

Systematic review: managing anaemia in Crohn's disease

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SUMMARY

Background

Anaemia is a serious complication of Crohn's disease that triggers hospitalization and, if not interfered with, may lead to death.

Aims

To systematically summarize and compare the literature on anaemia in Crohn's disease.

Methods

For this systematic review the literature was searched for English-language articles using anaemia, Crohn* and IBD as key words. 144 articles were identified and sorted according to the following topics: prevalence, aetiology, diagnostic tests and therapy.

Results

The reported prevalence of anaemia varied between 6.2% and 73.7%, with higher reported frequencies in older studies and in in-patients. Iron deficiency is the most common underlying condition. Vitamin B12 deficiency is related to the extent of ileal resection but has rarely impact on anaemia. Diagnostic criteria are not established and treatment guidelines are missing. Oral iron supplementation seems effective for short periods but intolerance leads to discontinuation in up to 21%. Eleven of 11 studies show that oral iron enhances intestinal inflammation and colon carcinogenesis in animal models of colitis. Intravenous iron supplementation with iron sucrose has been tested in over 250 Crohn's disease patients, is safe, effective and does not carry such hazards.

Conclusions

As disease activity is determining the degree of anaemia in Crohn's disease, implementation of more effective therapy for Crohn's disease will lower its incidence. However, further studies regarding the safety and effectiveness of iron supplementation are needed.

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INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disease involving small and/or large bowel. The aetiology of CD is attributed to a genetic predisposition and to environmental factors (which are mostly – with the exception of cigarette smoking – unknown).¹ Several susceptibility regions have been linked to inflammatory bowel disease (IBD), some genes (such as Nod2) were identified but the functional relationship between disease-associated mutations and the development of chronic bowel inflammation is still obscure.² One striking feature of CD is its phenotypic heterogeneity. This is obvious with regard to the variety of mucosal lesions (from normal to deep penetrating ulcers), the intestinal pattern of disease location, and the mixture of symptoms. Attempts to classify common disease patterns reach back to the 1970s and are still ongoing.^{3–5}

Patients do not only suffer from symptoms arising from the inflamed bowel, such as bowel cramps, abdominal pain or diarrhoea, but may also be affected by certain extraintestinal manifestations at joints, skin or eyes. Systemic disease symptoms include malnutrition and certainly anaemia. Anaemia is commonly complicating CD. It affects quality of life,^{6, 7} cognitive function, the ability to work and is a comorbid condition that is associated with other diseases (e.g. transfusion-associated hepatitis C) or even death.⁸ Many underlying conditions lead to anaemia but the most often ones are iron deficiency anaemia (IDA), anaemia of chronic disease (ACD) and a combination of both.⁹ Diagnosis is sometimes difficult, i.e. when vitamin B12 deficiency and iron deficiency occur at the same time and the erythrocytes are neither macrocytic nor hypochrome. Careful laboratory evaluation and the surveillance of treatment efficacy are a prerequisite to successful therapy. Taken together anaemia is a common complication in CD that is easily diagnosed by regular blood counts and is crucial for the patient's physical and emotional well-being.

DEFINITION

The World Health Organization defines anaemia as haemoglobin concentration <12 g/dL for non-pregnant women and <13 g/dL for men. These values vary between countries, regions and laboratories. A haemoglobin level below 10 g/dL is commonly considered as severe anaemia.

METHODS

A review of the medical literature was conducted to identify original studies, case reports and reviews concerning anaemia and CD. In February 2006, PubMed was searched for English-language articles. The terms used for the online bibliographic search included: anaemia, Crohn* and IBD. A total of 403 articles (69 reviews) were identified, 305 of which (51 reviews) were in English language. Non-relating articles were discarded, while additional articles (on 'iron, vitamin B12, cobalamine, folic acid, or erythropoietin') were identified through a manual search. One-hundred and forty-four articles were finally selected and sorted according the following topics: prevalence, aetiology, diagnostic tests and therapy.

PREVALENCE

A total of 19 articles contained data about the prevalence of anaemia in CD or IBD.^{10–28} The reported prevalence of anaemia in these patients varies between 6%¹² and 74%²¹ (Table 1). This discrepancy may be partially caused by differences in the criteria used and in the patient population (in-patient vs. out-patient). Anaemia seems to be a trigger for hospitalization, which is reflected, in the higher prevalence of anaemia in hospitalized patients. However, incidence of anaemia is decreasing during the last years. Possible reasons may involve improvements in the treatment of the underlying diseases or in iron supplementation.¹⁰ Most studies were performed at referral centres and may thereby overestimate the actual prevalence. Population-based case-control studies are needed.

