± 238 mg (infusion) / 883 ± 296 mg (bolus).	219 (66/153)	36 (median)	8		NS	≤20	<12
		Oral, iron sulfate, 200 mg daily for 8 weeks. Total dose: 11 200 mg.	108 (37/71)	35 (median)			NS	≤20	<12
Howaldt et al. (2022)[22]	RCT, parallel	IV, ferric carboxymaltose, between 500 mg and 2500 mg (median, 1500 mg; 500-1500 mg per injection) over 1 to 5 injections (median 2 injections).	125 (79/46)	40.4 (mean)	52		<20	<30	8 - 11 / 8 - 12
		Oral, Ferric maltol, 30 mg twice daily for ≥ 12 weeks.	125 (79/46)	40 (mean)			<20	<30	8 - 11 / 8 - 12

3.1.1. Risk of Bias Assessment

The quality of the retrieved RCTs were evaluated by the Cochrane risk of bias assessment tool 2, which included the following domains: Sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other potential sources of bias. The level of bias in the authors' conclusions is classified as "Low risk," "High risk," or "Unclear risk." The overall risk of bias in the included studies was found to be high on a number of levels. The risk of bias assessment items are summarized in Figure 2 and Figure 3.

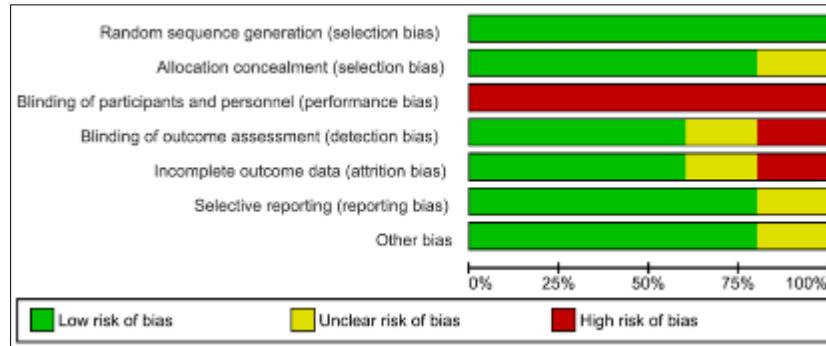
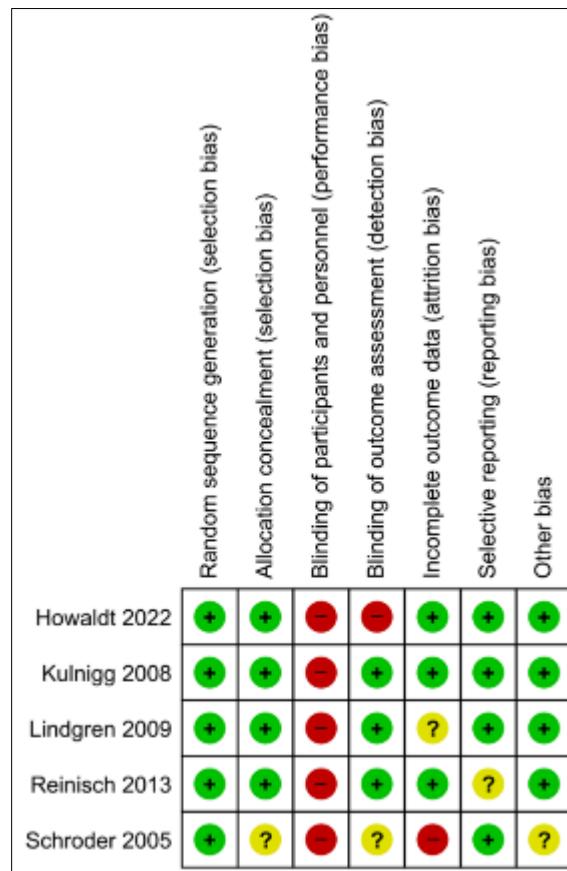


Figure 2 Summary of Risk of Bias Assessment



Symbols: green (+), low risk of bias; yellow (?), unclear risk of bias; red (-), high risk of bias.

