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REVIEW ARTICLE

Management of iron-deficiency anemia following acute gastrointestinal hemorrhage: A narrative analysis and review

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Abstract

Many patients experiencing acute gastrointestinal bleeding (GIB) require iron supplementation to treat subsequent iron deficiency (ID) or iron-deficiency anemia (IDA). Guidelines regarding management of these patients are lacking. We aimed to identify areas of unmet need in patients with ID/IDA following acute GIB in terms of patient management and physician guidance. We formed an international working group of gastroenterologists to conduct a narrative review based on PubMed and EMBASE database searches (from January 2000 to February 2021), integrated with observations from our own clinical experience. Published data on this subject are limited and disparate, and those relating to post-discharge outcomes, such as persistent anemia and re-hospitalization, are particularly lacking. Often, there is no post-discharge follow-up of these patients by a gastroenterologist. Acute GIB-related ID/IDA, however, is a prevalent condition both at the time of hospital admission and at hospital discharge and is likely underdiagnosed and undertreated. Despite limited data, there appears to be notable variation in the prescribing of intravenous (IV)/oral iron regimens. There is also some evidence suggesting that, compared with oral iron, IV iron may restore iron levels faster following acute GIB, have a better tolerability profile, and be more beneficial in terms of quality of life. Gaps in patient care exist in the management of acute GIB-related ID/IDA, yet further data from large population-based studies are needed to confirm this. We advocate the formulation of evidence-based guidance on the use of iron therapies in these patients, aiding a more standardized best-practice approach to patient care.

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Introduction

Acute gastrointestinal bleeding (GIB), both upper and lower, is a medical emergency with an annual incidence rate of 5–15 per 10 000 and case fatality of up to 10% (especially in the elderly population).[1–4] Many patients who experience an acute GIB, whether upper or lower, require iron supplementation to treat the iron-deficiency anemia (IDA) or iron deficiency (ID) that can result from the acute blood loss.[5–7] Furthermore, although the bleeding episode is acute, some patients will already have underlying ID at the time of presentation, whereas others will not have detectable ID until a few weeks afterwards when iron stores are depleted. Although iron supplementation—as a fundamental aspect of ID/IDA treatment—is widely acknowledged,[6–8] there are no formal guidelines/recommendations relating to many aspects of patient management in this clinical context. The last decade has seen emerging data in this field and, in recent years, data on the benefit of newer intravenous (IV) iron regimens have been published.[9,10]

As an international group of gastroenterologists/endoscopists with clinical experience across four continents and with a common interest in this field, we formed a working group focused on identifying areas of unmet need, in terms of patient management and practical guidance for the treating physician. In this narrative analysis, we aimed to provide a comprehensive, up-to-date review of published data on this topic, including a summary of the prevalence of ID and IDA in the context of acute GIB seen in clinical practice.

Methods

We performed structured literature searches of the PubMed and EMBASE databases from January 2000 to January 2022, combining relevant keywords for GIB with those for ID, IDA, specific iron supplementation drugs, and transfusion (see supporting information for the full list of keywords). From over 200 articles identified from the searches, we limited articles to those published in the English language and excluded conference abstracts. We identified articles that clearly related to acute GIB and disregarded those that included patients with chronic GIB; however, we retained studies where the inclusion of patients with chronic GIB was ambiguous if the study was deemed pertinent to the review. We included studies irrespective of the definitions and indices used for ID/IDA or "anemia," reporting these definitions whenever specified. Additionally, and where appropriate, we integrate aspects of the working group's clinical experience in this field. Finally, we provide recommendations for practical steps forward to address the identified areas of unmet need.

Results

Iron investigations and prevalence of iron deficiency/iron-deficiency anemia

At hospital admission/during hospitalization. Although limited, available data suggest substantial under-investigation of acute GIB-related ID in clinical practice (Table 1), especially at the time of initial presentation when patient may not necessarily display ID symptoms. In a single study from the USA of 307 patients admitted to hospital with acute GIB, El-Halabi *et al.*[11] reported that less than one third (31%, 95/307) were investigated for ID during their hospitalization. Although almost half (47%, 45/95) of those investigated were subsequently confirmed to have IDA, only half (49%, 22/45) had this documented in their hospital record. This lack of ID testing is consistent with anecdotal evidence from our own clinical practice in the USA, Israel, Turkey, and Spain, where there is no routine testing of iron levels in patients admitted with acute GIB, thereby providing no baseline comparator for post-treatment iron indices. In the state of South Australia, however, it has become more routine to measure iron levels in patients admitted with acute GIB who are anemic at admission and/or have red blood cell (RBC) indices suggestive of ID—a result of increasing proactivity by gastroenterologists, despite no formal evidence-based guidance. This practice has developed from growing local awareness of the need for improvement in recognizing, investigating, and managing ID in hospital practice,[12] increasing recognition of the advantage of adopting restricted blood transfusion policy, and the associated role of IV iron.[13]

