

# Evolving Evidence-Based Treatment Guidelines for Iron Deficiency Anemia in Inflammatory Bowel Disease: Considerations in Managed Care

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## HIGHLIGHTS

- › Diagnosis and Management of Iron Deficiency Anemia in Inflammatory Bowel Disease
- › Impact of Treatment of Iron Deficiency Anemia in Inflammatory Bowel Disease: Considerations in Managed Care
- › CE Sample Posttest

# Evolving Evidence-Based Treatment Guidelines for Iron Deficiency Anemia in Inflammatory Bowel Disease: Considerations in Managed Care

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## Intended Audience

Pharmacists and managed care professionals

## Activity Overview

Iron deficiency anemia (IDA) is closely linked to inflammatory bowel disease (IBD). Treatment often consists of iron replacement therapy, and novel intravenous (IV) iron formulations have impacted the management of patients with both IBD and IDA. Managed care professionals must understand the role of IV iron in treating patients with IBD and IDA, as well as safety and efficacy considerations. This activity will review the role of IV iron replacement in IBD and IDA and focus on the economic burden of these disease states and the impact of IV iron on healthcare resource use.

## Statement of Educational Need

Inflammation in the gastrointestinal tract can result in iron deficiency anemia (IDA), which is the most common complication of inflammatory bowel disease (IBD). Treatment options for IBD can also contribute to the condition, with between 36% and 90% of patients with IBD developing IDA. These patients experience higher rates of hospitalization, longer lengths of stay, and high healthcare costs. Managed care professionals should be familiar with newer intravenous (IV) iron replacement therapies that are entering the treatment landscape of iron deficiency in IBD with the potential to reduce healthcare resource utilization and lessen disease severity for patients. The market for IV iron is expected to increase considerably through 2026, and payers must be equipped to address challenges affecting utilization of and access to these therapies, such as ensuring access to infusions when products require higher doses. To appropriately individualize the treatment of IDA in patients with IBD, managed care professionals must recognize the indications, risks, and benefits of IV iron replacement therapies to develop and implement evidence-based pathways and management plans.

## Educational Objectives

Upon completion of this activity, participants should be able to:

- Examine the biologic pathways relevant to iron hemostasis in inflammatory bowel disease (IBD) as well as appropriate monitoring of iron status.
- Compare iron replacement therapies, including risks and benefits, for the treatment of patients with IBD and iron deficiency.
- Explore the health-related quality of life and economic burden of iron deficiency anemia in relation to the evolving evidence-based treatment protocols for patients with IBD and iron deficiency to improve outcomes and efficiently allocate healthcare resources.

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### OVERVIEW

Through this supplement to *The American Journal of Managed Care*<sup>®</sup>, managed care professionals will become more aware of the prevalence of iron deficiency anemia in inflammatory bowel disease and opportunities to optimize care of patients through evidence-based treatment protocols for iron replacement therapies.

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# Diagnosis and Management of Iron Deficiency Anemia in Inflammatory Bowel Disease

Nicole Bohm, PharmD, BCPS

## Introduction

Inflammatory bowel disease (IBD) is an overarching term used to describe chronic relapsing gastrointestinal (GI) inflammatory disorders, which may cause mucosal ulceration and bleeding, specifically Crohn disease (CD) and ulcerative colitis (UC). The incidence and prevalence of IBD are increasing with Westernized nations having the highest rates.<sup>1</sup> Pathogenesis is multifactorial, including genetic, lifestyle, immune, and intestinal microbiota factors.<sup>2</sup> IBD is associated with extraintestinal manifestations in more than 25% of patients, including hematologic or renal effects.<sup>2,3</sup> The most common causes of anemia in IBD include iron deficiency, which is present in more than half of all cases, as well as vitamin B<sub>12</sub> deficiency, and anemia of chronic disease.<sup>2,4</sup>

Patients with IBD have a higher incidence of anemia compared with a matched cohort without IBD, with an incidence of 92.8 per 1000 person-years compared with 51.2 per 1000 person-years.<sup>5</sup> Patients with IBD also have an almost 2-fold increase in duration of anemia, compared with those without: 52 days versus 27 days per year. This prevalence is greater in females than males, and in CD compared with UC.<sup>4,6</sup>

IDA significantly affects patient quality of life, and in patients with IBD is associated with higher rates of hospitalization and surgery.<sup>2,4</sup> Unfortunately, IDA is underdiagnosed and undertreated in patients with IBD. For example, results of a Veterans Affairs study found more than one-third of patients with anemia and UC were not tested for IDA. Moreover, among those who were diagnosed with IDA, 25% did not receive iron replacement therapy.<sup>7</sup> The purpose of this document is to review the diagnosis and management of IDA in patients with IBD.

## Iron Homeostasis and Effect of Inflammation

Iron, an essential component of hemoglobin (Hb), is required for various cellular functions, including enzymatic processes, DNA synthesis, and mitochondrial energy generation.<sup>8</sup> Iron homeostasis is regulated systemically by multiple mechanisms, but without an excretion regulation pathway, iron status is controlled primarily by dietary intake, intestinal absorption, and iron recycling.<sup>1,9</sup> Patients

## ABSTRACT

Inflammatory bowel disease (IBD) is associated with extraintestinal manifestations in more than one-quarter of patients. Anemia is one of the most common concerns. Patients with IBD and comorbid iron deficiency anemia (IDA) are at risk for hospitalization and surgery, and IDA impacts health-related quality of life. IDA in IBD is often underdiagnosed and undertreated. Prompt treatment has the potential to improve patient quality of life and clinical outcomes. Although the treatment goals for IDA in IBD are well-defined, selecting a treatment is not as straightforward. Traditional oral iron replacement therapies are generally only recommended in patients with mild anemia who do not have active inflammatory disease. Novel oral iron formulations may circumvent some of the limitations associated with traditional oral products.

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For author information and disclosures, see end of text.

with IBD may experience iron loss due to intestinal bleeding, and iron depletion may be compounded by the fact that patients with IBD may have disordered eating and often experience malabsorption related to duodenal disease or inflammation.