Figure 3 Risk-of-bias assessment for the randomized trials included in the meta-analysis

3.2. Results of Meta-Analyses

Hemoglobin Increase ≥ 2.0 g/dL

Five RCTs contributed to this analysis. Each study reported a higher percentage of responders (defined as the proportion of patients with a hemoglobin increase of 2.0 g/dL) in the IV iron group compared to the oral iron group. The ORs with their 95% CIs for the individual studies, and the pooled results, are presented in a forest plot shown in Figure 4.

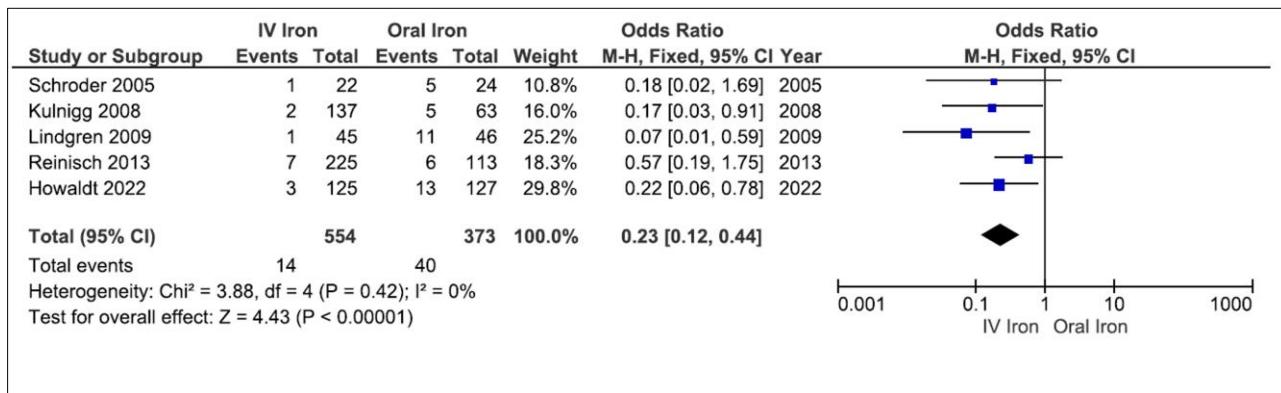


Figure 4 Forest plot for hemoglobin response (ie, an increase of ≥ 2.0 g/dL): results from individual studies and meta-analysis. CI = confidence interval, IV = intravenous, OR = odds ratio

The pooled results of five studies showed that patients receiving IV iron were associated with higher rates of Hemoglobin response than those receiving oral iron (OR 1.44; 95% CI= 1.09 - 1.91; $P = 0.01$). There was no heterogeneity between the results provided from included studies regarding response outcome ($I^2 = 0\%$; P for Cochran $Q = 0.80$).

3.3. Treatment discontinuation

Compared to the oral iron group, the IV iron group showed a lower treatment discontinuation rate (2.5%) than the oral iron group (10%). The pooled effect estimate was statistically significant (OR =0.23; 95% CI= 0.12 - 0.44; $P < 0.0001$). There was no heterogeneity between the results provided from included studies regarding Treatment discontinuation ($I^2 = 0\%$; P for Cochran $Q = 0.42$). Results from the primary studies, and meta-analysis, are shown in Figure 5.