The prevalence of anemia in the study by El-Halabi *et al.*[11] was 77% (236/307) at hospital admission and 92% (282/307) during hospitalization. A high anemia prevalence (83%) was also found in a study of 382 patients hospitalized with non-variceal GIB in Romania. Other single-center studies from Europe have shown that, on average and based on mean/median hemoglobin (Hb) levels, acute GIB patients are moderately/severely anemic at hospital admission (Table 2).[9,14]

At hospital discharge. Available evidence indicates that the vast majority of patients with acute GIB remain iron deficient and/or moderately anemic at the time of hospital discharge (Table 3). In the clinical trial by Ferrer-Barceló *et al.*,[9] 90.6% of patients in the oral iron arm and 79.3% in the IV iron arm were iron deficient (transferrin saturation [TSAT] $< 25\%$) at hospital discharge. Bager and Dahlerup[15] found that 84% (142/169) of Danish patients with acute non-variceal upper GIB (UGIB) had ongoing anemia at the time they were discharged home, with a median Hb at discharge of 10.3 g/dL. In a study from Korea of 102 patients hospitalized for acute UGIB and who received packed RBC transfusion, mean Hb at discharge was 8.8 g/dL (±0.7).[16] In another observational study, of 84 patients with acute GIB-related anemia in Spain, Ballester-Clau *et al.*[14] reported the mean Hb at discharge to be 9.4 and 9.3 g/dL in those subsequently treated with transfusion plus ferric carboxymaltose (FCM) or FCM only, respectively. We expect similar observations to become increasingly common in clinical practice due to the wider adoption of restrictive blood transfusion practices that are associated with better patient outcomes in acute GIB.[17]

Treatments for iron deficiency/iron-deficiency anemia used in clinical practice. Underuse of iron therapy for ID/IDA in patients with acute GIB has been consistently documented (Table 4). El-Halabi *et al.*[11] found that only 23% (71/307) of patients admitted to hospital with acute GIB received some form of iron supplementation during hospitalization, and among the 45 patients with IDA, 64% received an iron preparation. Furthermore, only 22% of all patients and 64% of those with IDA had instructions in their hospital discharge summary for their primary care practitioner (PCP) to prescribe iron, and for only four

Table 1 Prevalence of ID/IDA or anemia at hospital admission and/or during hospitalization among patients with acute GIB

Author(s) (year)	Country/ study period	Study type/ setting	Acute GIB population	Data source(s)	ID/IDA[†] prevalence
El-Halabi *et al.* (2016)[11]	USA 3-month period; Nov 2011 to Jan 2012	Observational; single center	307 adult patients admitted with acute GIB	Hospital EMRs and chart review	ID prevalence during hospitalization 31% (95/307) investigated for ID during hospitalization; 47% (45/95) were ID IDA[‡] documented in hospital chart 49% (22/45) Anemia[§] at admission 77% (236/307) Anemia[§] at some point during hospitalization 92% (282/307)
Popovici *et al.* (2013)[32]	Romania 2010	Observational; single center	382 patients hospitalized with non-variceal GIB[¶]; 51% UGIB, 49% LGIB	Laboratory data	Mild anemia (Hb ≥ 10 g/dL)[††] 17% (65/382) Moderate anemia (Hb 7–10 g/dL)[††] 39.5% (151/382) Severe anemia (Hb ≤ 7 g/dL)[††] 26.7% (102/382)
Hreinsson *et al.* (2013)[33]	Iceland 2010	Observational; single center	156 patients with acute UGIB (71% were hospitalized, 24% were already hospitalized, and 5% presented to the emergency room but were not hospitalized)	Standardized form completed by senior gastroenterologists	90% had anemia[‡‡] at presentation

[†]Data on anemia are presented irrespective of whether IDA is specified.
[‡]Laboratory-proven IDA, where ID was defined as either iron saturation < 15% or ferritin < 45 μg/L.
[§]Anemia was defined as Hb < 13 g/dL for men and < 12 g/dL for women.
[¶]GIB not specified as acute or chronic.
[††]Not specified whether at admission or at some point during hospitalization.
[‡‡]Definition of "anemia" was not reported.
EMRs, electronic medical records; GIB, gastrointestinal bleeding; Hb, hemoglobin; ID, iron deficiency; IDA, iron-deficiency anemia; LGIB, lower gastrointestinal bleeding; UGIB, upper gastrointestinal bleeding.

patients were there instructions for the PCP to check the patient's iron levels. In a web-based survey completed by 203 gastroenterologists and hepatologists across Canada,[18] fewer than 15% said they routinely prescribed iron to patients who were anemic at hospital discharge following acute UGIB. And, in the aforementioned study by Bager and Dahlerup,[15] only 16.2% of patients with anemia at discharge following acute non-variceal UGIB were advised to take an iron supplement.