The impact of inflammation is mediated primarily via hepcidin, a small protein secreted by hepatocytes. Hepcidin negatively regulates ferroportin, the major cellular iron exporter found predominantly on the intestinal epithelium, macrophages, and hepatocytes.<sup>9,10</sup> Ferroportin enables the transport of iron absorbed via the intestine into circulation, and also mediates iron release from other cells.<sup>10,11</sup> In the presence of iron, hepcidin binds to ferroportin and induces its internalization and degradation by lysosomes, ultimately hindering absorption and export of iron with a net result of depressing serum iron levels.<sup>10,11</sup> Typically hepcidin is upregulated in the presence of high iron concentrations and downregulated by iron deficiency, erythropoiesis, hypoxia, and endocrine signals.<sup>8</sup> However, patients with active inflammatory diseases such as IBD often have elevated hepcidin levels suppressing iron absorption even in states of iron deficiency.

## Signs and Symptoms of IDA

IDA can range from mild (Hb 10 to 13 grams/dL) to severe (Hb <8 grams/dL).<sup>12</sup> The symptoms of iron deficiency are nonspecific, including fatigue, weakness, headache, and dyspnea on exertion. Severe IDA may present with tachycardia, a functional systolic heart murmur, syncope, dyspnea at rest, or angina.<sup>1,8</sup>

## Monitoring Iron Status and Diagnosing IDA

Anemia is defined by the World Health Organization as a blood Hb concentration below 13 grams/dL for males and 12 grams/dL for females.<sup>12</sup> Laboratory evaluation is necessary to establish iron deficiency as the cause of anemia. Serum ferritin, the storage molecule for iron, is less than 30 µg/L in patients with isolated iron deficiency. Transferrin, the carrier molecule for iron, is typically elevated, while serum iron and the transferrin saturation (TSAT) are low. TSAT below 20% is required for the diagnosis of IDA.<sup>1,13</sup>

No single assay is sufficient for diagnosing iron deficiency in patients with concomitant inflammation. If findings indicative of inflammation are present (eg, elevated C-reactive protein), the threshold for IDA is a ferritin less than 100 µg/L.<sup>1,2,14</sup> Iron-restricted erythropoiesis can occur with even higher ferritin levels. Transferrin levels may be normal or reduced in chronic inflammatory states.<sup>2</sup> Serum and urinary hepcidin concentrations are significantly decreased in isolated IDA but are often increased in patients with IBD and IDA.<sup>1,2</sup> Additional markers may aid in diagnosing iron-restricted erythropoiesis in the setting of chronic inflammatory disease, such as soluble transferrin receptor, which is typically elevated, and a reduced reticulocyte Hb level. Thus, clinicians should consider a constellation of laboratory parameters related to

iron for diagnosis of iron restriction or deficiency, and these same values can also be used to evaluate response to therapy.

Once a patient receives a diagnosis of IDA, appropriate treatment strategies must be selected. Elevated C-reactive protein, interleukin-6, or hepcidin are consistent with ferroportin downregulation, which may preclude adequate absorption of oral iron and bolster the role of intravenous (IV) iron replacement.<sup>1,13</sup>

## Management of IDA in IBD

Patients diagnosed with IDA, regardless of overt clinical symptoms, should be promptly treated with an emphasis on replenishing iron stores and addressing the underlying cause.<sup>15,16</sup> The goals of IDA treatment include normalization of Hb and iron stores and improving quality of life.<sup>2</sup>

Although there is a clear consensus among experts worldwide on overall treatment goals, there are various approaches for iron replenishment in patients with IBD. For example, in Europe, IV iron has become the preferred first-line therapy for patients with IBD and active disease, while in the United States, oral iron is still preferred in certain guidelines.<sup>17</sup> Both routes have demonstrated clinical efficacy. Adverse effects (AEs) associated with oral iron therapies are often dose dependent, and may be minimized with newer oral iron products.<sup>18-20</sup> Considerations with IV replacement therapy include the need for administration by a healthcare provider as well as cost, which may impact access to care.

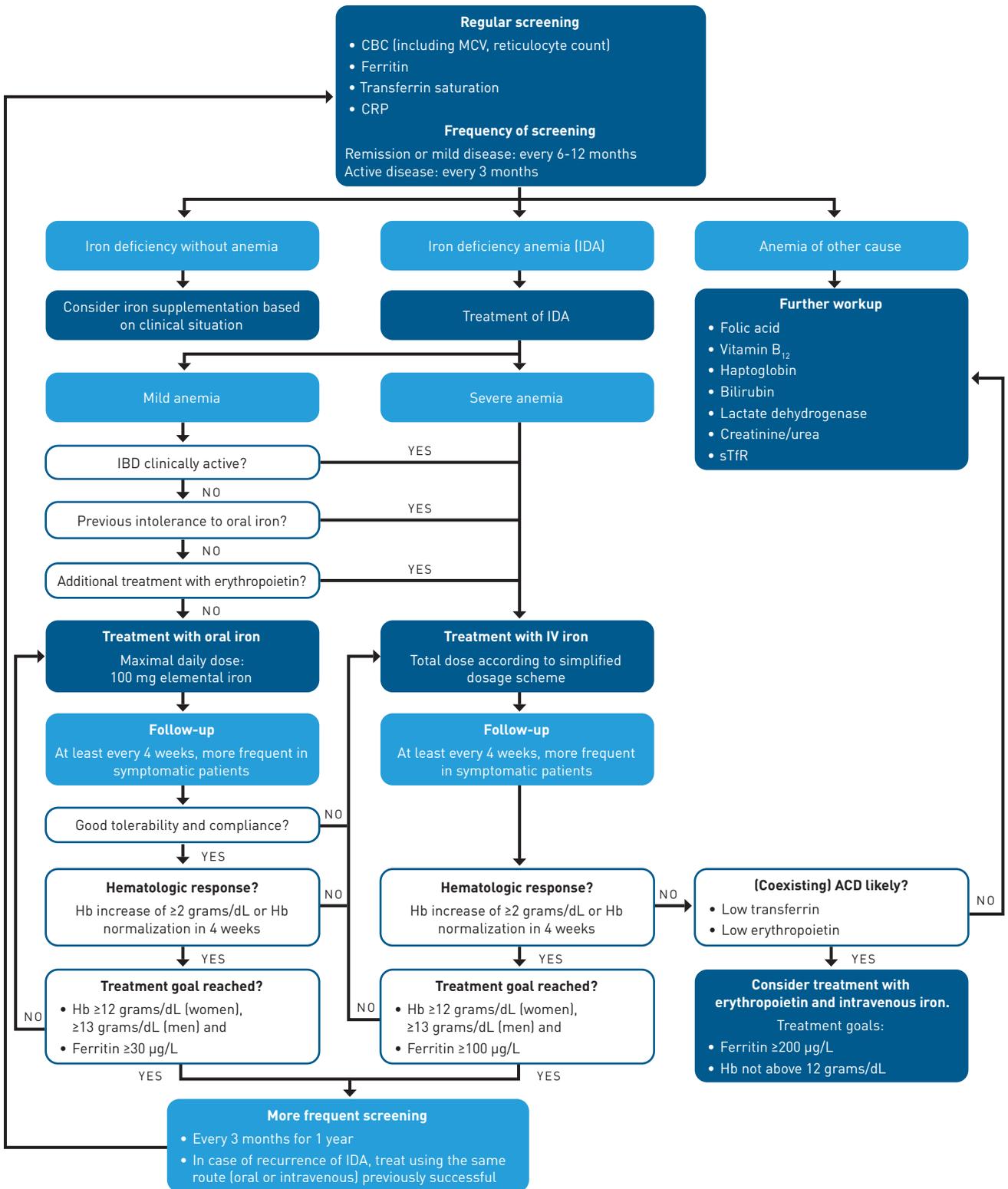
An algorithm from Niepel and colleagues provides some guidance for screening and treatment of patients with IDA in IBD based on the 2015 European Consensus Guidelines, as well as the 2007 Crohn's & Colitis Foundation Guidelines (**Figure 21**). Specifically in patients with IBD and anemia, several factors must be taken into account, including degree of intestinal inflammation, history of GI surgery, and potential vitamin deficiency or dietary restrictions. Specifically in patients with duodenal disease or in those taking a proton pump inhibitor, the ability to absorb iron may be impaired.<sup>21</sup>