AETIOLOGY

Four review articles on anaemia and IBD were identified,^{9, 29, 30, 31} and one on haematological complications in IBD in general.³² The most important causal conditions are iron deficiency and ACD. Besides, the aetiology of anaemia in IBD may involve various impairments of erythropoiesis and haemolysis, but these seem to be rare events. All original articles concerning the aetiology of anaemia in CD were organized according to the following topics.

Table 1. Prevalence of anaemia in CD

Study	Country	n	Phenotype	Hospitalization	Definition of anaemia	Prevalence (%)	Publication
Vijverman <i>et al.</i> ¹⁰	Belgium	80 (1993)	IBD	No	M: Hb < 13 g/dL; F: Hb < 11.6 g/dL	34	2006
Ershler <i>et al.</i> ¹¹	USA	7200	IBD	No	M: Hb < 13 g/dL; F: Hb < 11.6 g/dL	17	
Ebinger <i>et al.</i> ¹²	Germany	390	CD	No	nd	13	2005
Lakatos <i>et al.</i> ¹³	Hungary	254	CD	No	nd	6	2004
Oldenburg <i>et al.</i> ¹⁴	The Netherlands	nd	CD	No	nd	60	2003
Revel-Vilke <i>et al.</i> ¹⁵	Israel	63	IBD*	No	M: Hb < 12.5 g/dL; F: Hb < 11.6 g/dL	29	2001
Schreiber <i>et al.</i> ¹⁶	Germany	334	CD	No	< 12 g/dL	41	2000
Gasche <i>et al.</i> ¹⁷	Austria	49	CD	No	Hb < 10 g/dL	26	1996
Horina <i>et al.</i> ¹⁸	Austria	85	IBD	No	Hb < 12 g/dL	34	1994
Harries <i>et al.</i> ¹⁹	England	55	CD	No	Hb ≤ 12 g/dL	33	1993
Bambach and Hill ²⁰	Australia	36	IBD with extensive small intestine resection	No	M: Hb < 13.5 g/dL F: Hb < 11.5 g/dL	44	1984
Werlin and Grand ²¹	USA	19	Severe colitis*	Yes	hct < 0.30	17	1982
Reilly <i>et al.</i> ²²	USA	9	Small bowel CD	Yes	nd	74	1977
Greenstein <i>et al.</i> ²³	USA	14	Large bowel ± small bowel CD	Yes	nd	33	1976
Burbige <i>et al.</i> ²⁴	USA	160	CD or ileocolitis	Yes	nd	71	1975
Beeken ²⁵	USA	58	CD*	No	Hb < 11 g/dL	52	1975
Beeken ²⁶	USA	63	Regional enteritis	Yes	hct < 0.40	70	1975
Dyer <i>et al.</i> ²⁷	England	11	CD*	No	Hct < 0.36	73	1973
Hoffbrand <i>et al.</i> ²⁸	England	63	Active CD	Yes	M: Hb < 13.5 g/dL F: Hb < 11.5 g/dL	64	1972
		64	CD	24 (64)	nd	44	1968

* Children and adolescents.
Hb, haemoglobin; Hct, haematocrit; IBD, inflammatory bowel disease; CD, Crohn's disease; nd, not defined; M, males; F, females.

Table 2. Prevalence of iron deficiency, impaired iron intake and impaired iron absorption in CD

Study	<i>n</i>	Phenotype	Parameter	Iron deficiency	Publication
Lakatos <i>et al.</i> ¹³	254	CD	Not defined	36%*	2003
Revel-Vilke <i>et al.</i> ¹⁵	26*	IBD	MCV < 66 fl + ferritin < 6 (female)/23 (male) µg/L	42%*	2000
Gasche <i>et al.</i> ¹⁷	49	CD	Ferritin < 60 µg/L TfS < 20%	76% 90%	1994
DeVizia <i>et al.</i> ³³	11	CD with malnutrition	TfS < 12%, ferritin < 12 µg/L	72%	1992
Iron intake					
Lomer <i>et al.</i> ³⁴	91	CD in remission	7-day food diary	Low†	2003
Hodges <i>et al.</i> ³⁵	47	CD	Descriptive study	25% impaired (females)	1984
Iron absorption					
De Vizia <i>et al.</i> ³³	11	CD with malnutrition	Fe absorption (serum increase after 2 h)	90% impaired	1992
Bartels <i>et al.</i> ³⁶	31	CD	⁵⁹ Fe absorption test	Normal	1978

MCV, mean corpuscular volume; MCHC, mean corpuscular haemoglobin concentration; TfS, transferrin saturation; Hb, haemoglobin; IBD, inflammatory bowel disease; CD, Crohn's disease.