Few studies have described the types of iron therapies used in clinical practice in the setting of acute GIB (Table 4), and none have specified the study period, limiting their interpretation considering the introduction of newer IV iron treatments this last decade. Nonetheless, these data do suggest wide variation between healthcare systems and/or countries in the types of iron therapies. We are further aware of international variation in iron therapy prescribing patterns from our own clinical practice. In South Australia, patients receive restrictive blood transfusion followed by IV iron with FCM. In the Zaragoza region of Spain, most patients with acute GIB also receive IV iron upon discharge, in contrast to Hong Kong and Turkey, where most receive oral iron, and to the USA and Israel, where there is little awareness among gastroenterologists about the iron therapy, if any, that patients receive at hospital discharge.

Efficacy/effectiveness and safety of iron therapies. Only a small number of observational studies and trial, all from Europe, have evaluated the efficacy/effectiveness and safety of different iron therapies (Table 5). In their retrospective study, Ballester-Clau *et al.*[14] analyzed the clinical outcomes of the 84 patients admitted with acute GIB-related anemia (94% with UGIB). All patients had received a single 1000-mg dose of IV FCM with/without blood transfusion during their hospital stay. Mean Hb at 2-month post-discharge follow-up was 12.4 (SD ± 2.5; transfusion plus FCM) and 13.7 g/dL (SD ± 1.8; FCM only)—significant increases from both admission and lowest in-hospital Hb levels ($P < 0.001$) in both groups. Sixty percent of the transfusion plus FCM group and 75.0% of the FCM group achieved normalization of Hb levels at 2 months post-discharge. However, patients administered FCM plus blood transfusion may

Table 2 Average Hb levels at hospital admission/during hospitalization

Author(s) (year)	Country/study period	Study type/ setting	Population with acute GIB	Data sources	Mean/median serum Hb level
Ballester-Clau *et al.* (2019)[14]	Spain Oct 2012 to Dec 2015	Observational; single center	84 patients with acute GIB (94% had UGIB and 6% had LGIB) treated with a single 1000-mg dose of FCM with blood transfusion or without blood transfusion (n = 26)	Pharmacy records and medical records	Mean Hb at admission Patients receiving transfusion + FCM: 8.2 g/dL (SD ± 2.0) Patients receiving FCM†: 10.8 g/dL (SD ± 1.4) Mean lowest Hb during hospitalization and before transfusion/FCM Patients receiving transfusion + FCM: 7.2 g/dL (SD ± 1.3) Patients receiving FCM†: 8.8 g/dL (SD ± 0.6)
Ballester-Clau *et al.* (2020)[34]	Spain Oct 2012 to Dec 2015	Observational; single center	15 patients with cirrhosis and acute GIB treated with a single 1000-mg dose IV infusion of FCM	Pharmacy records and medical records	Median serum Hb at admission Patients receiving transfusion + FCM: 6.2 g/dL Patients receiving FCM†: 8.3 g/dL Mean lowest serum Hb on admission‡ 7.26 g/dL (SD ± 1.14) Mean serum Hb prior to transfusion 6.1 g/dL (SD ± 1.5)
Ferrer-Barceló *et al.* (2019)[9]	Spain NR	Randomized trial; single center	Patients with IDA (< 10 g/dL at discharge) secondary to non-variceal acute GIB and clinically stable (N = 61) 42-day study with 2 arms: IV FCM (n = 29) of 1000 mg at baseline and 500/1000 mg at Day 7, per label (i.e. weight-adjusted and Hb-adjusted dose) *versus* oral ferrous sulfate (FeSulf; n = 32; 325 mg BD for 6 weeks)	Blood samples/ laboratory data	Mean Hb at hospital admission FCM: 9.4 g/dL (SD ± 2.6) Oral ferrous sulfate: 9.7 g/dL (SD ± 2.6) Mean Hb at baseline FCM: 9.3 g/dL (SD ± 0.5) Oral ferrous sulfate: 9.2 g/dL (SD ± 0.7)

†Without transfusion.

‡For the 14 inpatients.