## Oral Iron

Oral iron is a commonly prescribed treatment for iron replacement due to low cost with easy access and administration (**Table 1**<sup>4,10,22,23</sup>). Oral iron is recommended in patients with mild IDA, and for most patients without active IBD unless there is a contraindication or intolerance.<sup>1,24,25</sup> Oral iron products require an acidic environment for optimal absorption and as a polyvalent cation, it has notable drug interactions that must also be considered. An increase of 2 grams/dL of Hb may be observed within 4 weeks of treatment initiation, but oral treatment for 6 months is typically required to fully replenish iron stores.<sup>2,15</sup>

Clinical efficacy and safety of oral iron in patients with IBD have been demonstrated in multiple studies.<sup>10,26</sup> A 2009 study of 100 patients reported results on 78 patients with mild anemia

**FIGURE.** Algorithm for Screening and Treatment of IDA in IBD<sup>21</sup>



ACD, anemia of chronic disease; CBC, complete blood count; CRP, C-reactive protein; Hb, hemoglobin; IBD, inflammatory bowel disease; IDA, iron deficiency anemia; IV, intravenous; MCV, mean corpuscular volume; sTfR, soluble transferrin receptor.

(Hb >10 grams/dL) and inactive disease, finding that 89% of participants had complete normalization of Hb, with only 5.1% being intolerant and requiring IV iron.<sup>27</sup> Moreover, IBD activity did not increase, and quality of life improved as Hb levels normalized.

**Ferrous iron.** Due to bioavailability, ferrous iron preparations (ie, ferrous sulfate, ferrous gluconate, ferrous fumarate) are most commonly used.<sup>10</sup> The optimal oral dose of iron for patients with IDA has not been fully elucidated; however, as only 10% to 25% is absorbed, it is recommended not to exceed 200 mg of oral iron daily to minimize AEs, which are often dose dependent and may suppress ferroportin.<sup>10</sup> An alternate-day single-dose has been shown to be more effective than daily dosing, as iron absorption is decreased with more frequent dosing due to increased serum hepcidin and its inhibitory effects on iron transfer.<sup>28</sup> Patients should be counseled to take on an empty stomach if tolerated, or with either 250 mg ascorbic acid or a glass of orange juice to improve absorption.<sup>23</sup>

**Ferric maltol (FM)** is a newer oral iron preparation created from a stable complex of ferric iron (Fe<sup>3+</sup>) with trimaltol.<sup>29</sup> FM is less toxic to the GI tract mucosa than ferrous preparations. The Food and Drug Administration (FDA) approved ferric maltol in 2019 for IDA, but it is not yet commercially available.<sup>29</sup> FM has been used in the European Union for IDA treatment since 2016.<sup>30</sup> The efficacy and tolerability of FM in IDA in IBD was examined in a randomized, double-blind, placebo-controlled trial that included patients with disease remission or nonsevere disease activity and those whose treatment of other ferrous oral preparations previously failed.<sup>18</sup> More participants who received FM achieved Hb normalization within 12 weeks, 66% compared with 13% in the placebo group, but the lack of an active comparator was a limitation. Subsequent studies have shown acceptable safety profiles for FM, with most patients achieving Hb normalization within 3 months.<sup>26</sup> Preliminary clinical trial data demonstrated FM demonstrates similar improvement in quality of life compared with IV ferric carboxymaltose.<sup>31</sup> Although the proportion of responders for Hb increase was not statistically significantly different, the study may have been underpowered and the difference was particularly noticeable among patients with an Hb less than 9.5 at baseline (80% vs 32%).<sup>32</sup>

**Sucrosomial iron** is an oral formulation of ferric iron enveloped in a phospholipid bilayer designed to overcome ferroportin inhibition.<sup>33</sup> Sucrosomial iron has greater bioavailability and lower dose

requirements compared with ferrous sulfate, but is not currently available in the United States. This iron does not directly contact the GI mucosa; therefore, it has lower GI impact and decreased reports of associated AEs.<sup>34</sup> A pilot interventional study in 30 patients with nonsevere IBD and mild IDA had a 96.6% study completion rate, and 80% of participants took all scheduled doses of sucrosomial iron.<sup>33</sup>

Despite the well-established safety profile, affordability, and ease of administration, oral iron preparations have multiple challenges and barriers to their use. As mentioned, the high proportion (75%-90%) of unabsorbed iron within the GI tract frequently results in intolerability and discontinuation of therapy in up to 20% of patients.<sup>4,13,16,24</sup> The most common AEs associated with oral iron therapies include constipation, nausea/vomiting, and abdominal pain.<sup>4</sup> Dose-dependent AEs may be minimized by delayed-release or enteric-coated preparations; however, these products may inadvertently reduce absorption, which occurs predominantly in the duodenum.<sup>10</sup> In addition, free iron in the GI tract may provoke oxidative stress and has the potential to exacerbate the inflammatory state of IBD.<sup>4</sup> Mucosal inflammation may worsen iron malabsorption, thus compounding the state of iron deficiency. Finally, oral iron may disrupt gut microbiota composition, which plays a role in IBD disease activity.<sup>35</sup>

