

Guidelines on the Diagnosis and Management of Iron Deficiency and Anemia in Inflammatory Bowel Diseases

Christoph Gasche, MD,* Arnold Berstad, MD,[†] Ragnar Befrits, MD, PhD,[‡] Christoph Beglinger, MD,[§] Axel Dignass, MD, PhD,^{||} Kari Erichsen, MD, PhD,^{||} Fernando Gomollon, MD,** Henrik Hjortswang, MD,^{††} Ioannis Koutroubakis, MD,^{‡‡} Stefanie Kulnigg, MD,* Bas Oldenburg, MD, PhD,^{§§} David Rampton, DPhil,^{||} Oliver Schroeder, MD, PhD,^{||||} Jürgen Stein, MD, PhD,^{||||} Simon Travis, DPhil,^{***} and Gert Van Assche, MD, PhD^{†††}

Anemia is a common complication of inflammatory bowel diseases. An international working party has formed and developed guidelines for evaluation and treatment of anemia and iron deficiency that should serve practicing gastroenterologists. Within a total of 16 statements, recommendations are made regarding diagnostic measures to screen for iron- and other anemia-related deficiencies regarding the triggers for medical intervention, treatment goals, and appropriate therapies. Anemia is a common cause of hospitalization, prevents physicians from discharging hospitalized patients, and is one of the most frequent comorbid conditions in patients with inflammatory bowel disease. It therefore needs appropriate attention and specific care.

(*Inflamm Bowel Dis* 2007;13:1545–1553)

Received for publication July 31, 2007; Accepted August 17, 2007.

From the *Division of Gastroenterology and Hepatology, Medical University of Vienna, Austria, [†]Institute of Medicine, Haukeland University Hospital, Bergen, Norway, [‡]Department of Gastroenterology and Hepatology, Karolinska University Hospital, Stockholm, Sweden, [§]Division of Gastroenterology and Hepatology, University Hospital, Basel, Switzerland, ^{||} Department of Medicine I, Markus-Krankenhaus, Frankfurt, Germany, ^{|||}Surgical Clinic, Haugesund Hospital, Haugesund, Norway, ^{**}Servicio de Aparato Digestivo, Hospital Clínico Universitario, Zaragoza, Spain, ^{††}Division of Gastroenterology and Hepatology, Linköping University Hospital, Sweden, ^{‡‡}Department of Gastroenterology, University Hospital Heraklion, Crete, Greece, ^{§§}Department of Gastroenterology, University Medical Centre Utrecht, The Netherlands, ^{||} Department Gastroenterology, Barts and the London NHS Trust, London, UK, ^{||||}Division of Gastroenterology and Hepatology, Johann Wolfgang Goethe University Medical Center, Frankfurt, Germany, ^{***}Gastroenterology Unit, John Radcliffe Hospital, Oxford, UK, ^{†††}Department of Gastroenterology, University Hospital Gasthuisberg, Leuven, Belgium.

Most of the authors have variously received unrestricted educational grants, consultancy fees, and/or hospitality from various pharmaceutical companies in the field of inflammatory bowel disease and anemia therapy. No author was paid for this work, nor did any company contribute to the consensus statements or text.

Reprints: Prof. Christoph Gasche, AKH Wien, Gastroenterologie, Währinger Gürtel 18-20, A-1090 Vienna, Austria (e-mail: christoph.gasche@meduniwien.ac.at).

Copyright © 2007 Crohn's & Colitis Foundation of America, Inc.

DOI 10.1002/ibd.20285

Published online November 2007 in Wiley InterScience (www.interscience.wiley.com).

Key Words: guidelines, anemia, inflammatory bowel diseases, iron deficiency, ferritin

Anemia in inflammatory bowel disease (IBD) is the most common systemic complication of IBD.¹⁻³ Several studies have addressed the epidemiologic, etiologic, or therapeutic aspects of this condition^{4,5}; however, until now guidelines for the diagnosis and management of anemia in IBD do not exist. Anemia has great impact on the quality of life of affected individuals in addition to, but also independent of, IBD, but this topic has been omitted from previous (American and European) IBD guidelines. Consequently, this group of authors recognized the need for guidelines specific to anemia and IBD and set about developing them. The British guidelines on the management of iron deficiency anemia⁶ focused on the endoscopic approach for diagnostic purposes, rather than on IBD-related diagnostic or therapeutic guidance. The goal of the current recommendations is to reduce the incidence of anemia, its severity, and need for blood transfusions in order to achieve a better quality of life and reduced comorbidity in patients with IBD.^{7,8}

Anemia in IBD has multiple causes (reviewed in Refs. 1,9), with iron deficiency being the most prevalent¹⁰ (Table 1). Almost every anemic patient with IBD demonstrates some degree of iron deficiency¹¹ as a consequence of dietary restrictions, malabsorption, or intestinal bleeding.^{12,13} Iron deficiency anemia occurs when iron stores are exhausted and the supply of iron to the bone marrow is compromised. Iron deficiency anemia is a severe stage of iron deficiency in which hemoglobin (or the hematocrit) declines below the lower limit of normal. Iron deficiency anemia is defined as anemia with biochemical evidence of iron deficiency. The precise biochemical definition agreed on by the group is given below (see also Tables 2, 3). In active disease, inflammatory mediators may alter iron metabolism (by retaining iron in the reticular-endothelial system), erythropoiesis, and erythrocyte survival. This condition is termed anemia of chronic disease (ACD).¹⁴ Many other causes of anemia exist in IBD but are generally less common (Table 1).