BD, twice daily; FCM, ferric carboxymaltose; GIB, gastrointestinal bleeding; Hb, hemoglobin; IDA, iron-deficiency anemia; IV, intravenous; LGIB, lower gastrointestinal bleeding; NR, not reported; SD, standard deviation; UGIB, upper gastrointestinal bleeding.

have had a more serious GIB, needing blood to maintain hemodynamic stability; furthermore, the retrospective study design means residual confounding cannot be excluded.

Data from clinical trials. In a 13-week double-blind randomized placebo-controlled trial from Denmark, Bager and Dahlerup[10] randomized 91 patients with anemia following acute UGIB to one of three arms: 1000-mg IV FCM at baseline followed by daily placebo tablets, daily oral iron (ferrous sulfate), or IV saline infusion at baseline followed by daily placebo tablets. At the end of treatment (EOT), 70% of the placebo group remained anemic *versus* 17% in the iron treatment groups ($P < 0.01$). Repletion of iron stores was 41.0% (IV iron group), 23.5% (oral ferrous sulfate group), and 10.0% (placebo group). Mean ferritin levels were higher in the IV iron *versus* oral iron/placebo groups from Week 1 ($P < 0.01$), but no clear difference was seen between groups in mean TSAT levels at EOT ($P = 0.13$). The non-blinded trial by Ferrer-Barceló *et al.*[9] of 61 clinically stable participants with IDA secondary to acute non-variceal GIB was randomized at hospital discharge to either IV FCM or oral ferrous sulfate for 6 weeks. Mean Hb at the time of randomization was 9.3 (FCM arm) and 9.2 g/dL (ferrous sulfate arm), and just over half received blood transfusion. Complete response (attaining Hb ≥ 12 g/dL in women and ≥ 13 g/dL in men) in the FCM and ferrous sulfate arms, respectively, was achieved in 85.7% *versus* 45.2% at 3 weeks ($P = 0.001$) and in 100% *versus* 61.3% at 6 weeks ($P = 0.001$). Furthermore, TSAT was normal (> 25%) at 1, 3, and 6 weeks in the FCM arm but < 25% at all time points in the ferrous sulfate arm; at study end, normal TSAT was achieved by 76.9% *versus*

Table 3 Prevalence of ID or anemia at hospital discharge among patients with acute GIB

Author(s) (year)	Country/ study period	Study type/ setting	Patients with acute GIB population	Data sources	Prevalence of ID/anemia or mean/median serum Hb at hospital discharge
Ferrer-Barceló *et al.* (2019)[9]	Spain NR	Randomized trial; single center	61 patients with IDA (< 10 g/dL at discharge) secondary to non-variceal acute GIB and clinically stable (*N* = 61) 42-day study with 2 arms: IV FCM (*n* = 29) of 1000 mg at baseline and 500/1000 mg at Day 7, per label (i.e. weight-adjusted and Hb-adjusted dose) *versus* oral ferrous sulfate (FeSulf; *n* = 32; 325 mg BD for 6 weeks)	Blood samples/ laboratory data	TSAT < 25% at hospital discharge FCM: 79.3% Oral ferrous sulfate: 90.6%
Bager and Dahlerup (2013)[15]	Denmark 8-month period in 2009	Observational; single center	169 patients admitted to hospital with non-variceal acute UGIB	Hospital EMRs and chart review	84% (142/169) had anemia† at discharge home (median Hb 10.3 g/dL, IQR 9.3–11.1, range 7.4–12.9)
Ballester-Clau *et al.* (2019)[14]	Spain Oct 2012 to Dec 2015	Observational; single center	84 patients with acute GI bleeding (94% UGIB and 6% LGIB) treated with a single 1000-mg dose of FCM with blood transfusion or without blood transfusion (*n* = 26)	Pharmacy records and medical records	Mean Hb at discharge Transfusion + FCM: 9.4 g/dL (SD ± 1.2); $P < 0.001$ for change from lowest in-hospital value FCM: 9.3 g/dL (SD ± 0.8); $P < 0.017$ for change from lowest in-hospital value
Ballester-Clau *et al.* (2020)[34]	Spain Oct 2012 to Dec 2015	Observational; single center	15 patients with cirrhosis and acute GIB treated with a single 1000-mg dose IV infusion of FCM	Pharmacy records and medical records	Median serum Hb at discharge Transfusion + FCM: 8.3 g/dL FCM: 8.8 g/dL
Lee *et al.* (2016)[16]	Korea Jan 2012 to Jan 2014	Observational; NR	102 patients with acute UGIB who received pRBCs during hospitalization	Medical records and lab data	50 patients had low discharge Hb levels at discharge (< 10 g/dL); mean Hb 8.8 g/dL (SD ± 0.7)

†Hb < 13 g/dL in men or < 12 g/dL in non-pregnant women.