## IV Iron

IV iron is recommended in the 2015 European consensus guideline as first-line treatment for IDA in IBD among patients with moderate to severe anemia (Hb <10 grams/dL), in active IBD, when oral iron preparations are ineffective or not tolerated, or in patients who require erythropoiesis-stimulating agents.<sup>25</sup> Compared with oral iron salts, IV iron bypasses the inflammation-induced blockade of iron absorption and may be given in larger doses, allowing for faster iron repletion.<sup>2</sup> A comparison of IV iron preparations is available in [Table 2](#).<sup>4,10,23,36-40</sup>

Despite advantages, IV iron is expensive, and administration may be less convenient as it must be administered by a healthcare professional. Of note, all IV iron products have been associated with infusion-related reactions or very rarely anaphylaxis, so monitoring for 30 minutes after administration is complete is recommended. Several studies conducted in patients with IBD demonstrated that IV iron was more effective in increasing Hb with lower treatment-related

**TABLE 1.** Comparison of Oral Iron Supplementation Therapy<sup>4,10,22,23</sup>

Oral iron	Strength	Elemental	Administration
Ferrous sulfate	325 mg	65 mg	50-200 mg elemental iron daily or every other day; absorption enhanced in acidic environment
Ferrous gluconate	240, 324, or 325 mg	28-36 mg	
Ferrous fumarate	324 mg or 325 mg	106 mg	
Ferrous sulfate elixir	220-300 mg	44-60 mg/5 mL	

AEs.<sup>41</sup> Furthermore, an observational study by Stein et al showed that IV iron improved clinical scores, decreased hospitalizations, and reduced total healthcare costs.<sup>42</sup>

**Iron sucrose** is the most studied IV preparation in patients with IBD.<sup>4,43</sup> It has a molecular weight of 34 to 60 kDa and a short half-life of 5 to 6 hours.<sup>44,45</sup> Typically, it is administered as 100 to 200 mg over 30 minutes 2 to 3 times weekly, but larger doses up to 500 mg can be diluted and infused slowly.<sup>4,45</sup> Multiple treatment sessions are required to replenish iron stores fully.<sup>45</sup> AEs such as dyspnea, tachycardia, and transient hypotension may occur if iron sucrose is infused too quickly (faster than 4 mg/min) or greater than 7 mg/kg is given as a single dose.<sup>4</sup> In randomized trials, patients receiving iron sucrose are more likely to achieve resolution of anemia and normalization of ferritin compared with those receiving oral iron. An association has also been demonstrated between quality of life and iron treatment response rate

(65%-75%), which is typically seen in the first 4 to 8 weeks.<sup>4</sup> Iron sucrose is also safe to use in pregnant women during the second and third trimesters and postpartum.<sup>44</sup>

**Ferric carboxymaltose (FCM)** is another IV iron preparation that has been extensively studied and used in patients with IBD.<sup>21</sup> It has a molecular weight of 150 kDa and is highly stable; therefore, 1000 mg over 15 minutes can be safely administered in 1 or 2 infusions separated by a week.<sup>4,13,46</sup> FCM has demonstrated noninferiority to oral iron and was more likely to achieve Hb normalization than iron sucrose 200 mg doses up to twice weekly in patients with IBD. It has an acceptable safety profile and patients are adherent to therapy.<sup>47,48</sup> Preliminary clinical trial data indicate the potential to be more effective than oral ferric maltol for increasing Hb.<sup>32</sup> One unique and common AE associated with this formulation is prolonged hypophosphatemia. Patients may be asymptomatic, but hypophosphatemia may be observed within 24 hours of administration, and

**TABLE 2.** Comparison of Intravenous Iron Supplementation Therapy<sup>4,10,23,36-40</sup>

	Iron sucrose	Ferric carboxymaltose	LMW iron dextran	Ferric gluconate	Ferumoxtyol	Ferric derisomaltose
Product	Venofer	Injectafer	INFeD	Ferrlecit	Feraheme	Monoferric
Half-life	5-6 hours	7-12 hours	5-20 hours	1 hour	14-21 hours	1-4 days
Molecular weight	34-60 kDa	150 kDa	73 kDa	37 kDa	750 kDa	1000 kDa
Typical dose	100 mg to 300 mg (max 500 mg) every 2 to 14 days for a cumulative dose of 1000 mg	15 mg/kg up to 750 mg per dose; may repeat after 1 week (off label use up to 1000 mg/dose with 2000 mg max dose)	25 mg test dose over 1-2 minutes followed by up to 1000 mg over 4-6 hours	125 mg thrice weekly for 8 doses	510 mg followed by a second dose in 3 to 8 days	20 mg/kg up to 1000 mg per dose
Maximum injectable single dose	200 mg over 2 to 5 min	750 mg over at least 7.5 min	100 mg daily (test dose still required)	125 mg over at least 10 min	510 mg; consider infusion	500 mg over at least 2 min
Maximum infusion rate	Up to 200 mg over 15 min minimum; larger doses over 1.5 to 4 hours	1000 mg over at least 15 min	Not to exceed 50 mg/min	250 mg over 1 to 2 hours	510 mg over at least 15 min	1000 mg over at least 20 min
Disadvantages	Usually requires 3 to 5 doses, higher labile iron	Hypophosphatemia, transient hypertension/flushing	May have slightly higher rate of anaphylaxis; test dose required	Usually requires 4 to 8 doses, higher labile iron, may contain benzyl alcohol; lacks data outside of CKD	Boxed warning for anaphylaxis, interferes with MRI; lacks data specific to IBD	Only IBD study did not show benefit over oral iron
Benefit	Safe in history of dextran-induced anaphylaxis; strongest evidence in IBD	May be given as single dose, lower labile iron; greater response rate vs iron sucrose in IBD	Total dose infusion, lower cost	Safe in history of dextran-induced anaphylaxis	Requires 2 doses, lower labile iron	May be given as single dose, lower labile iron
Recommended post-infusion monitoring	Infusion-related reactions may occur, including hypotension, flushing, shortness of breath, headache, or urticaria; anaphylaxis is very rare. Monitor for at least 30 minutes after infusion completed					