* All with anaemia.

† Mainly due to low Fe density in food.

Iron deficiency

Original articles were found on the prevalence of iron deficiency,^{13, 15, 17, 33} on iron intake^{34, 35} and on iron absorption^{33, 36} (summarized in Table 2). One review was identified on iron and IBD.¹⁴ According to these reports, iron deficiency seems to be a common condition in CD. Its prevalence varies between 36% and 90% depending on the cohort and even more on the definition of iron deficiency. This points to the high variability in recognition of iron deficiency in clinical practice. The most appropriate definition of iron deficiency is the proliferative response of the bone marrow to intravenous iron supplementation, an approach that has not been studied so far in IBD. Epidemiological data from larger cohort analyses are missing, but would be of great interest to the IBD community. In normal subjects, the daily iron loss averages 1–2 mg and the same amount is absorbed from food sources. Upon iron deficiency, these figures may increase. A prospective case–control study assessing the dietary iron intake revealed low amounts of bioavailable iron in CD.³⁴ Inadequate iron intake was already reported 20 years earlier.³⁵ In contrast to this unanimous evi-

dence for dietary iron avoidance in CD, data on iron absorption are conflicting. Bartels *et al.* tested iron absorption (by a radioactive test) rigorously in a cohort of CD patients and controls and found no general (but some individual) absorption deficit.³⁶ In a paediatric cohort, however, abnormal absorption was suspected in 90%.³³ As iron is absorbed in the duodenum and upper jejunum, only patients with upper gastrointestinal (GI) disease (L4 at the Vienna Classification⁴) should be at risk of iron malabsorption. Appropriate studies (using sensitive and specific tests) linking iron absorption and disease location and disease activity are missing.

Intestinal blood loss through ulcerated mucosal surface is regarded the predominant cause of iron deficiency. We did not identify a single study that used quantitative tests to estimate the loss of intestinal blood. Faecal occult blood test was positive in six of 11 children with CD.³³ Again, correlation with disease location, extent and severity of iron deficiency would be informative. The low iron uptake and high iron loss; however, cause a negative iron balance resulting in reduced haemoglobin production and microcytic, hypochromic anaemia. As iron is essential for all cells

of the body, symptoms of iron deficiency are not only limited to anaemia-specific signs (such as fatigue and shortness of breath), but also affects nail growth, skin defects, mucosal regeneration (that might impair healing of CD lesions), headache, sleeping disorder, libido, erectile dysfunction and many more. All of this adds to the impairment in quality of life that makes the diagnosis and treatment of iron deficiency so important in CD.

Anaemia of chronic disease

As the diagnostic criteria for ACD are vague, no reliable data are available on the prevalence of ACD in CD. One difficulty is based on the exclusion of concomitant iron deficiency. Before testing erythropoietin (EPO) therapy for ACD, Horina *et al.* supplemented their anaemic patients with high amounts of intravenous iron,¹⁸ which is considered the most accurate measure to exclude iron deficiency. Of 28 anaemic IBD patients, only three were identified with ACD (11%). In a paediatric cohort, when ferritin and mean cell volume (MCV) was applied to separate IDA from ACD these figures were much higher (26 with anaemia, 11 with ACD; 42%).¹⁵ Tsitsika *et al.* linked ACD to the presence of active disease.³⁷

From these few data, ACD seems to be the second most frequent aetiology of anaemia in CD that typically coexists with IDA. The pathogenesis of ACD has been recently reviewed and involves altered erythropoiesis, iron homeostasis and red cell survival.³⁸ In IBD, the inflamed intestine and the surrounding mesentery is considered as the main source of cytokine production [including tumour necrosis factor (TNF)- α , interleukin (IL)-1, IL-6, IL-10 and interferon (IFN)- γ] that may drive such pathways.^{39, 40} Only few studies have tried to link elevated cytokine levels to the presence of ACD.^{16, 17}

Vitamin B12 deficiency

Although megalocytic anaemia has been described as a possible feature of CD long time ago,⁴¹ only two reports were found on the prevalence of macrocytic anaemia: Lakatos *et al.* found a prevalence of 4.3% (without distinguishing between folate and cobalamine deficiency)¹³ compared with 26.6% in a smaller series by Hoffbrand *et al.*²⁸ Out of these, only one case showed subnormal vitamin B12 levels (1.5%).