EMRs, electronic medical records; FCM, ferric carboxymaltose; GIB, gastrointestinal bleeding; Hb, hemoglobin; ID, iron deficiency; IDA, iron-deficiency anemia; IQR, interquartile range; LGIB, lower gastrointestinal bleeding; NR, not reported; pRBCs, packed red blood cells; SD, standard deviation; TSAT, transferrin saturation; UGIB, upper gastrointestinal bleeding.

24.1% ($P < 0.001$). Mean serum ferritin levels increased early in the FCM arm, remaining above 100 μg/L from 1 week. Considering that adherence in clinical trials is higher than in clinical practice, these data indicate significantly increased repletion of iron stores with IV iron than with oral iron.

Safety and tolerability of iron preparations. There are limited safety/tolerability data for iron preparations in the treatment of acute GIB-related ID/IDA. Very few serious adverse events (AEs) occurred in the small clinical trial by Bager and Dahlerup,[10] none were related to the study drug, and their distribution was similar between the trial arms. In the IV iron arm of the Ferrer-Barceló *et al*. trial,[9] 14% of patients experience a non-treatment-related AE (TRAE), but there were no TRAEs, withdrawals, or dose reductions. In contrast, almost one third of patients in the oral ferrous sulfate arm reported TRAEs. In the observational study of Ballester-Clau *et al*.,[14] none of the 84 patients with acute GIB had a severe AE associated with FCM during hospitalization or post-discharge. Anaphylaxis—the most important safety concern with IV iron, albeit rare—was not experienced by any FCM-treated patient in these studies. Further data on anaphylaxis risks with use of IV iron preparations would, however, be beneficial, as a large claims database study[19] of patients receiving IV iron (albeit not restricted to the acute GIB context) found that the risk of anaphylaxis with iron dextran (82 per 100 000 persons, 95% confidence interval [CI]: 70.5–93.1) differed from that with iron sucrose (21 per 100 000 persons, 95% CI: 15.3–26.4).

While the safety profile for IV iron in the acute GIB scenario is excellent and allows faster and more complete resolution of Hb

Table 4 Use of iron supplementation following an acute GIB

Author(s) (year)	Country/ study period	Study type/ setting	Patients with acute GIB	Data sources	Findings
El-Halabi *et al.* (2016)[11]	USA 3-month period; Nov 2011 to Jan 2012	Observational; single center	307 adult patients admitted with acute GIB	Hospital EMRs and chart review	23% (71/307) of all patients and 64% (29/45) of patients with ID[†] received iron supplementation during hospitalization
Fortinsky *et al.* (2016)[18]	Canada NR	Web-based survey	Patients with acute UGIB	Gastroenterologists and hepatologists	15% routinely prescribed iron to patients with acute UGIB who were anemic[‡] at discharge, of whom the majority (81%) prescribed oral iron
Bager and Dahlerup (2013)[15]	Denmark 8-month period in 2009	Observational; single center	169 patients admitted to hospital with non-variceal acute UGIB	Hospital EMRs and chart review	16.2% (23/142) of patients with anemia[§] at discharge were advised to take iron supplementation

[†]ID was defined as either iron saturation < 15% or ferritin < 45 μg/L.
[‡]Definition of "anemic" was not reported.
[§]Hemoglobin < 13 g/dL for men and < 12 g/dL for women.
EMRs, electronic medical records; GIB, gastrointestinal bleeding; ID, iron deficiency; NR, not reported; UGIB, upper gastrointestinal bleeding.

without the use of unwarranted blood transfusion, the benefit–risk assessment for chronic use in other clinical settings could differ. For example, there is a growing awareness of hypophosphatemia with use of IV iron.[20] Analyses of data from clinical trials among patients receiving iron-replacement therapy for IDA[21] or ID (due to a variety of other reasons)[22] have indicated that, in these contexts, the incidence of hypophosphatemia might be lower with use of IV ferric derisomaltose *versus* FCM. While the clinical significance remains uncertain, caution should be adopted; clinical pathways should involve repeated IV iron administration as opposed to resolution of the underlying problem causing the ID.