CKD, chronic kidney disease; IBD, inflammatory bowel disease; LMW, low-molecular weight; MRI, magnetic resonance imaging.

typically peaks within 1 to 2 weeks.<sup>49</sup> Multiple infusions may result in hypophosphatemia, and rarely, may cause osteomalacia.<sup>49,50</sup>

**Iron dextran** is one of the oldest formulations of IV iron. Low-molecular-weight iron dextran (73 kDa) is safer (2-12-fold lower risk of AEs) compared with the high molecular weight products historically used.<sup>4</sup> The risk for anaphylaxis is similar to the newer IV iron preparations, but a test dose should be administered. The major advantages of this product include the ability to give a total dose infusion at one time and a lower cost than other IV iron products. In patients with IBD, iron dextran showed greater increase in Hb in a case-matched comparison with oral treatment and raised Hb substantially by 4 weeks in patients refractory to other therapies.<sup>51,52</sup>

**Ferric gluconate** is a free iron formulation with a molecular weight of 37 kDa.<sup>46,53</sup> Ferric gluconate has been studied primarily in patients with chronic kidney disease undergoing dialysis.<sup>4</sup> The typical dose is 125 mg 3 times weekly for up to 8 doses.<sup>53</sup> Hypotension, tachycardia, dyspnea, and edema are the most common AEs.<sup>4</sup> More studies are needed to elucidate further the role of ferric gluconate in patients with IBD and anemia.

**Ferumoxytol** is a novel IV iron product designed to minimize immunologic sensitivity.<sup>54</sup> Ferumoxytol has a molecular weight of 750 kDa, and should be diluted in 50 to 200 mL of normal saline and infused over 15 minutes or longer.<sup>36,55</sup> It is indicated in patients with IDA with an intolerance or an unsatisfactory response to oral iron and patients with chronic kidney disease (CKD).<sup>36</sup> Ferumoxytol does not require a test dose.<sup>55</sup> Ferumoxytol can also fully replenish iron stores with 2 administrations.<sup>54-56</sup> Studies with ferumoxytol do not specify results in patients with IBD, and there is no direct comparison with oral therapy. The most common AEs noted in patients with CKD who received ferumoxytol were nausea, dizziness, hypotension, and peripheral edema.<sup>36</sup> More studies are needed to understand the role of ferumoxytol in treating patients with IBD and IDA.

**Ferric derisomaltose** is an iron carbohydrate complex of ferric hydroxide and derisomaltose with a molecular weight of 155,000 Da.<sup>39</sup> It is approved in patients who have an intolerance or an unsatisfactory response to oral iron, and non-hemodialysis-dependent CKD. FDA approval was granted based on 2 randomized, open-label, actively controlled clinical trials in 3050 patients with IDA in various etiologies and CKD.<sup>57,58</sup> Noninferiority to iron sucrose was established in both trials regarding Hb increase from baseline to week 8. The only study in IBD was not able to establish a benefit of a 1000-mg dose compared with oral iron, and the authors suggested higher doses might be necessary, particularly in patients with Hb less than 9 grams/dL and elevated C-reactive protein. It was well tolerated and can still be considered in patients who are not candidates for oral therapy.<sup>59</sup>

Each of the IV iron preparations is considered effective in the treatment of iron deficiency<sup>60</sup>; however, in patients with IBD, ferric carboxymaltose and iron sucrose have the most substantial clinical

evidence.<sup>61</sup> While the unique AE of hypophosphatemia must be considered, ferric carboxymaltose may be considered if a high iron dose and quick iron store replenishment are required.<sup>47,62</sup>

IV iron preparations differ based on cost, formulary/purchasing agreements, dosing and administration time, and the number of visits required for iron replenishment.<sup>60</sup> The agents can also be distinguished by iron assimilation into stable iron complexes or release as labile or semi-labile iron. Newer IV iron preparations are associated with infusion reactions (eg, urticaria, palpitations, dizziness, neck/back spasm) in fewer than 1% of patients, and usually do not progress to more serious reactions.<sup>60,63</sup> It is important to monitor patients and provide education on expectations before IV iron administration.

IDA relapse in IBD is common, occurring in more than 50% of patients within 10 to 12 months.<sup>64</sup> Therefore, Hb indices and iron status should be monitored every 3 months for a minimum of 1 year after anemia correction and then every 6 to 12 months once Hb normalization and replenishment of iron stores occur.<sup>25</sup> The FERGImain study evaluating FCM and the PROCEED extension trial assessing iron isomaltoside showed that IDA recurrence may be prevented in patients with IBD with IV iron treatment every 2 to 3 months based on ferritin levels.<sup>65,66</sup>

If rapid recurrence of IDA occurs after anemia correction, the patient should be further evaluated for subclinical inflammation.<sup>60,67</sup> IDA refractory to IV iron should similarly be evaluated for other etiologies or ongoing inflammation. Notably, only patients with quiescent to moderately active IBD are included in iron replacement studies, and newer medications under development, such as hepcidin antagonists and prolyl hydroxylase inhibitors, may expand the treatment portfolio for patients with IBD and IDA in the future.

## Conclusions

In summary, IDA is the most common extraintestinal manifestation of IBD, and it is underdiagnosed and undertreated. As IDA is known to decrease quality of life and is associated with hospitalizations and healthcare costs, it is essential that patients are screened, diagnosed, and treated appropriately. Due to the underlying pathogenesis of IBD, oral iron is not appropriate in all clinical scenarios. Newer IV iron preparations significantly improve iron stores compared with oral iron. Various factors must be considered when selecting a formulation, including dosing, potential AEs, administration time, and patient-specific barriers to access. □

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# Impact of Treatment of Iron Deficiency Anemia in Inflammatory Bowel Disease: Considerations in Managed Care

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## Introduction

Iron deficiency anemia (IDA) is one of the most documented extraintestinal manifestations and clinical complications relating to inflammatory bowel disease (IBD), occurring in 17% to 76% of patients with IBD.<sup>1</sup> IDA is largely due to iron depletion from acute or chronic blood loss or from decreased iron absorption secondary to poor diet, inflammation, or surgery.<sup>1</sup> Factors associated with an increased prevalence of anemia in this population include a greater number of IBD-related outpatient visits, younger age, being a woman, as well as a diagnosis of Crohn disease (CD).<sup>2</sup> Anemia is associated with a more severe disease course, poor quality of life (QOL), frequent hospitalizations, longer hospital stays, and overall increased healthcare burden.<sup>3</sup> Therefore, appropriate diagnosis and management of IDA related to IBD is crucial.