TABLE 1. Etiology of Anemia in Inflammatory Bowel Diseases

Common	Iron deficiency Anemia of chronic disease
Occasional	Vitamin B ₁₂ deficiency Folate deficiency
Exceptional	Drug-induced (sulfasalazine, thiopurines) Hemolysis Myelodysplastic syndrome Aplasia (often drug-induced) Inborn hemoglobinopathies or disorders of erythropoiesis

Purpose of the Guidelines

The principal purpose of this working group was to provide simple guidelines for gastroenterologists (rather than hematologists or general practitioners) who care for patients with IBD. Since this was the first attempt to develop such guidelines and because the quality and quantity of the literature is limited, a certain amount of disagreement between experts was anticipated. If such disagreement persisted after detailed discussion, this is reported in the article.

The guidelines address the appropriate uses of diagnostic measures to screen for iron and other deficiencies related to anemia in IBD, discuss iron and other supplements to prevent and treat anemia in this context, and define therapeutic goals. The article is structured into 4 sections: evaluation of anemia in IBD; triggers for therapy; treatment targets; and treatment recommendations.

It is important to remember that these are guidelines, not rules or protocols for blind adherence. The actual treatment may vary on the availability of products, views of the patient, cost considerations, and the type of health service.

Development of Guidelines

The group was formed in 2005 by C. Gasche. Members were selected on the basis of their contributions to research in the area of anemia in IBD. Four meetings were held during

TABLE 2. Minimum Hemoglobin and Hematocrit Levels Used to Define Anemia in People Living at Sea Level

Age or Sex Group	Hemoglobin		Hematocrit
	(g/dL)	(mmol/L)	(%)
Children 6 months to 5 years	11.0	6.83	33
Children 5-11 years	11.5	7.14	34
Children 12-13 years	12.0	7.45	36
Nonpregnant women	12.0	7.45	36
Pregnant women	11.0	6.83	33
Men	13.0	8.07	39

From WHO/UNICEF/UNU, 1998. (17)

the occasion of the United European Gastroenterology Week (UEGW) (2005 and 2006), Falk Symposium (2006) and the Digestive Disease Week (DDW) (2007). The first 2 meetings were used to discuss the various aspects of the topic. During the third meeting the guidelines process was initiated by using a general questionnaire, which primarily circulated to a subgroup of 8 board members (A.D., K.E., C.G., F.G., I.K., B.O., D.R., O.S.) in February 2007. It was revised upon response (March 2007) and finally voted upon in April 2007. The results of this process were presented at the final meeting and used as a basis for the decision process. In parallel, a comprehensive literature search was performed using PubMed English-language articles or reviews (keywords: inflammatory bowel disease or ulcerative colitis or Crohn's disease AND anemia or anaemia) by S.K. A secondary literature was selected from literature references with regard to iron, vitamin B₁₂, folic acid, or erythropoietin. Parts of this search (related to Crohn's disease) were published previously.³³ A preliminary document was drafted by C.G. and circulated to all board members. A revised document was agreed upon before submission to the journal. The process was independently supervised by Eduard Stange, Stuttgart, whose contribution we gratefully acknowledge.

Grading of Recommendations

The guidelines conform to the North of England evidence-based guidelines development project.¹⁵ The grading of each recommendation is dependent on the category of evidence supporting it: Grade A requires at least 1 randomized controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation (evidence level 1). Grade B requires the availability of clinical studies without randomization on the topic of consideration (evidence levels 2 or 3), or evidence from extrapolation of evidence level 1. Grade C requires evidence from a case-control study or from a nonindependent reference standard (evidence level 4) or evidence from extrapola-

TABLE 3. Degree of Iron Deficiency Evaluated by Serum Ferritin or Transferrin Saturation in Adults

	Serum Ferritin (μg/L)	Transferrin Saturation %
Depleted iron stores in healthy adults or patients with quiescent IBD	<30	<16
Depleted iron stores during active IBD	<100	<16
Adequate iron stores	>100	16-50
Potential iron overload	>800	>50

tion of evidence levels 2 or 3. Grade D requires evidence from expert committee reports or opinions or clinical experience of respected authorities, in the absence of directly applicable clinical studies of good quality (evidence level 5).

1. Anemia Evaluation

Definition of Anemia

Statement 1A: The WHO definitions of anemia (Table 2) apply to patients with IBD. All patients with IBD should be assessed for the presence of anemia (Grade D).

Comment: It is well known that normal hemoglobin varies with age and gender, at different stages of pregnancy, with altitude, smoking, and ethnicity.¹⁶ The correct interpretation of hemoglobin or hematocrit values, therefore, requires the consideration of modulating factors in selecting appropriate cutoff values. The definitions of anemia in IBD is indifferent to other conditions and thus the WHO criteria apply.¹⁷ The recommendation that IBD patients should be regularly assessed for the presence of anemia is based on its high prevalence, impact on the quality of life, and on morbidity.⁵

Screening Parameters

Statement 1B: Hemoglobin, serum ferritin, and C-reactive protein (CRP) should be used for laboratory screening. For patients in remission or mild disease, measurements should be performed every 6 to 12 months. In outpatients with active disease such measurements should be performed at least every 3 months. Patients at risk for vitamin B₁₂ or folic acid deficiency (e.g., small bowel disease or resection) need proper surveillance. Serum levels of vitamin B₁₂ and folic acid should be measured at least annually, or if macrocytosis is present (Grade D).