Patient follow-up and post-discharge outcomes. Data relating to management and outcomes of patients with acute GIB post hospital discharge are similarly limited and disparate. Clear lack of standardized follow-up was seen among 169 patients in Denmark discharged following acute UGIB, and median time to resolution of anemia differing by management strategy.[15] Among patients with anemia and available follow-up data, three received post-discharge blood transfusion, a fifth were advised to take iron supplements (Hb range 8.1–11.6 g/dL), and three quarters neither received blood transfusion nor advice to take iron supplementation; median time to anemia was less than 1, 4, and 2 months, respectively. In Korea, Lee *et al.*[16] followed up 102 patients after a first-time acute UGIB, 50 with Hb < 10 g/dL at hospital discharge and 52 with Hb ≥ 10 g/dL at discharge. Mean Hb in the "low" and "high" Hb groups, respectively, was 10.4 (SD ± 0.71) and 11.4 (SD ± 1.1) at 7 days post-discharge ($P < 0.001$) and 12.2 and 11.9 g/dL at 45 days post-discharge ($P = 0.75$). Four patients (8%) in each group were readmitted to hospital (for any reason), and 12% ("high" Hb group) and 22% ("low" Hb group) reported dizziness ($P = 0.004$). Among 1697 patients with UGIB/lower GIB (LGIB) in Japan,[23] 30.8% of UGIB cases and 26.01% of LGIB cases experienced re-bleeding and/or had persistent IDA (≥ 2 g/dL) within 7 days of their initial emergency hospital admission. Re-hospitalization and mortality data are sparse; however, a UK population-based study among patients with IDA and gastrointestinal disease found that patients treated with IV iron were almost 50% less likely to be readmitted to hospital within 30 days.[24] Furthermore, we recognize from our own clinical experience that, in the USA, Israel, Hong Kong, Spain, and Turkey, there is generally no or limited post-discharge follow-up by the gastroenterologist for patients with acute GIB; the responsibility for follow-up and care of patients with ID/IDA thereafter is generally transferred to the PCP. In contrast, in South Australia, the gastroenterologist generally instructs the PCP (via the discharge summary) to schedule a further dose of IV iron if the patient was anemic at the time of hospital discharge and/or had signs of ID on their pre-transfusion blood test.

Quality of life. Published data on this topic come from the two aforementioned clinical trials. Bager and Dahlerup performed a 6-month follow-up of the 97 participants randomized to receive IV FCM, oral iron, or placebo for 3 months.[25] Twenty-one percent of patients were anemic at 3 and 6 months of follow-up. No significant differences were observed between anemic and non-anemic patients in overall health-related quality of life (HRQoL) mean index (EuroQoL 5 Dimensions [EQ-5D-3L]) at any time points ($P = 0.87$, 0.53, and 0.13 at 1, 3, and 6 months, respectively). The proportion of patients who achieved a normalized age-matched and gender-matched HRQoL was, however, higher in patients without anemia at EOT *versus* those with anemia at EOT ($P < 0.05$), although no difference was seen at 1 or 3 months. There was also evidence to suggest that general and physical fatigue (Multidimensional Fatigue Inventor [MFI-20] questionnaire) was significantly higher in patients who were anemic at EOT ($P = 0.09$ and $P = 0.06$, respectively). Ferrer-Barceló *et al.*[9] evaluated quality of life (QoL) measures between patients randomized to IV FCM or oral ferrous sulfate. Based on the responses of participants who completed the EQ-5D-3L questionnaire (48% of

Table 5 Efficacy/effectiveness of iron treatments in patients with acute GIB

Author(s) (year)	Country/ study period	Study type/ setting	Acute GIB population	Findings
Bager and Dahlerup (2014)[10]	Denmark Apr 2010 to Jan 2013	Double-blind, single-center placebo-controlled RCT 3 arms: IV iron (1000-mg IV FCM in a saline solution at baseline and two placebo tablets per day for 12 weeks; *n* = 42) *versus* oral iron (100-mg ferrous sulfate tablets BD for 3 months + IV saline infusion at baseline; *n* = 41) *versus* placebo (IV saline infusion at baseline and two placebo tablets per day for 12 weeks; *n* = 14) Follow-up for 13 weeks after baseline	97 patients admitted to hospital with non-variceal acute UGIB and anemia at discharge	% anemia[†] at EOT (patients who completed the study) Placebo: 70% Iron treatment: 17%, $P < 0.01$ % full iron stores (based on TSAT and ferritin levels) at EOT Placebo: 10% Oral iron: 23.5% IV iron: 41.0% $P = 0.11$ Mean Hb at EOT (g/dL) Placebo: 11.5 (95% CI: 10.3–12.9) Oral iron: 13.5 (95% CI: 12.9–14.1) IV iron: 13.9 (95% CI: 13.4–14.3) $P < 0.01$ for difference between iron groups and placebo group Mean Hb at Week 4 (g/dL) Placebo: 11.4 (95% CI: 10.3–12.5) Oral iron: 12.5 (95% CI: 11.9–13.1) IV iron: 12.9 (95% CI: 12.5–13.2) $P < 0.05$ for difference between iron groups and placebo group No difference in median Hb levels between oral and IV iron groups at 1, 4, or 13 weeks; $P = 0.97$, $P = 0.38$, and $P = 0.46$, respectively Mean ferritin levels were higher in the IV FCM group than in the oral iron or placebo groups from Week 1 ($P < 0.01$) Mean TSAT levels at EOT were 24%, 26%, and 17% in the IV FCM, oral iron, and placebo groups, respectively ($P = 0.13$)
Ferrer-Barceló *et al.* (2019)[9]	Spain NR	Randomized trial; single center 42-day study with 2 arms: IV FCM (*n* = 29) of 1000 mg at baseline and 500/1000 mg at Day 7, per label (weight-adjusted and Hb-adjusted dose) *versus* oral ferrous sulfate (*n* = 32) 325 mg BD for 6 weeks	61 patients with IDA (< 10 g/dL at discharge) secondary to non-variceal acute GIB and clinically stable	Complete response at Day 21 (reached Hb ≥ 12 g/dL for women or ≥ 13 g/dL for men) IV FCM: 85.7% Oral ferrous sulfate: 45.2%; $P = 0.001$ Complete response at Day 42 IV FCM: 100% Oral ferrous sulfate: 61.3%; $P < 0.001$