## Direct Healthcare Costs

IBD is one of the costliest chronic diseases, with substantial direct and indirect costs in the United States.<sup>3</sup> An estimated 1 million people in the United States have IBD, with direct medical costs calculated to exceed \$6 billion in 2004.<sup>4</sup> The major contributors to costs include hospitalizations, surgery, ambulatory costs, and pharmaceuticals. Healthcare costs are expected to continue increasing as the prevalence of IBD is expected to grow exponentially due to advances in diagnostics and screenings, in conjunction with low disease mortality.<sup>4</sup> Additionally, patients with IBD may have extraintestinal manifestations, including hematologic or renal adverse effects.<sup>5,6</sup> Anemia is one of the most common complications, and patients with IBD have a higher incidence and duration of anemia compared with those without, which may impact the cost of care.<sup>7</sup>

Data from the Crohn's and Colitis Foundation's Cost of Inflammatory Bowel Disease Care Initiative have shown that in this patient population, the cost of care is driven by patient comorbidities and disease severity. Patients with IBD incurred greater than 3-fold direct healthcare costs when compared with non-IBD controls (\$22,987 vs \$6956 per member per year paid claims) and had more than twice the out-of-pocket costs (\$2213 compared with \$979 per year).<sup>8</sup> This study found the presence of concomitant anemia was

## ABSTRACT

Inflammatory bowel disease (IBD) is commonly associated with iron deficiency anemia (IDA), with a multifactorial pathophysiology. Diagnosis of both IDA and IBD places patients at risk for poor quality of life, as well as increased hospitalization and healthcare utilization. Treatment of IDA involves iron repletion with either oral or intravenous iron products. When selecting therapy, the total expenses of care must be considered, including direct and indirect costs, as well as patient clinical outcomes.

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associated with higher use of healthcare resources, mainly due to hospitalizations. After adjusting for other factors, patients with anemia had 8% higher costs when compared with patients without anemia, with a cost ratio of 1.081 ( $P < .001$ ).<sup>8</sup>

A 2015 study aimed to investigate the use patterns of emergency department visits of patients with IBD in relation to hospitalizations and surgical rates. This cross-sectional analysis used the Nationwide Emergency Department Sample to evaluate adult patients with IBD as a primary diagnosis during emergency department visits and found that 20% of patients had concomitant anemia. Anemia was found to be one of the most significant factors associated with hospitalization (OR, 7.54), with about an 8-fold higher risk of hospitalization compared with those patients with IBD without anemia.<sup>9</sup> This finding indicates the potential need to proactively treat anemia in an effort to reduce inpatient hospitalization.

The impact of anemia severity on healthcare use has also been assessed. In a retrospective chart review of adult patients between 2014 and 2018, health resource use and cost were assessed in patients with IBD. The records of 1763 patients with IBD were included, 966 of which (55%) had CD, 799 (44%) had ulcerative colitis (UC), and 18 (1%) had unspecified IBD. Of these patients, 951 (54%) had concomitant anemia. Patients with anemia had significantly higher direct healthcare costs, a greater number of hospitalizations, an increase in hospital length of stay, and more frequent emergency department, and both gastrointestinal and primary care physician, visits than those with IBD without anemia. Total mean costs for patients with IBD and anemia were estimated to be \$19,627 compared with \$7976

for those without anemia ( $P < .0001$ ). In addition, the severity of anemia was directly correlated to higher healthcare costs, as shown in **Table 1**. Patients with severe anemia had an increased number of hospitalizations (mean [SD] severe anemia 2.2 [2.8] vs moderate anemia 1.3 [2.34] vs mild anemia 0.7 [1];  $P = .0001$ ) in addition to increased inpatient length of stay, averaging 2.8 days longer for patients with severe anemia compared with those with mild (95% CI, 2.28-3.48;  $P < .0001$ ) and moderate anemia (95% CI, 1.28-1.82;  $P < .0001$ ). Surprisingly, patients who were treated with either oral or intravenous (IV) iron did not have lower overall healthcare use or costs when compared with those who did not receive iron therapy (**Table 2**).<sup>3</sup> Although treatment may not be associated with decreased cost or healthcare use, the authors suggest that treating symptoms of IBD, including anemia, early in the disease may have an impact on prevention of severe disease, and that additional analysis may be needed due to the acuity of the patients studied.

## Indirect Healthcare Costs

### Absenteeism, Presenteeism

Indirect healthcare costs include lost labor earnings due to absence from paid work (absenteeism), reduced productivity at work (presenteeism), and reduced opportunities for unpaid activities (loss of leisure).<sup>10</sup> A large systematic review aimed to evaluate the economic burden of UC, specifically related to indirect costs. Although hard to estimate, the study concluded average indirect costs accounted for 35% of total UC healthcare costs.<sup>10</sup> Additionally, a retrospective analysis assessed lost workdays due to IBD, finding that those with

**TABLE 1.** Mean Direct Cost in Patients With Inflammatory Bowel Disease and Mild and Severe Anemia<sup>3</sup>

Cost category	Mild (mean cost [\$], SD)	Severe (mean cost [\$], SD)	P
Clinic cost	532.66 (820.53)	929.92 (1408.09)	.0115
Emergency department cost	262.18 (617.68)	575.57 (1057.18)	<.0001
Pharmacy cost	10,549.39 (26,149.74)	11,768.77 (29,252.23)	.0009
Admission cost	897.06 (1874.50)	4600.46 (8188.20)	<.0001
Total cost	18,384.42 (33,083.72)	25,741.77 (26,063.58)	.0003

**TABLE 2.** Mean Direct Cost of Iron Supplementation in Patients With Inflammatory Bowel Disease and Mild and Severe Anemia<sup>3</sup>

Cost category	IV or oral iron supplementation, mean (\$), SD	No iron supplementation (\$), SD	P
Clinic cost	814.52 (1153.50)	534.11 (694.74)	.0025
Emergency department cost	597.31 (1182.50)	392.43 (1200.41)	.0003
Pharmacy cost	13,502.99 (29,421.73)	9196.12 (22,743.68)	<.0001
Admission cost	3111.71 (6400.29)	1455.73 (3191.36)	<.0001
Total cost	25,623.77 (36,965.18)	17,627.32 (29,468.32)	.0004