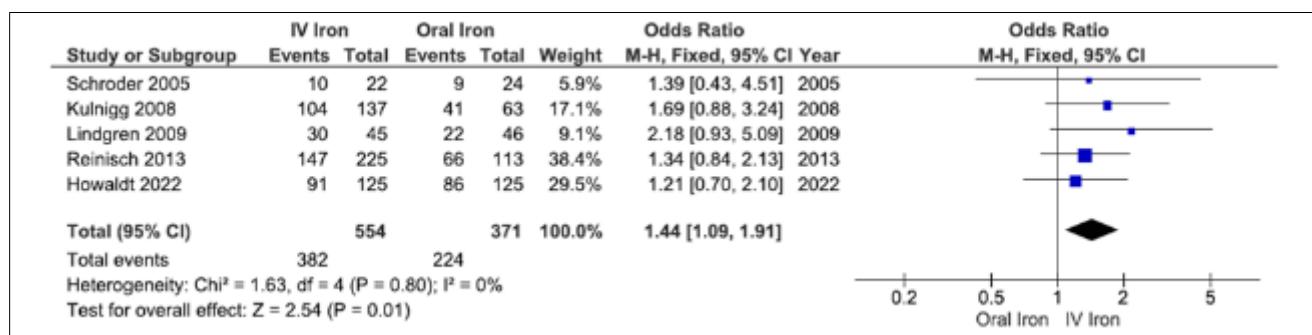


Figure 5 Forest plot for treatment discontinuation, due to adverse events or intolerance: results from individual studies and meta-analysis. CI = confidence interval, IV = intravenous, OR = odds ratio

4. Discussion

Anemia in IBD requires appropriate screening and therapeutic strategy since it is the most common extraintestinal consequence of IBD, and the quality of life significantly improves as a result of iron treatment [24]. The goal of treatment is to provide enough iron to restore hemoglobin levels and replace iron storage, improve quality of life, and improve illness prognosis [25].

Iron supplementation is advised for all IBD patients who have iron deficiency anemia. However, many physicians need clarification about which iron form to use [26]. For a long time, the conventional therapy route was oral iron supplementation. However, oral iron consumption is associated with gastrointestinal side effects [4,23] and has been proven to affect the microbiome's composition, which is essential in the pathophysiology of IBD [13,27].

Newer intravenous iron compounds like iron sucrose (IS), ferric carboxymaltose (FCM), and iron isomaltoside (ISM) have been found to be efficacious and usually safe, in contrast to earlier intravenous iron products like high molecular weight (HMW) iron dextran, which were previously linked to significant safety problems ²⁸. Additionally, it has been shown that intravenous iron administration results in quicker and more effective replenishment of body iron reserves than oral iron supplementation [29].

Many systematic reviews that address the diagnosis and management of anemia in IBD have been found in the current literature. In the review by Nielsen et al., several randomized and nonrandomized prospective trials, with or without control groups were included. However, a meta-analysis was not part of its broad scope [29]. Bonovas et al., Another review that shares the same scope as ours, was found to include one study with a cross-over study design[16,30]. Furthermore, no previous reviews included the recently published study of Howaldt et al., which contributed to more than 27% of the population in our analysis [22].

In this systematic review and meta-analysis, we incorporated five RCTs comparing IV versus oral iron supplementation for correcting iron deficiency anemia in adult patients with IBD. Intention-to-treat analysis was used, which is recognized as the least biased method of estimating intervention effects in randomized trials. This review has some limitations; (1) as determined by the Cochrane Collaboration's tool, all included trials had a high risk of bias. (2) Treatments were not costed, which is an essential concern in clinical practice. (3) No differentiation was made between various IV or oral iron formulations. To advance our understanding of the alternative treatment modalities for iron-deficiency anemia in patients with IBD, additional high-quality randomized studies with correctly specified patient populations, disease activity status, and degree of anemia are required.

Iron deficiency anemia (IDA) is becoming more recognized in individuals with inflammatory bowel disease as a prevalent complication (IBD). IDA significantly affects both healthcare expenditures and quality of life. It is essential to consider how to manage IDA. When a patient is diagnosed with iron deficiency anemia, iron supplementation needs to be initiated every once.

5. Conclusion

In our meta-analysis, we included five randomized controlled trials investigating the safety and efficacy of intravenous versus oral iron for iron deficiency anemia in adult patients with inflammatory bowel disease. IV iron demonstrated a higher efficacy in achieving a hemoglobin response of at least 2.0 g/dL than oral iron supplementation. Patients treated with IV iron preparations had decreased treatment termination rates due to side effects or intolerance.

The available randomized studies show that IV iron is more effective and well-tolerated for treating anemia in adult patients with IBD than oral iron supplementation. Further studies are needed to examine this crucial area to help establish the optimal management of iron deficiency in these patients and to determine whether IV iron therapy is cost-effective.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

All the authors disclose no conflict of interest.

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