(Continues)

Table 5 (Continued)

Author(s) (year)	Country/ study period	Study type/ setting	Acute GIB population	Findings
				Partial response (Hb increment ≥ 2 g/dL from baseline) at Day 21 IV FCM: 100% Oral ferrous sulfate: 67.7%; $P = 0.001$ Partial response (Hb increment ≥ 2 g/dL from baseline) at Day 42 IV FCM: 100% Oral ferrous sulfate: 74.2%; $P = 0.003$ Normalization of TSAT at Day 42 to > 25% IV FCM: 76.9% Oral ferrous sulfate: 24.1%; $P < 0.001$
Ballester-Clau *et al.* (2019)[14]	Spain Oct 2012 to Dec 2015	Observational; single center	84 patients with acute GIB (94% UGIB and 6% LGIB) treated with a single 1000-mg dose of FCM with blood transfusion or without blood transfusion ($n = 26$)	Mean Hb at 2-month follow-up (g/dL) Transfusion + FCM: 12.4 (SD ± 2.5) FCM: 13.7 (SD ± 1.8) $P < 0.001$ for change from admission level and for change from lowest in-patient level in both groups Hb normalized (≥ 12 g/dL in women and ≥ 13 g/dL in men) at follow-up Transfusion + FCM: 60.0% FCM: 75.0% Mean increase (SD) in Hb from lowest in-hospital level to discharge (g/dL) Transfusion + FCM: 2.1 (1.6) FCM: 0.3 (0.6) Mean increase (SD) in Hb from lowest in-hospital level to follow-up visit (g/dL) Transfusion + FCM: 5.6 (2.2) FCM: 4.6 (1.7)
Ballester-Clau *et al.* (2020)[34]	Spain Oct 2012 to Dec 2015	Observational; single center	15 patients with cirrhosis and acute GIB treated with a single 1000-mg dose IV infusion of FCM	Median serum Hb at 2.5–3 months of follow-up visit (g/dL) Transfusion + FCM: 10.0 FCM: 12.8

[†]Hb < 13 g/dL for men and < 12 g/dL for women.

BD, twice daily; CI, confidence interval; EOT, end of treatment; FCM, ferric carboxymaltose; GIB, gastrointestinal bleeding; Hb, hemoglobin; IDA, iron-deficiency anemia; IV, intravenous; LGIB, lower gastrointestinal bleeding; NR, not reported; RCT, randomized controlled trial; SD, standard deviation; TSAT, transferrin saturation; UGIB, upper gastrointestinal bleeding.

FCM group and 59% of oral ferrous sulfate group), overall health status at 6 weeks was significantly better in patients treated with FCM than with oral ferrous sulfate ($P = 0.02$).

Cost-effectiveness of different iron therapies. While there have been evaluations of the cost-effectiveness of different iron therapies in patients with IDA,[26–29] we are unaware of any such analyses specifically in the context of acute GIB-related ID/IDA. Delays in the administration of iron replacement are common and likely impact both direct medical costs and indirect costs in terms of the negative effect on the patient's QoL and productivity losses. Given the significant cost differences attributed to each treatment, future studies assessing this aspect of treatment would enable a fuller comparison of all aspects of different iron therapies. Such studies would require careful planning because identifying patients who are readmitted following acute GIB may be challenging—in practice, it is not uncommon for readmissions to be coordinated by a non-gastroenterology department and/or to occur at a facility different to the first admission.