IBD missed more workdays than those without (13.4 missed days vs 9.9;  $P = .004$ ), with indirect costs accounting for \$249 million per year in the United States.<sup>11</sup>

Zand and colleagues prospectively evaluated presenteeism and potential work limitations in patients with IBD, assessing work-related productivity, patient QOL, and overall disease activity. In this study, absenteeism was calculated based on the number of work hours missed due to disease based on the percentage of hours worked per week. Presenteeism and work activity impairment were assessed using questionnaires completed by patients during clinic visits. In 440 patients assessed, presenteeism was significantly higher in those with IBD compared with controls (62.9% vs 27.3%;  $P = .004$ ), with no significant difference in absenteeism. A total of 98.9% of patients with active disease had a high incidence activity impairment. Even after disease remission was obtained, patients continued to experience presenteeism. Additionally, these patients had increased indirect costs compared with controls: \$17,766 vs \$9179 per year ( $P < .03$ ), as well as a decrease in productivity suggesting long-term effects of IDA.<sup>12</sup>

A cross-sectional study was conducted as part of the ongoing web-based WORK-IBD study to evaluate the impact of indirect costs of IBD, mainly focusing on predictors of work productivity loss, fatigue, and reduced health-related QOL (HRQOL).<sup>13</sup> The study included 510 patients with IBD who were employed. Study participants were given multiple surveys including Work Productivity and Activity Impairment, Multidimensional Fatigue Inventory, and Short Inflammatory Bowel Disease Questionnaire. Investigators found that disease activity and disease burden led to loss of work productivity in approximately half of study participants. Fatigue was found to be the most important reason for productivity loss, accounting for 56% of absenteeism and 70% of presenteeism. Although fatigue in IBD may be multifactorial, anemia is a likely contributor. Tight disease control to manage anemia and related fatigue have been recommended to reduce disease burden and contributing indirect costs.<sup>13</sup>

### Impact of Iron Repletion on Health-Related Quality of Life

IDA has been shown to have negative consequences on patient HRQOL in patients with IBD. Treatment of IDA with either oral or IV iron is recommended as first-line treatment.<sup>14</sup> Although easily accessible and low in cost, many patients are not able to tolerate oral iron therapy or may not have an adequate response; therapy selection is often guided by patient specifics, including degree of iron deficiency, patient tolerability, and access for drug administration.<sup>15,16</sup>

In a study by LaVallee and colleagues, investigators assessed the likelihood that patients with chronic diseases, including IBD, would receive full planned iron replacement dosing, and also achieve a normalized hemoglobin. Over 46,000 patients with IDA

were enrolled in the study, with 1167 patients with IBD. In the IBD cohort, 201 (29.3%) received ferric carboxymaltose (FCM), 129 (31.8%) received ferric maltol (FM), and 837 (44.6%) received sodium ferric gluconate, iron dextran, or iron sucrose (IS). Although outcomes were not reported specifically for the IBD subgroup, across the entire cohort, 53.9% of patients had normalized hemoglobin within 1 year of treatment initiation with parenteral iron, and those patients who received FCM specifically were more likely to have normalized hemoglobin compared with those receiving FM or another parenteral iron preparation (average OR [AOR], 1.88;  $P < .001$  compared with FM; AOR, 1.4;  $P = .004$  compared with other iron products). Those receiving FCM were more likely to receive full iron replacement doses as well (AOR, 5.1;  $P < .001$  compared with FM; AOR, 3.71;  $P < .0001$  compared with other iron products). Additionally, those patients receiving FCM also had a decreased number of outpatient clinic visits compared with those receiving other iron formulations (5.9 vs 9.2 visits;  $P \leq .001$  compared with FM; 5.7 vs 11.8 visits;  $P \leq .001$  compared with other iron products). The investigators concluded that the choice of parenteral iron products impacts clinical outcomes, and also may decrease outpatient clinic visits.<sup>17</sup>

In a phase 3, double-blind, placebo-controlled trial of patients with IBD whose oral iron replacement treatment failed, results showed a statistically significant and clinically meaningful improvement in outcomes when patients were treated with IV ferumoxytol; 81.1% of patients responded to IV iron replacement, compared with 5.5% of those treated with placebo ( $P < .0001$ ). Additionally, an improvement in the Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-Fatigue) score was improved at week 5 in the treatment arm compared with placebo ( $P < .0001$ ).<sup>18</sup> To explore the durability of this outcome, a subgroup analysis was conducted over a 6-month period of the trial to evaluate the impact of patient-reported outcomes following one dose of ferumoxytol. Results remained favorable; the FACIT-Fatigue scores were increased from baseline to week 5 of the study, with improvement seen over the 6-month period.<sup>15</sup>

A Swiss study aimed to evaluate the cost-effectiveness for FCM versus iron isomaltoside 1000 (IIM), IS, and oral iron therapy. The study developed a health economic model to assess the additional cost per additional responder defined as normalization or increase in hemoglobin of at least 2 grams/dL. Results of the study found that response rates were 81% with FCM, 74% with IIM, 75% with IS, and 69% with oral iron therapy. FCM was determined to be the most cost-effective treatment. The FCM and IIM formulations used in the study required the same number of infusions; however, due to the lower dose of FCM and thus the lower cost, FCM was found to be less costly. Compared with IS, FCM required fewer infusions and, therefore, was associated with cost savings; however, the precise economic impact in the United States has not been elucidated.<sup>19</sup>

## Impact of Undertreatment of Iron Deficiency Anemia

IDA appears to have a high prevalence and affects overall QOL, although the condition is unfortunately undertreated.<sup>20</sup> The European Crohn's and Colitis Organisation recommend annual screening for IDA in patients with IBD. Reasons for undertreatment of IDA are multifactorial, including underscreening for anemia and misconceptions regarding iron products.<sup>21,22</sup> Undertreatment may present missed opportunities for improvements in QOL. Additionally, as anemia is a symptom of more severe disease, earlier treatment may play a factor in reducing disease severity.<sup>3</sup>