Comment: The risk of developing anemia relates to disease activity, because both blood loss and ACD are triggered by intestinal inflammation. Complete (or full) blood count, CRP, and serum ferritin are minimum requirements to detect anemia, an inflammatory flare, or iron deficiency in an early stage. Diagnostic measurement of complete blood counts and CRP have been part of previous recommendations in IBD.¹⁸ The serum ferritin was added to these recommendations because iron deficiency is a prevalent nutritional deficiency with a strong impact on anemia.³⁹ The recommended timelines are based on expert opinion and reflect common clinical practice, but do not apply to hospitalized patients. In patients with extensive small bowel resection, extensive ileal Crohn's disease, or ileal-anal pouch, evidence of vitamin B₁₂ or folic acid deficiency should be sought more frequently than once a year.²⁰

Anemia Workup

Statement 1C: Anemia workup should be initiated if the hemoglobin is below normal. The minimum workup includes serum ferritin, transferrin saturation (TfS), and CRP concen-

tration. More extensive workup should be performed if these investigations do not identify the cause of anemia, or if a therapeutic intervention is unsuccessful. More extensive workup includes serum concentrations of transferrin, vitamin B₁₂, folic acid, haptoglobin, lactate dehydrogenase, and creatinine, a reticulocyte, and a differential white blood cell count. Advice from a hematologist is appropriate if the cause of anemia remains unclear after more extensive workup (Grade D).

Comment: Gastroenterologists tend to tolerate reduced hemoglobin levels better than their patients. As endoscopists, they are commonly exposed to severe blood loss and very low hemoglobin levels. The purpose of the current recommendations is to halt this complacency, to set an appropriate threshold to trigger action, and to advise on necessary tests. The mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) are useful parameters and available within the complete blood count. Low MCV and MCH are clear indicators of iron deficiency. In areas with a high prevalence of beta-thalassemia, thalassemia traits should be excluded. In ACD, they may be normal or low.¹⁴ Macrocytosis is indicative of vitamin deficiency, but also arises from thiopurine treatment (azathioprine or 6-mercaptopurine), other medications, alcohol misuse, and hypothyroidism. Platelet and white blood cell counts are also available within the complete blood count and help distinguish isolated anemia from pancytopenia. A truncated, soluble form of the transferrin receptor (sTfR) circulates in the plasma and its concentration is directly proportional to the total body mass of cellular TfR.²¹ It is largely influenced by the level of erythropoietic activity and to a lesser extent by iron stores. sTfR is an excellent indicator of iron-deficient erythropoiesis, particularly helpful in the differential diagnosis of iron deficiency (increased sTfR and low serum ferritin) versus inflammation (normal sTfR and serum ferritin), or for detecting iron deficiency in a patient with concomitant inflammation (increased sTfR and normal serum ferritin).¹⁴ In clinical practice, however, sTfR is expensive and not available in many laboratories. Therefore, it was not included as a standard recommendation. Since disease activity is not always associated with an increase in acute phase proteins (particularly in ulcerative colitis) and may not be accompanied by clinical symptoms, endoscopy may be needed to evaluate disease activity in patients with a low CRP.

Iron Deficiency

Statement 1D: Diagnostic criteria for iron deficiency depend on the level of inflammation (Table 3). In patients without biochemical or clinical evidence of inflammation, appropriate criteria are a serum ferritin <30 µg/L or TfS <16%. In the presence of inflammation, the lower limit of serum ferritin consistent with normal iron stores is 100 µg/L (Grade B).

Comment: In IBD, the distinction between iron defi-

ciency anemia and ACD is important, since both conditions typically overlap. Iron deficiency may be caused by continuous blood loss from the ulcerated surface of the bowel, malnutrition with reduced iron intake, or impaired iron uptake through the duodeno-jejunal mucosa. In the absence of biochemical (CRP, leukocyte count) or clinical evidence (diarrhea, hematochezia, endoscopic findings) of inflammation, iron stores are likely to be zero if the serum ferritin is $<30 \mu\text{g/L}$. In the presence of inflammation, serum ferritin levels can be high despite empty iron stores.^{22,23} In such cases, $100 \mu\text{g/L}$ is considered an appropriate cutoff level.¹⁴ During or shortly after intravenous iron therapy, serum ferritin levels do not correlate with body iron stores.²⁴ Iron deficiency may cause an array of clinical or subclinical symptoms such as cognitive function or ovulatory fertility.^{25,26}

Anemia of Chronic Disease

Statement 1E: In the presence of biochemical or clinical evidence of inflammation, the diagnostic criteria for ACD are a serum ferritin $>100 \mu\text{g/L}$ and TfS $<16\%$. If the serum ferritin level is between 30 and $100 \mu\text{g/L}$, a combination of true iron deficiency and ACD is likely (Grade B).