Discussion

In summary, ID/IDA is a prevalent condition in patients who experience an acute GIB. It is seen at admission, during hospitalization, at hospital discharge, and during follow-up. Furthermore, RBC indices and iron stores—the most meaningful clinical parameters—are not routinely checked before blood transfusion in these patients, and ID/IDA may likely be underdiagnosed and undertreated. We believe this is an increasingly important issue because ID and IDA will probably become more prevalent with the progressive adoption of restrictive blood transfusion practices in this clinical context.

Long-term restoration of normal Hb and iron storage levels after acute GIB is needed to prevent persistent anemia and, thereby, the need for hospital readmission. However, owing to the challenge in maintaining patient contact post-discharge, data on these outcomes are lacking. However, there is some evidence that aspects of QoL are impaired in patients with anemia following acute GIB and that IV iron may be more effective than oral iron in preventing this. There is a clear lack of standardized follow-up once patients with acute GIB are discharged, with management transferred to the PCP, often without clear instruction and no routine further contact with the treating gastroenterologist/endoscopist.

Only two small randomized trials have compared the efficacy and safety of an IV (FCM) and oral (ferrous sucrose) formulation, with the data favoring the IV regimen in terms of speed of iron restoration and tolerance profile. However, only one was double-blinded and this found little difference between the IV and oral regimens investigated in terms of overall restoration of Hb levels. Data relating to various formulations of iron administered in clinical practice are limited and disparate and do not necessarily reflect contemporary/recent practice in the era of newer IV and oral iron products. Nonetheless, the available published data and anecdotal evidence from our working group regarding contemporary clinical practice indicate notable variations in iron prescribing practices, with IV iron substantially more commonly prescribed over oral iron in some, but not all, countries. Furthermore, we also recommend data matching efforts to more accurately evaluate outcomes after acute GIB given the magnitude of the problem globally and the cost to healthcare systems.

In conclusion, significant care gaps exist for patients with acute GIB-related ID/IDA, and there is notable variation in the ways they are managed. We provide recommendations from our working group to address this (Recommendations Box), providing guidance within this specific context. These supplement other recommendations for ID/IDA in broader clinical settings, for example, the British Society of Gastroenterology guidelines for the management of ID[30] and those from Cotter and colleagues for the management of IDA for any GIB (i.e. acute or chronic).[31] However, we advocate the formulation of international evidence-based recommendations/guidance to enable a more standardized, best-practice approach to patient care. Further data from large population-based studies on ID/IDA prevalence and clinical practice patterns of iron therapies are needed to increase the evidence base on this topic. Both clinical trial and observational studies would be beneficial to determine any differences between iron treatments in persistent anemia, re-hospitalization, mortality, and QoL post-discharge.BoxRecommendationsPractical steps to address areas of unmet needs in the context of ID/IDA in patients with acute GIB

Identified unmet need	Recommendations
Potential under-investigation of iron indices at hospital admission/during hospitalization	Large, multicenter, and well-designed observational studies need to be conducted to determine the actual prevalence of ID and IDA among patients hospitalized for acute GIB, both during hospitalization and at discharge.
Potential underuse of iron therapy during hospitalization and at discharge	Large, multicenter, and well-designed observational studies need to be conducted to determine the proportion of patients treated with iron during hospitalization for acute GIB and at discharge.
Lack of standardized patient follow-up by the gastroenterologist	Clinical guidelines developed between gastrointestinal and primary care societies should be established based on the current evidence.
Limited data on effectiveness/ safety of different iron therapies	Large database observational studies should be conducted to investigate the safety and tolerability of iron products that are currently being prescribed in clinical practice.
Limited data on long-term patient outcomes associated with different iron therapies, for example, hospital readmissions	Large double-blind RCTs should be conducted to compare IV and oral iron therapies targeting Hb levels and iron storage, clinical outcomes such as hospital readmission, and morbidity and mortality at precise time intervals.

(Continues)

Table (Continued)

Identified unmet need	Recommendations
Limited data on quality of life associated with different iron therapies	Large double-blind RCTs should be conducted to compare IV and oral iron therapies targeting QoL parameters at precise time intervals.
Lack of data on the cost-effectiveness of different iron therapies	Studies on cost-effectiveness of different iron therapies should be conducted, considering both direct and indirect costs including those related to work-related variables (e.g. time off work and work performance).

GIB, gastrointestinal bleeding; Hb, hemoglobin; ID, iron deficiency; IDA, iron-deficiency anemia; IV, intravenous; QoL, quality of life; RCTs, randomized controlled trials.

Data availability statement. Not applicable.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Supporting Information.