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

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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.

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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 anemia[6] 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 prevalent[10] (Table 1). Almost every anemic patient with IBD demonstrates some degree of iron deficiency[11] 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 |
| | Drug-induced (sulfasalazine, thiopurines) |
| Exceptional | Hemolysis |
| | Myelodysplastic syndrome |
| | Aplasia (often drug-induced) |
| | Inborn hemogobinopathies or disorders of erythropoiesis |

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

| | Hemoglobin | | Hematocrit |
|---|---|---|---|
| Age or Sex Group | (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)

## 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 heath 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 the occasion of the United European Gastroenterolgy 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 $B_{12}$, 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.

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

| | Serum Ferritin ($\mu$g/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 |

## 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-

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 $B_{12}$ or folic acid deficiency (e.g., small bowel disease or resection) need proper surveillance. Serum levels of vitamin $B_{12}$ 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 $B_{12}$ 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 concentration. 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 $B_{12}$, 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 $<30$ $\mu$g/L or TfS $<16\%$. In the presence of inflammation, the lower limit of serum ferritin consistent with normal iron stores is 100 $\mu$g/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 $<30$ $\mu$g/L. In the presence of inflammation, serum ferritin levels can be high despite empty iron stores.[22,23] In such cases, 100 $\mu$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 $>100$ $\mu$g/L and TfS $<16\%$. If the serum ferritin level is between 30 and 100 $\mu$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 $>100$ $\mu$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 $<10.0$ 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 $B_{12}$ or folic acid should be initiated if serum concentrations are below normal (Grade D).

*Comment:* Measurement of serum folate and vitamin $B_{12}$ 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 ($Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH\cdot + OH^-$).

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 $\mu$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 | Ferrlecit | 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.
[a]According to Kulnigg (37) et al, 2007, Seid (54) et al, 2006.
[b]Prescribing information of marketed products.
[c]According to Crichton et al, 2005. (52)
[d]According 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, epoietin alfa has been used at 200 U/kg bodyweight twice per week[32] 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 $\mu$g/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) 450 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 $B_{12}$ 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 $B_{12}$ 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.

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