Comment: In patients with active IBD, certain cytokines or hepcidin may reduce iron absorption, retain iron within cells of the reticular-endothelial system, and inhibit erythropoiesis.¹³ These mechanisms may lead to ACD, a condition that is frequently found in hospitalized patients.⁵⁰ ACD is likely if the serum ferritin is $>100 \mu\text{g/L}$ and TfS $<16\%$. In addition, the sTfR/log serum ferritin may be a useful tool to exclude iron deficiency (if the ratio is <1).¹⁴

2. Triggers for Treatment of Anemia

Initiation of Therapy

Statement 2A: Treatment should be considered for all patients with a hemoglobin below normal. The decision to initiate therapy depends on symptoms, etiology, and severity of anemia, rate of change, comorbidity, and potential adverse effects of therapy (Grade D).

Comment: The large variation of clinical scenarios (from borderline hemoglobin without iron deficiency to extremely low hemoglobin levels, overt bleeding or to hemolytic anemia) requires an array of actions depending on the clinical scenario and symptoms of the patient. The initiation of therapy depends on individual symptoms (such as fatigue, headache, dyspnea, or palpitations), but also on disease activity, overt bleeding, and hemoglobin levels. It is important to consider that anemia impairs quality of life even in the absence of specific symptoms^{7,27} and that its treatment leads to improvement in the quality of life.²⁸ These simple facts are often unrecognized or neglected by gastroenterologists caring for patients with IBD.

Initiation of Iron Supplementation

Statement 2B: Iron supplementation should be initiated when iron deficiency anemia is present (Grade A). For iron deficiency without anemia, different approaches to iron replacement should be considered and discussed with the patient. If patients are likely to develop iron deficiency anemia the monitoring frequency should be increased (Grade D).

Comment: Several randomized trials have tested the effect of iron therapy on patients with IBD-associated iron deficiency anemia.^{28–30} The decision to supplement iron in patients without anemia is more complicated and depends on the clinical scenario, the patient's history, and individual preference. Oral iron would be a simple option. However, in IBD nonabsorbed ferrous iron has the potential to worsen IBD symptoms and to aggravate intestinal inflammation through the Fenton reaction,* which releases reactive oxygen species.^{30,31} On the other hand, intravenous iron therapy may be considered inappropriately interventional, especially when using iron dextran with its risk for dextran-associated anaphylactic reactions.

Initiation of Erythropoietic Therapy

Statement 2C: The use of erythropoietic agents is effective for the treatment of ACD and may improve the quality of life. It should be considered if the hemoglobin is $<10.0 \text{ g/dL}$ or if there is no response to intravenous iron therapy within 4 weeks (Grade B).

Comment: Erythropoietic agents (such as epoetin alfa, epoetin beta, darbepoetin alfa) are effective in the treatment of ACD at a hemoglobin below 10.0 g/dL .^{11,28,32} The actual need for erythropoietic agents in this scenario is uncommon, because intravenous iron alone has a response rate of 70%–80%.^{28,33} Certain laboratory parameters such as the serum erythropoietin, sTfR, or transferrin levels may predict cases that will not respond to intravenous iron alone and may profit from combination therapy.³⁴

Initiation of Vitamin Supplementation

Statement 2D: Replacement of vitamin B₁₂ or folic acid should be initiated if serum concentrations are below normal (Grade D).

Comment: Measurement of serum folate and vitamin B₁₂ levels has many limitations and are not always reliable. In the presence of macrocytosis or unexplained anemia, especially in patients with ileal resection serum homocysteine and methylmalonic acid levels, should be measured.³⁵

Blood Transfusion

Statement 2E: Indications for replacement of blood after acute or chronic gastrointestinal bleeding vary depend-

*The Fenton reaction is the iron-salt-dependent decomposition of hydrogen peroxide, generating the highly reactive hydroxyl radical, possibly via an oxoiron intermediate ($\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{OH} \cdot + \text{OH}^-$).

ing on the clinical situation (including the rate of bleeding, hemodynamic state, hemoglobin, age, concomitant disease) and are best judged by the physician. Management should be directed at diagnosing and stopping intestinal bleeding. Blood transfusion is no substitute for the treatment of iron deficiency anemia with intravenous iron, possibly in combination with erythropoietic agents. Should transfusion be judged necessary, iron replacement therapy is still required (Grade D).

Comment: The need for blood transfusion should be considered carefully, because most patients suffer from chronic bleeding and repeated blood transfusions are not an appropriate therapy for chronic blood loss. A principal purpose of these guidelines is to reduce the need for blood transfusion by timely recognition and appropriate treatment of anemia. Options other than blood transfusion (including intravenous iron with or without erythropoietic therapy) should always be considered and replacement of iron stores is necessary even if the hemoglobin is corrected by transfusion.

3. Targets of Anemia Therapy

Treatment Goals

Statement 3A: The goals of anemia treatment are to increase the hemoglobin, serum ferritin, and TfS above the lower threshold of normal (Tables 2, 3), to prevent a further fall in hemoglobin, to avoid the use of blood transfusion, to relieve symptoms related to anemia, and to improve the quality of life (Grade D).

Comment: Anemia is a frequent trigger for hospitalization and is a common factor delaying discharge from hospital. Anemia is one of the most frequent comorbid conditions in IBD-related mortality.³⁶ It therefore needs appropriate attention and specific care.

Response to Treatment

Statement 3B: The erythropoietic response to iron or hematinic replacement is considered appropriate if the hemoglobin concentration increases by at least 2 g/dL or reaches normal (Table 2) within 4 weeks of treatment (Grade C).