We identified 18 original studies on vitamin B12 absorption and vitamin B12 serum levels^{20, 27, 28, 42-56} (Table 3). Vitamin B12 deficiency seems to be common in patients with ileal CD or resection of the ileum, but its haematopoietic consequence in CD is unclear. An odd case of pernicious anaemia caused by intrinsic factor deficiency in gastroduodenal CD highlights the wide spectrum of clinical findings.⁵⁷ In general, as most of these studies have been performed decades ago, the quality of these data are limited. The daily requirement for vitamin B12 is 1-3 μg ; body stores contain about 5 mg, which explains why clinical manifestation of vitamin B12 deficiency occurs late. Routine vitamin B12 measurements are not necessary, only if patients have macrocytic anaemia or do not respond to iron treatment.

Folic acid deficiency

Two studies described the prevalence of macrocytic anaemia (4.3%¹³ and 26.6%,²⁸ respectively). All patient with macrocytosis had subnormal folate levels.²⁸ Eleven original articles report on folic acid absorption or concentrations^{20, 28, 35, 44, 49-51, 53, 54, 58, 59} (Table 4). In general, folate deficiency seems to be more common than vitamin B12 deficiency, specifically in patients on sulfasalazine. However, a correlation between intake of sulfasalazine and folate levels was not found in the studies of Elsborg and Larsen⁵⁹ and Bechi *et al.*⁶⁰ This dispute may originate in the simple fact that most of the data are observational and uncontrolled. Nowadays, as sulfasalazine has been commonly replaced by mesalazine, this debate lacks clinical relevance. Routine measurements of folic acid levels are not required. Nevertheless patients with low levels of folate acid or vitamin B12 should receive appropriate replacement therapy, because it has been shown, that low levels of these vitamins correlate with high levels of homocysteine which is a risk factor for thromboembolism.⁴⁹⁻⁵¹ Vice versa, hyperhomocysteinaemia may be indicative for folate acid or vitamin B12 deficiency.

Drug-induced anaemia

The comparative tolerability of various treatments in IBD was reviewed previously.⁶¹ Several anti-inflammatory drugs that are used for treatment of IBD, such as sulfasalazine, mesalazine and purine analogues may interfere with erythropoiesis.

Table 3. Prevalence of impaired vitamin B12 absorption and vitamin B12 deficiency in CD				
Study	n	Phenotype	Impaired vitamin B12 absorption	Publication
Behrend <i>et al.</i> ⁴²	82	CD, <10 cm resection	38%	1995
		CD, 10–60 cm resection	53%	
		CD, >60 cm resection	100%	
Bayat <i>et al.</i> ⁴³	7	CD	86%	1994
Kennedy <i>et al.</i> ⁴⁴	51	IBD with ileostomy, resection > 17 cm	Low absorption	1982
Papazian <i>et al.</i> ⁴⁵	14	CD with ileal resection	Negative correlation between length of lesion/resection and absorption	1981
Filipsson <i>et al.</i> ⁴⁶	70	CD, <30 cm resection	21%	1978
		CD, 30–60 cm resection	48%	
		CD, >60 cm resection	60%	
Jagenburg <i>et al.</i> ⁴⁷	34	Ileostomy	15%	1975
Valman and Roberts ⁴⁸	10	Paediatric CD, >45 cm resection	70%	1974
Dyer <i>et al.</i> ²⁷	nd	CD, not operated	60%	1973
Vitamin B12 deficiency				
Vasilopoulos <i>et al.</i> ⁴⁹	125	CD	Normal	2001
		CD with terminal ileum resection	Decreased levels	
Koutroubakis <i>et al.</i> ⁵⁰	55	CD	Normal	2000
Chowers <i>et al.</i> ⁵¹	105	CD	Normal	2000
		CD, diseased terminal ileum	Decreased levels	
Lambert <i>et al.</i> ⁵²	21	CD	Normal	1996
Kuroki <i>et al.</i> ⁵³	24	CD	Normal	1993
Fernandez-Banares <i>et al.</i> ⁵⁴	8	CD, small bowel or ileocaecal	Decreased levels	1989
	15	IBD, extensive colitis	Normal	
Shaw <i>et al.</i> ⁵⁵	nd	CD, diseased or resected ileum	Low levels	1989
		IBD, colitis	Normal	
Nilsson <i>et al.</i> ⁵⁶	213	CD, ileostomy	27% subnormal/borderline	1984
Kennedy <i>et al.</i> ⁴⁴	51	Ileostomy	Normal	1982
Bambach and Hill ²⁰	31	CD, small intestinal resection	Frequent	1982
Hoffbrand <i>et al.</i> ²⁸	54	CD	6% subnormal levels	1968

IBD, inflammatory bowel disease; CD, Crohn's disease; nd, not defined.