One study aimed to evaluate the prevalence of IDA in a cohort at time of first diagnosis of IBD and early in disease course. Factors evaluated included iron treatment frequency, route of iron administration, and effectiveness of subsequent treatments. Hemoglobin levels of 279 patients (183 with CD, 90 with UC, and 6 with indeterminate colitis) were evaluated. Laboratory data further identified the type of anemia present in 70% of patients. At the time of first diagnosis of IBD, IDA was also diagnosed in 26 of the 68 patients with anemia (38.2%; 20 with CD, 4 with UC, and 2 with indeterminate colitis). Only 9 of these patients (34.6%) received iron replacement therapy at the time of diagnosis. At 1 year, 27 patients had concomitant IDA, and 20 (71.4%) received iron replacement therapy. Of the entire cohort with a diagnosis of IDA throughout the study treatment period, 38 (54.3%) did not receive any iron replacement therapy. Additionally, the majority of patients that did receive treatment were administered oral iron products (61; 82.4%), and many patients continued to have IDA despite treatment at 1 year (55.5%). The authors concluded there were inconsistencies in not only diagnosing IDA, but also in managing IDA therapies. This study highlighted potential undertreatment of IDA, and the potential to impact patient outcomes if IDA is managed.<sup>23</sup>

In recognition of the gap of undertreatment and underscreening of IBD and IDA, in 2016 the Anemia Care Pathway (ACP) was developed by the Crohn's and Colitis Foundation to address the inconsistencies seen in clinical practice. Specifically, an explicit algorithm detailing steps to treat IDA, treatment thresholds, and specific time frames for laboratory monitoring was developed. One study aimed to implement the ACP in a managed care setting and identify where improvements in practice habits were seen, as well as barriers to care. The ACP was implemented from July 2016 to June 2017 and retrospectively studied. Results were compared with other providers in the same center not using the ACP. Out of the 640 IBD encounters evaluated in the ACP clinic, patients received iron therapy in 30% of encounters at baseline. Three months after implementation of the ACP, the percentage of patients with anemia prescribed iron therapy rose to a median of 80%. The incidence of anemia decreased from 48% to 25%. There was no improvement seen in the actual screening for iron deficiency, and no shifts in practice were seen in the non-ACP clinics despite awareness of the ACP and other

guidelines. The investigators concluded that although screening rates for IDA did not improve, the ACP did appear to reduce missed opportunities for iron therapy by about half, which resulted in an overall decrease of anemia. Barriers identified by the investigators included the lack of a formal system to track patients including those with an incomplete screening, who screened positive for anemia, or who needed iron infusions. Additionally, laboratory tests were typically ordered after the point-of-care visit, meaning that if a suboptimal hemoglobin level was found, follow-up for additional screening and laboratories were delayed until the next scheduled visit, as many patients did not return to the clinic solely for follow-up laboratories.<sup>22</sup> This study provides a framework for areas of improvement, specifically for patient follow-up.

## Conclusions

In conclusion, IDA is one of the most common clinical complications of IBD. IDA has shown to increase direct healthcare costs by contributing to increased hospital admissions, increased hospital lengths of stay, and increased pharmacy costs. The severity of anemia seems to be directly correlated to use of healthcare resources. Although the indirect healthcare use impact such as absenteeism and presenteeism has been studied less, fatigue is likely a contributing factor for missed time at work and reduced productivity. Treatment with IV or oral therapy has shown a positive impact on patient HRQOL. Although there are clinical practice guidelines for the management of IDA associated with IBD with iron replacement, IDA may be undertreated. Treatment of IBD-related IDA may improve patient outcomes, mitigate healthcare expenses, and improve patient QOL. □

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# Evolving Evidence-Based Treatment Guidelines for Iron Deficiency Anemia in Inflammatory Bowel Disease: Considerations in Managed Care

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## Sample of Online Posttest

Choose the best answer for each of the following:

1. If elevated, which of the following may indicate a need to initiate intravenous (IV) therapy in a patient diagnosed with iron deficiency anemia (IDA) and inflammatory bowel disease (IBD)?
  - A. C-reactive protein
  - B. Ferritin
  - C. Ferroportin
  - D. Hemoglobin
2. Which of the following is a treatment goal in IBD-associated IDA?
  - A. Normalized hemoglobin
  - B. Increased C-reactive protein
  - C. Decreased total iron saturation
  - D. Normalization of hepcidin
3. Which pathophysiologic process may worsen iron malabsorption and further worsen IDA in patients with IBD?
  - A. Reduced gastric pH
  - B. Low hepcidin level
  - C. Increased mucosal inflammation
  - D. Elevated ferroportin production
4. Although efficacious in patients with IBD and IDA, which of the following is a disadvantage associated with the use of iron sucrose?
  - A. Safety in pregnancy
  - B. Multiple treatments to replenish iron stores
  - C. Requirement for long transfusion time
  - D. Low incidence of anaphylaxis
5. Which IV iron preparation has data to support the use in patients with IBD?
  - A. Iron sucrose and ferric carboxymaltose (FCM)
  - B. Ferric derisomaltose and iron sucrose
  - C. Ferric gluconate and iron sucrose
  - D. Ferric gluconate and ferumoxytol
6. RJ is a 45-year-old woman with IBD who presents to the clinic with reports of fatigue, resulting in missed workdays. Her lab work reveals a hemoglobin level of 9 grams/dL, and her physician diagnoses her with IDA. She wants to keep her time in clinic at a minimum, but also wants to treat her IDA quickly. Which treatment would be appropriate to consider for her?
  - A. Oral ferrous sulfate
  - B. IV FCM
  - C. IV ferric gluconate
  - D. IV iron sucrose
7. Which statement accurately describes screening and treatment for IBD-related IDA? IBD-related IDA:
  - A. Screening has improved with the use of clinical guidelines.
  - B. Screening and preferred treatment strategies are inconsistent in clinical practice.
  - C. Is often overtreated, resulting in increased healthcare use.
  - D. Is rarely treated due to expenses associated with therapy.
8. Which of the following has been shown to have the greatest impact on loss of productivity in patients with IBD?
  - A. Treatment-associated adverse effects
  - B. Time associated with treatment
  - C. Discomfort associated with disease
  - D. Fatigue

9. When treating IBD and concomitant IDA, which statement is true regarding patient quality of life? Quality of life is:
- A. Not impacted by treatment with iron replacement therapies.
  - B. Greatly improved with the use of oral iron therapies.
  - C. Improved with iron replacement therapy for a short period of time.
  - D. Improved with IV iron replacement therapy, with sustained results.
10. Which costs are associated with the greatest healthcare-related costs in patients with IBD and IDA?
- A. Clinic costs in patients with mild IDA
  - B. Emergency department costs in patients with mild IDA
  - C. Pharmacy costs in patients with severe IDA
  - D. Hospital admission costs in patients with severe IDA

# SAMPLE POSTTEST