Comment: Human erythrocytes have a mean lifespan of about 120 days. This implies that ≈ 200 billion new erythrocytes, carrying collectively 6 g of hemoglobin, are produced every day, i.e., 2–3 million new red cells every second. In situations of anemia, which decreases oxygen supply, red cell production can expand up to 20 times over baseline rates, underlying the very dynamic nature of erythropoiesis. Laboratory methodology and fluid balance cause diurnal changes up to 1 g/dl. The 2 g/dL increase can be reached by intravenous iron therapy within 2–4 weeks.^{28,29} If the therapeutic response is inappropriate, treatment should be intensified (oral iron switched to intravenous iron treatment), changed (addition of erythropoietic agents), or the cause of anemia should be reevaluated (possibly with the assistance of a hematologist, see Statement 1C).

Treatment Evaluation

Statement 3C: To evaluate the response to therapy, hemoglobin should be measured within 4 weeks in asymptomatic patients and sooner in symptomatic patients in order to adjust treatment accordingly. When monitoring oral iron supplementation, a serum ferritin above 100 $\mu\text{g/L}$ indicates appropriate iron stores. Serum ferritin is not useful for monitoring intravenous iron supplementation, but a TfS $>50\%$ indicates iron overload (Grade D).

Comment: Measurement of TfS falsely overestimates the therapeutic response to iron therapy because the increase in TfS is only temporary, for as long as oral or intravenous iron is being administered. In the setting of intravenous iron therapy serum ferritin levels are falsely high.²⁴ In this situation a TfS $>50\%$ is the most useful indicator of iron overload.

4. Treatment of Anemia

Iron Supplementation

Statement 4A: The preferred route of iron supplementation in IBD is intravenous, even though many patients will respond to oral iron. Intravenous iron is more effective, better tolerated, and improves the quality of life to a greater extent than oral iron supplements (Grade A). Absolute indications for intravenous iron include severe anemia (hemoglobin <10 g/dL), intolerance, or inappropriate response (see Statement 3B) to oral iron, severe intestinal disease activity, concomitant therapy with an erythropoietic agent, or patient preference. Dosing and infusion intervals depend on the compound (Table 4). Oral iron supplements can be used if absolute indications for intravenous iron therapy are not met. If oral iron is used, the response (Statement 3C) and tolerance should be monitored and treatment changed to intravenous if necessary (Grade C). Since side effects of oral iron are dose-related, and because its absorption and efficacy are no greater when high doses are used, no more than 100 mg elemental iron daily should be prescribed (Grade C).

Comment: There are many factors in favor of intravenous iron therapy. Clinical comparative trials^{29,37} show faster and prolonged response with intravenous iron. Oral iron may not be able to compensate ongoing blood loss.³² Studies in animal models of IBD demonstrate with consistency an increase in oxidative stress, disease activity, intestinal inflammation, and even colorectal cancer development through oral iron supplementation (reviewed in Ref. 4). This is not surprising, as about 90% of the ingested iron is not absorbed, passes the sites of intestinal inflammation, and induces local oxidative stress at sites of active inflammation (through the Fenton reaction, see above). Further studies indicate that nutritional iron may be one of the exogenous factors responsible for the onset of colitis.^{38,39} In human IBD, oral iron induces oxidative stress,³¹ increases local disease activity,⁴⁰ and its absorption is inhibited, possibly through a hepcidin-

TABLE 4. Intravenous Iron Compounds

	High MW Iron Dextran	Low MW Iron Dextran	Iron Gluconate	Iron Sucrose	Ferric Carboxy-maltose ^a
Trade names ^b (US, Europe)	Dexferrum	Infed, Cosmofer	Ferlecit	Venofer	Injectafer, Ferinject
Manufacturer	Luitpold Pharmaceuticals	Pharmacosmos	Sanofi-Aventis	Vifor Int.	Vifor Int.
Chemical properties^c					
MW [kD]	265	165	< 50	30–100	> 100
Complex stability	High	High	Low	Moderate	High
Acute toxicity	Low	Low	High	Medium	Low
Dosing^b					
Test dose required	Yes	Yes	No	Yes*/No	No
Maximal dose	1000 mg	1000 mg	62.5–125 mg	200–500 mg	1000 mg
Max. infusion time	360 min	360 min	60 min	30–210 min	15 min
Max. injectable single dose	100 mg	100 mg	125 mg	200 mg	200 mg
Max. injection time	2 min	2 min	10 min	10 min	Bolus push
Safety profile^d					
Risk of dextran-induced anaphylaxis	Yes	Yes	No	No	No
Relative risk of serious adverse events	High	Moderate	Low	Lowest	n.a.

n.a., Not available; MW, molecular weight.

^aAccording to Kulnigg (37) et al, 2007, Seid (54) et al, 2006.

^bPrescribing information of marketed products.

^cAccording to Crichton et al, 2005. (52)

^dAccording to Auerbach (41) et al, 2007, Chertow (53) et al, 2006.

*Only in Europe.

mediated mechanism.¹³ The main factor in favor of oral iron is convenience, not efficacy. The inconvenience of intravenous iron is offset by the benefit in achieving therapeutic goals.