Mesalazine and sulfasalazine

Sulfasalazine effects erythropoiesis by several mechanisms including folate absorption, haemolysis and aplasia.⁶² While haemolysis may be prevalent in 11–43% of patients with only little effects on haemoglobin concentrations,^{63, 64} pancytopenia is a rare complication that may also occur on mesalazine.^{65, 66}

Azathioprine and mercaptopurine

As purine analogues are widely used for treatment of CD and may interfere with erythropoiesis, they may contribute to the occurrence of anaemia in a large number of patients. However, as long as they do not

cause pancytopenia, the degree of bone marrow inhibition is moderate and the clinical presentation of anaemia is rare. The toxicity related to treatment with purine antagonists was the topic of various recent reviews.^{67–69} This is specifically true for the role of thiopurine methyltransferase (TPMT) activity.^{70–72} Connell *et al.* reviewed in 739 IBD patients that received azathioprine.⁷³ Significant bone marrow toxicity was identified in 5%, a figure that was a little higher than what was published for mercaptopurine (6-mercaptopurine, MP; 2%).⁷⁴ The risk of developing aplasia or leukopenia is high in individuals with low TPMT activity. This is genetically determined and genotyping has been suggested as a means for identifying patients at risk.^{75, 76} In clinical practice, however,

Table 4. Prevalence of impaired folic acid absorption and deficiency in CD

Study	<i>n</i>	Phenotype	Folic acid absorption	Publication
Steger <i>et al.</i> ⁵⁸	100	CD	16% impaired	1994
Kuroki <i>et al.</i> ⁵³	24	CD	Decreased	1993
Folate deficiency				
Vasilopoulos <i>et al.</i> ⁴⁹	125	CD	No deficiency (8% received supplementations)	2001
Koutroubakis <i>et al.</i> ⁵⁰	55	CD	No deficiency	2000
Chowers <i>et al.</i> ⁵¹	105	CD	No deficiency	2000
Fernandez-Banares <i>et al.</i> ⁵⁴	23	IBD	Decreased levels	1989
Hodges <i>et al.</i> ³⁵	24	CD, female	26%	1984
	23	CD, male	21%	
Kennedy <i>et al.</i> ⁴⁴	51	IBD (12 CD)	2%	1982
Bambach and Hill ²⁰	31	CD with major small intestinal resection	Frequent	1982
Elsborg and Larsen ⁵⁹	216	IBD (serum level)	59% low serum levels	1979
		IBD (erythrocyte level)	26% low erythrocyte levels	
Hoffbrand <i>et al.</i> ²⁸	64	CD	81% subnormal (vs. 42% controls)	1968

IBD, inflammatory bowel disease; CD, Crohn's disease.

concerns have been raised about the value of this test.⁷⁷ As treatment recommendations changed over the past decades, the relative importance of drug-induced anaemia shifted from sulfasalazine to 6-MP and azathioprine. In fact, the increase in MCV is commonly used as marker of drug efficacy.^{78, 79} The coexistence of iron deficiency may obstruct this feature and vice versa. This MCV increase is typically not associated with significant anaemia and rarely needs dose adaptation.

Interleukin-10

Interesting observations on the role of IL-10 in development of ACD have been derived from clinical trials that tested this cytokine for treatment of IBD.⁸⁰⁻⁸² IL-10 caused a temporary decline in haemoglobin levels that was associated with hyperferritinaemia and increased soluble transferrin receptor (sTfR) levels indicating iron restriction to the erythroid progenitor cells. IL-10 is not available for treatment of IBD.

Others

Mattis *et al.* reported a case of ceftriaxone-induced haemolytic anaemia in a child with CD.⁸³

Haemolytic anaemia

Most reports on haemolytic anaemia in IBD are actually reporting on findings in patients with ulcerative colitis (UC). In CD, only five case reports were found.⁸⁴⁻⁸⁸ Interestingly, these are cases of UC-like Crohn's colitis that were associated with pANCA positivity or primary sclerosing cholangitis. One patient was reported with haemolytic anaemia upon treatment with infliximab.⁸⁹ This type of anaemia seems to be extremely rare in CD.