Various intravenous iron products are currently available with differences in biochemical characteristics, side effects, dosing, and country-to-country availability (Table 4). High molecular weight iron dextran is obsolete, because of its potential to cause severe anaphylactic shock and associated mortality.⁴¹ Ganzoni's formula is useful to estimate iron needs.⁴² In the IBD clinic, however, anemic patients will rarely have a deficit less than 1000 mg. In fact, by using a TfS >50% as a guide to stop therapy (Statement 3C), 3600 mg iron sucrose has been administered safely in controlled trials without liver damage or iron overload.^{24,28} The risk of iron overload can be considered very low in a population with ongoing blood loss.³⁴ If oral iron is used, no reliable data exist to prefer any one compound over another. Slow-release products should be avoided as they are released *beyond* the area of iron absorption and may impact or cause ulceration at Crohn's strictures.⁴³ The optimal dose of oral iron has still not been established. Since a maximum of 10–20 mg of oral iron can be absorbed per day, higher doses are questionable. Low-dose iron (100 mg elemental iron daily) is effective in other causes of iron deficiency.^{44,45}

Erythropoietic Agents

Statement 4B: Erythropoietic agents (Table 5) are effective for the treatment of ACD. To optimize the effect of erythropoietic agents, treatment should be combined with intravenous iron supplementation. Dosing and injection intervals depend on the compound used (Grade A).

Comment: Erythropoietic agents are used for the treatment of ACD. Together with iron replacement, response rates of 75%–100% have been reported in clinical trials.^{11,28,32,33,46,47} There are no dose-finding trials in IBD. Consequently, dosing and injection intervals are derived from treatment of other causes of ACD (such as cancer patients) (Table 5). In IBD studies, epoetin alfa has been used at 200 U/kg bodyweight twice per week³² or 150 U/kg bodyweight three times per week.^{28,33,46} Darbepoetin alfa has been tested in 1 study in IBD, with 0.9 µg/kg body weight once per week, a dose that might be considered low.⁴⁷ Erythropoietic agents should always be combined with intravenous iron supplementation because functional iron deficiency is likely to develop.⁹ Functional iron deficiency is defined as an inappropriate availability of iron for erythropoiesis despite normal body iron stores, which may be encountered during treatment with erythropoietic agents. In IBD, erythropoietic agents are considered safe. In general, subcutaneous administration is associated with fewer side effects and greater benefit.

TABLE 5. Characteristics of Erythropoiesis Stimulating Agents

	Epoetin alfa	Epoetin beta	Epoetin delta	Epoetin omega	Darbepoetin alpha	Pegylated Epoetin beta
Trade names (US, Europe)	Epogen, Procrit Eprex, Erypo	NeoRecormon	Dynepo Gene Activated Erythropoietin	Epomax Hemax Hemax-Eritron	Aranesp, Nespo	Mircera
Manufacturer	Amgen, Jansen-Cilag	Roche	Shire, Cell Genesys	Baxter	Amgen	Roche
Chemical properties						
MW [kD]	30.4	32–40	26–32	39	37.1	60
T 1/2	4–6 h (IV) 24 h (SC)	4–12 h (IV) 13–28 h (SC)	4.7–13.2 h (IV) 27–33 h (SC)	n.a.	21 h (IV) 49 h (SC)	134 h (IV) 139 h (SC)
Dosing						
Anemia in CKD	3 × 50 IU/kg/week (SC or IV)	3 × 20–40 IU/kg/ week (SC or IV)	2–3 × 50 IU/kg/ week (SC or IV)	2 × 25–50 IU/kg/ week (SC or IV)	0.45–0.75 µg/kg/weekly to once every two weeks (SC or IV)	n.a.
Cancer- and chemotherapy- related anemia	3 × 150 IU/kg/week (SC)	3 × 150 IU/kg/week (SC)			2.25–6.75 µg/kg weekly to once every three weeks (SC)	
Formulation	500 IU, 1000 IU, 2000 IU, 3000 IU, 4000 IU, 5000 IU, 6000 IU, 7000 IU, 8000 IU, 9000 IU, 10000 IU, 40000 IU	1000 IU, 2000 IU, 3000 IU, 4000 IU, 5000 IU, 6000 IU, 10000 IU, 30000 IU	1000 IU, 2000 IU, 3000 IU, 4000 IU, 5000 IU, 6000 IU, 8000 IU, 10000 IU	1000 IU, 2000 IU, 3000 IU, 4000 IU, 10000 IU	10 µg, 15 µg, 20 µg, 30 µg, 40 µg, 50 µg, 60 µg, 80 µg, 100 µg, 150 µg, 300 µg, 500 µg	n.a.
Safety profile						
Hypertension or thrombosis	Yes	Yes	Yes	Yes	Yes	Yes
Risk of PRCA	Yes	Yes	Unknown	Unknown	Yes	Unknown

n.a., not available; MW, molecular weight; IV, intravenous; SC, subcutaneous; PRCA, pure red cell aplasia (a very rare side effect of all commonly used erythropoietins); CKD, chronic kidney disease.

Adjustment of IBD Therapy

Statement 4C: Azathioprine or 6-mercaptopurine (thiopurines) are not considered a cause of isolated anemia. Nevertheless, for patients with pancytopenia thiopurines should be considered a cause and the dose adjusted appropriately. Patients with a high MCV should be checked for vitamin B₁₂ and folate deficiency before macrocytosis is attributed to thiopurines or other causes.

Comment: Isolated anemia in patients on azathioprine or 6-mercaptopurine is unlikely to be caused by drug treatment. Other causes should first be considered (Table 1). In some patients, however, a mild and asymptomatic reduction in hemoglobin may be seen. Precautions should be implemented to avoid leukopenia or pancytopenia and the dose adapted accordingly.^{48,49} Although macrocytosis is regarded as a feature of thiopurine therapy that has been suggested as a measure of appropriate dosing,^{50,51} vitamin B₁₂ or folic acid deficiency should be excluded in patients with a macrocytosis (Statement 1B) to avoid overlooking vitamin deficiency. Appropriate treatment of the underlying disease is a key to prevention of anemia.

REFERENCES

- Schreiber S, Wedel S. Diagnosis and treatment of anemia in inflammatory bowel disease. *Inflamm Bowel Dis*. 1997;3:204–216.
- Gasche C. Complications of inflammatory bowel disease. *Hepato-gastroenterology*. 2000;47:49–56.
- Gasche C, Lomer MC, Cavill I, et al. Iron, anemia, and inflammatory bowel diseases. *Gut*. 2004;53:1190–1197.
- Kulnigg S, Gasche C. Systematic review: managing anemia in Crohn's disease. *Aliment Pharmacol Ther*. 2006;24:1507–1523.
- Wilson A, Reyes E, Ofman J. Prevalence and outcomes of anemia in inflammatory bowel disease: a systematic review of the literature. *Am J Med*. 2004;116(Suppl 7A):44S–49S.
- Goddard AF, McIntyre AS, Scott BB. Guidelines for the management of iron deficiency anemia. British Society of Gastroenterology. *Gut*. 2000;46(Suppl 3-4):IV1–IV5.
- Pizzi LT, Weston CM, Goldfarb NI, et al. Impact of chronic conditions on quality of life in patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2006;12:47–52.
- Biancone L, Pavia M, Del Vecchio BG, et al. Hepatitis B and C virus infection in Crohn's disease. *Inflamm Bowel Dis*. 2001;7:287–294.
- Gasche C. Anemia in IBD: the overlooked villain. *Inflamm Bowel Dis*. 2000;6:142–150.
- Gasche C, Reinisch W, Lochs H, et al. Anemia in Crohn's disease. Importance of inadequate erythropoietin production and iron deficiency. *Dig Dis Sci*. 1994;39:1930–1934.
- Horina JH, Petritsch W, Schmid CR, et al. Treatment of anemia in inflammatory bowel disease with recombinant human erythropoietin: results in three patients. *Gastroenterology*. 1993;104:1828–1831.
- Lomer MC, Kodjabashia K, Hutchinson C, et al. Intake of dietary iron is low in patients with Crohn's disease: a case-control study. *Br J Nutr*. 2004;91:141–148.
- Semrin G, Fishman DS, Bousvaros A, et al. Impaired intestinal iron absorption in Crohn's disease correlates with disease activity and markers of inflammation. *Inflamm Bowel Dis*. 2006;12:1101–1106.
- Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med*. 2005;352:1011–1023.
- Eccles M, Clapp Z, Grimshaw J, et al. North of England evidence based guidelines development project: methods of guideline development. *BMJ*. 1996;312:760–762.
- Perry GS, Byers T, Yip R, et al. Iron nutrition does not account for the hemoglobin differences between blacks and whites. *J Nutr*. 1992;122:1417–1424.
- WHO, UNICEF, UNU. Iron Deficiency Anemia: Assessment, Prevention and Control. Report of a joint WHO/UNICEF/UNU consultation. Geneva: World Health Organization; 1998.
- Stange EF, Travis SP, Vermeire S, et al. European evidence based consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis. *Gut*. 2006;55(Suppl 1):i1–15.
- Rath HC, Caesar I, Roth M, et al. [Nutritional deficiencies and complications in chronic inflammatory bowel diseases]. *Med Klin*. 1998;93:6–10.
- Duerksen DR, Fallows G, Bernstein CN. Vitamin B12 malabsorption in patients with limited ileal resection. *Nutrition*. 2006;22:1210–1213.
- Beguini Y. Soluble transferrin receptor for the evaluation of erythropoiesis and iron status. *Clin Chim Acta*. 2003;329:9–22.
- Hansen TM, Hansen NE, Birgens HS, et al. Serum ferritin and the assessment of iron deficiency in rheumatoid arthritis. *Scand J Rheumatol*. 1983;12:353–359.
- Bartels U, Pedersen NS, Jarnum S. Iron absorption and serum ferritin in chronic inflammatory bowel disease. *Scand J Gastroenterol*. 1978;13:649–656.
- Ali M, Rigolosi R, Fayemi AO, et al. Failure of serum ferritin levels to predict bone-marrow iron content after intravenous iron-dextran therapy. *Lancet*. 1982;1:652–655.
- Bruner AB, Joffe A, Duggan AK, et al. Randomised study of cognitive effects of iron supplementation in non-anaemic iron-deficient adolescent girls. *Lancet*. 1996;348:992–996.
- Chavarro JE, Rich-Edwards JW, Rosner BA, et al. Iron intake and risk of ovulatory infertility. *Obstet Gynecol*. 2006;108:1145–1152.
- Wells CW, Lewis S, Barton JR, et al. Effects of changes in hemoglobin level on quality of life and cognitive function in inflammatory bowel disease patients. *Inflamm Bowel Dis*. 2006;12:123–130.
- Gasche C, Dejaco C, Waldhoer T, et al. Intravenous iron and erythropoietin for anemia associated with Crohn disease. A randomized, controlled trial. *Ann Intern Med*. 1997;126:782–787.
- Schroder O, Mickisch O, Seidler U, et al. Intravenous iron sucrose versus oral iron supplementation for the treatment of iron deficiency anemia in patients with inflammatory bowel disease—a randomized, controlled, open-label, multicenter study. *Am J Gastroenterol*. 2005;100:2503–2509.
- Erichsen K, Ulvik RJ, Nysaeter G, et al. Oral ferrous fumarate or intravenous iron sucrose for patients with inflammatory bowel disease. *Scand J Gastroenterol*. 2005;40:1058–1065.
- Erichsen K, Hausken T, Ulvik RJ, et al. Ferrous fumarate deteriorated plasma antioxidant status in patients with Crohn disease. *Scand J Gastroenterol*. 2003;38:543–548.
- Schreiber S, Howaldt S, Schnoor M, et al. Recombinant erythropoietin for the treatment of anemia in inflammatory bowel disease. *N Engl J Med*. 1996;334:619–623.
- Gasche C, Dejaco C, Reinisch W, et al. Sequential treatment of anemia in ulcerative colitis with intravenous iron and erythropoietin. *Digestion*. 1999;60:262–267.
- Gasche C, Waldhoer T, Feichtenschlager T, et al. Prediction of response to iron sucrose in inflammatory bowel disease-associated anemia. *Am J Gastroenterol*. 2001;96:2382–2387.
- Devalia V. Diagnosing vitamin B-12 deficiency on the basis of serum B-12 assay. *BMJ*. 2006;333:385–386.
- Cucino C, Sonnenberg A. Cause of death in patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2001;7:250–255.
- Kulnigg S, Rumyantsev V, Stoinov S, et al. A novel intravenous iron formulation for treatment of anemia in IBD: the Ferinject randomized, controlled trial. *Gastroenterology*. 2007;132(Suppl 1):A501.
- Seril DN, Liao J, West AB, et al. High-iron diet: foe or feat in ulcerative colitis and ulcerative colitis-associated carcinogenesis. *J Clin Gastroenterol*. 2006;40:391–397.
- Lee KM, Sartor RB. Oral iron potentiates immune-mediated colitis in IL-10 deficient mice. *Gastroenterology*. 2007;132:A701.
- De Silva AD, Tsironi E, Feakins RM, et al. Efficacy and tolerability of oral iron therapy in inflammatory bowel disease: a prospective, comparative trial. *Aliment Pharmacol Ther*. 2005;22:1097–1105.
- Auerbach M, Ballard H, Glaspy J. Clinical update: intravenous iron for anemia. *Lancet*. 2007;369:1502–1504.