Myelodysplastic syndromes

According to the French-American-British classification,⁹⁰ the myelodysplastic syndromes include refractory anaemia (type 1), refractory anaemia with ringed sideroblasts (type 2), chronic myelomonocytic leukaemia (type 3), refractory anaemia with excess blasts (type 4) and refractory anaemia with excess blasts in transformation (type 5). Myelodysplastic syndromes are rare and characteristically develop in patients older than 60 years of age. Eighteen patients in seven case reports on myelodysplastic syndrome have been identified by systematic literature search.⁹¹⁻⁹⁷ As in any population, the possibility of myelodysplastic

syndrome should be considered in patients over 60 years.

Inborn haemoglobin disorders

Glucose-6-phosphate dehydrogenase deficiency has been reported in single patients with IBD.^{98–102} It is still unclear whether this disorder is genetically linked to IBD susceptibility genes or not.

LABORATORY TESTS

Diagnosing iron deficiency in the setting of IBD may be difficult and no single laboratory test has been established. There is little doubt that serum ferritin levels below 20 µg/L are indicative of iron deficiency. However, in the presence of inflammation ferritin levels may increase in spite of iron deficiency. In fact, bone marrow studies in rheumatoid arthritis patients showed a 86% sensitivity to predict iron deficiency for ferritin levels below 60 µg/L.¹⁰³ Similar figures were described for IBD¹⁰⁴ indicating that in one of six patients iron deficiency is missed even when the ferritin cut-off level is set to 60 µg/L. Measurement of the sTfR which increases upon iron deficiency (and enhanced erythropoiesis) or the sTfR/log ferritin ratio may further help solving this dilemma.¹⁰⁵

Laboratory findings in ACD can be summarized as following: reduced transferrin saturation, reduced or normal transferrin, normal or increased ferritin and normal sTfR. In contrast, patients with iron deficiency have low transferrin saturation, increased transferrin, reduced ferritin and increased sTfR.³⁸ In CD, iron deficiency overlapping with ACD is difficult to judge but considered likely when ferritin levels are below 100 µg/L and the transferrin saturation is below 16%.³⁸ In these cases the sTfR/log ferritin ratio can be applied. A ratio above 2 is suggestive of iron deficiency. The MCV and mean corpuscular haemoglobin concentration (MCHC) are sensitive indicators of iron deficiency, but are also affected by immunosuppressive therapy or vitamin B12/folic acid deficiency (see above).

The EPO levels increase with the degree of anaemia.¹⁷ In some patients, however, EPO concentrations are not elevated despite significant anaemia.³⁷ This information maybe helpful when considering EPO therapy.¹⁰⁶

THERAPY

The variety of available iron compounds and the different routes of administration (oral and intravenous) have been a topic of several clinical trials (Table 5). In most studies testing oral iron, 100–200 mg of ferrous salts (fumarate or sulphate) were administered. As only small amounts of iron are absorbed (10–30 mg) the majority of ingested iron passes along within the bowel content. At sites of ulcers, the iron-rich luminal matter may increase the formation of hydroxyl radicals (by catalysing the Fenton reaction: $\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{OH}^\bullet + \text{OH}^-$). The hydroxyl radical is the primary oxidizing species; it can be used to oxidize and break apart organic molecules and thereby may enhance tissue damage and disease activity of the underlying IBD. As this hypothesis is difficult to test in patients, it has been subject of several studies using animal model of IBD (Table 6). Our search identified 11 publications that tested the effect of iron on intestinal disease activity, oxidative stress or the degree of mucosal inflammation in rodent models of IBD.^{107–117} Although the experimental setting, the iron dose and the readout are quite diverse, these studies unanimously support the hypothesis of iron-induced hydroxyl radical generation in the inflamed tissue leading to worsening of intestinal inflammation and increased colon carcinogenesis.

From eight studies that tested oral iron in IBD (Table 5),^{16, 118–124} intolerance was a common finding leading to discontinuation in up to 21%. Two studies using ferric iron reported fewer side effects despite good effectiveness.^{121, 124} Some case-control studies saw similar intolerance to non-IBD patients¹²³ in others the frequency and spectrum of side effects (increase in diarrhoea vs. constipation) was considerably different.¹²² A 15-year-old girl developed typical symptoms of UC after treatment of anaemia with ferrous sulphate.¹²⁵ Recently, some worsening of proctosigmoiditis was demonstrated by rigid sigmoidoscopy.¹¹⁸ Due to the location of intestinal inflammation in CD, similar tests have not been performed yet (as an ileocolonoscopy would be needed). One study aimed to compare tolerability of ferrous fumarate applying a crossover design.¹²⁰ CDAI increased in the oral group (due to worsening of general well-being and abdominal pain) but was unchanged in the intravenous group.

Intravenous iron therapy for IBD-associated anaemia has been suggested in the 1970s,³⁶ but clinical trials

Table 5. Iron therapy in CD

Study	Design	n	Phenotype	Dose	Compound	Duration Response (weeks)	Hb change (g/dL)	Adverse events	Publication
Oral iron									
De Silva <i>et al.</i> ¹¹⁸	Open-label	19	CD	3 × 200 mg/day	Ferrous sulphate	4	10.0–11.7	21% dct	2005
Schroeder <i>et al.</i> ¹¹⁹	Randomized, open-label, multicentre	46 (24 oral)	IBD	100/200 mg/day	Ferrous sulphate	6	9.6–11.7	21 AE*, 21% dct, Harvey-Bradshaw index increased	2005
Erichsen <i>et al.</i> ¹²⁰	Crossover, safety	19	IBD	120 mg/day	Ferrous fumarate	2	11.6–11.8	11% dct	2005
Erichsen <i>et al.</i> ¹²¹	Randomized, open-label, safety	41	IBD	100 mg 2×/day (n = 21) or 200 mg iron 1×/day (n = 20)	Ferrous sulphate	2	13.1–13.3	14% dct	2005
Erichsen <i>et al.</i> ¹²²	Open-label, safety	10	CD	120 mg/day	Ferrous fumarate	1	10.6–10.6	80% AE, 0% dct	2003
De Silva <i>et al.</i> ¹²³	Retrospective	53	IBD	Various	Various	Various	Not specified	25% AE, 8% dct	2003
Harvey <i>et al.</i> ¹²⁴	Open-label	23	IBD (n = 15)	2 × 30 mg/day	Ferric trimaltol	12	10.6–12.6	21% dct	1998
Schreiber <i>et al.</i> ¹⁶	Randomized double-blind (EPO)	34 (17)	IBD	100 mg/day + placebo	Iron-glycine-sulphate	12	8.7–7.8	Not specified	1996
Intravenous iron									
Schroeder <i>et al.</i> ¹¹⁹	Randomized, open-label, multicentre	46 (22 intravenous)	IBD	1418 mg total	Iron sucrose	6	9.8–12.3	20 AE*, 5% dct, Harvey-Bradshaw index unchanged	2005
Erichsen <i>et al.</i> ¹²⁰	Crossover, safety	19	IBD	200 mg 3×	Iron sucrose	2	10.6–11.3	0% dct	2005
Schroeder <i>et al.</i> ¹²⁷	Open, safety	31	CD (13)	7 mg/kg BW single infusion (maximum 500 mg)	Iron sucrose	Single infusion	10.2–10.8	32% AE (6.5% definitely related to medication)	2004
Bodemar <i>et al.</i> ¹²⁸	Retrospective	59	IBD	1400 mg total	Iron sucrose	Various	9.7–12.8	1 AE, 0% dct	2004
Mamula <i>et al.</i> ¹²⁹	Retrospective	70 (119 infusions)	IBD, children	Total dose iron	Iron dextran	Single infusion	Mean increase 2.9 reactions	11 allergic reactions	2002

Table 5. (continued)

Study	Design	n	Phenotype	Dose	Compound	Duration (weeks)	Response	Hb change (g/dL)	Adverse events	Publication
Gasche <i>et al.</i> ¹⁰⁶	Multicentre, open-label	103	IBD	1200 mg (6 × 200 mg)	Iron sucrose	4	65%	8.8–11.3	4 AE, 0% dct	2001
Gasche <i>et al.</i> ¹²⁶	Randomized double-blind (EPO)	40 (20)	CD	200–400 mg/week	Iron sucrose	8	80%	8.5–11.8	10 AE, 0% dct	1997
Gasche <i>et al.</i> ¹⁷	Open	2	CD	200 mg/week	Iron sucrose	5	50%	9.5–11.5	0%	1994
Bartels <i>et al.</i> ³⁶	Open	8	IBD	1 g total dose infusion	Iron dextran	Single infusion	Ferritin increase	Not reported	Not reported	1978

AE, adverse event; IBD, inflammatory bowel disease; CD, Crohn's disease; EPO, erythropoietin; dct, discontinued.