42. Ganzoni AM. [Intravenous iron-dextran: therapeutic and experimental possibilities]. *Schweiz Med Wochenschr.* 1970;100:301–303.
43. Shaffer JL, Higham C, Turnberg LA. Hazards of slow-release preparations in patients with bowel strictures. *Lancet.* 1980;2:487–
44. Rimon E, Kagansky N, Kagansky M, et al. Are we giving too much iron? Low-dose iron therapy is effective in octogenarians. *Am J Med.* 2005;118:1142–1147.
45. Zlotkin S, Arthur P, Antwi KY, et al. Randomized, controlled trial of single versus 3-times-daily ferrous sulfate drops for treatment of anemia. *Pediatrics.* 2001;108:613–616.
46. Dohil R, Hassall E, Wadsworth LD, et al. Recombinant human erythropoietin for treatment of anemia of chronic disease in children with Crohn's disease. *J Pediatr.* 1998;132:155–159.
47. Koutroubakis IE, Karmiris K, Makreas S, et al. Effectiveness of darbepoetin-alfa in combination with intravenous iron sucrose in patients with inflammatory bowel disease and refractory anemia: a pilot study. *Eur J Gastroenterol Hepatol.* 2006;18:421–425.
48. Derijks LJ, Gilissen LP, Hooymans PM, et al. Review article: thiopurines in inflammatory bowel disease. *Aliment Pharmacol Ther.* 2006;24:715–729.
49. Teml A, Schaeffeler E, Herrlinger KR, et al. Thiopurine treatment in inflammatory bowel disease: clinical pharmacology and implication of pharmacogenetically guided dosing. *Clin Pharmacokinet.* 2007;46:187–208.
50. Decaux G, Prosper F, Horsmans Y, et al. Relationship between red cell mean corpuscular volume and 6-thioguanine nucleotides in patients treated with azathioprine. *J Lab Clin Med.* 2000;135:256–262.
51. Jobson B, Garza A, Sninsky CA. Red cell mean corpuscular volume (MCV) correlates with 6 thioguanine nucleotide (6TG) levels during azathioprine or 6-MP therapy for Crohn's disease. *Gastroenterology.* 2001;120:A4.
52. Crichton RR, Danielson BG, Geisser P. Iron therapy with special emphasis on intravenous administration. Bremen: UNI-MED; 2005.
53. Chertow GM, Mason PD, Vaage-Nilsen O, et al. Update on adverse drug events associated with parenteral iron. *Nephrol Dial Transplant.* 2006; 21:378–382.
54. Seid MH, Mangione A, Valaoras TG, et al. Safety profile of iron carboxymaltose, a new high dose intravenous iron in patients with iron deficiency anemia. *Blood.* 2006;108:8B.