* Difference between groups only for the occurrence of abdominal pain (only in the oral group).

† 1 g/dL increase.

Response is defined as increase of haemoglobin of ≥ 2 g/dL.

have not been performed until the early 1990s.¹²⁶ We identified a total of nine trials, all of which tested iron sucrose except for two that analysed iron dextran (Table 5).^{17, 36, 106, 119, 120, 126–129} The first prospective, controlled trial tested iron sucrose as adjunct to EPO therapy.¹²⁶ A consecutive, multicentre trial followed a stepwise approach (first iron sucrose, then combination with EPO).¹⁰⁶ Iron sucrose was effective in 50–91% depending on the criteria used. Two comparative trials (oral vs. intravenous iron) have been published recently.^{119, 120} The only available randomized-controlled trial measuring efficacy (maximum increase in haemoglobin within 6 weeks) showed a comparable response in both groups (55% on iron sucrose vs. 53% on ferrous sulphate).¹¹⁹ Secondary end points, such as an increase in ferritin as marker of iron reserve were only met in the intravenous treatment group. The other study as mentioned above¹²⁰ was not designed to measure efficacy, but demonstrated better tolerability of intravenous iron therapy. At this point, larger and well-designed studies are needed to evaluate the efficacy and safety of various routes and compounds of iron supplementation.

Six original reports^{16–18, 126, 130, 131} (Table 7), one letter¹³² and one review¹³³ testing EPO in CD have been identified. There is grade A evidence (from two randomized-controlled trials) for the efficacy of EPO in IBD-associated anaemia. In all trials, however, EPO therapy was accompanied by iron supplementation again pointing to the importance of iron therapy. From a set of laboratory parameters high serum EPO levels, high sTfR levels or high transferrin levels were predictive of a response to iron therapy alone.¹⁰⁶ EPO therapy should be considered for patients with low levels or unresponsiveness to iron sucrose. No reports were identified on the use of vitamin B12 or folate therapy of CD-associated anaemia.

It is needless to mention that anaemia in CD can be managed with blood transfusions.¹³⁴ Perioperative autologous blood donations have been successfully tested as well.¹³⁵ In patients with frequent and therapy-resistant haemorrhage, surgical intervention or resection can be considered.^{136–138} Anti-TNF therapy (e.g. infliximab or etanercept), as it may interfere with specific mechanisms of ACD, has shown beneficial effects in single cases (when combined with intravenous iron).¹³⁹ This effect, however, may be caused by intestinal healing of ulcerated mucosal surface rather than the anti-TNF effects on the bone

Table 6. Iron therapy in various animal models of colitis

Study	Model	Application and iron dose	Disease activity	Oxidative stress	Intestinal inflammation	Colorectal tumour	Publication
Carrier <i>et al.</i> ¹⁰⁷	DSS colitis	3000 mg/kg diet Same + vitamin E	++ +	++ +			2006
Erichsen <i>et al.</i> ¹⁰⁸	DSS colitis	0.6 mg/kg BW oral			+		2005
Seril <i>et al.</i> ¹⁰⁹	DSS colitis	6 mg/kg BW i.p. 12 mg/kg BW i.p. 90 mg/kg diet	± ± +	±* ±* +*	± ± +	- - +	2005
	IL-2-/- mice	12 mg/kg BW i.p. 90 mg/kg diet	- +		- +	- +	
Reifen <i>et al.</i> ¹¹⁰	Iodoacetamide colitis	300 mg/kg diet			++		2004
Uritski <i>et al.</i> ¹¹¹	TNBS colitis	7 mg/kg diet 35 mg/kg diet 3000 mg/kg diet		± ± +	+ + ++		2004
Seril <i>et al.</i> ¹¹²	DSS colitis	100 mg/kg diet 250 mg/kg diet 5000 mg/kg diet	+ + +	+ + +	+ + ++	+ 	2002
Carrier <i>et al.</i> ¹¹³	DSS colitis	3000 mg/kg diet Same + vitamin E	++ +	+ +	++ +		2002
Carrier <i>et al.</i> ¹¹⁴	DSS colitis	3000 mg/kg diet 30 000 mg/kg diet	+ +	+ +	+ +		2001
Aghdassi <i>et al.</i> ¹¹⁵	DSS colitis	1000 mg/kg BW i.p.		+	+		2001
Reifen <i>et al.</i> ¹¹⁶	Iodoacetamide rat model	Dose not defined	+				2000
Oldenburg <i>et al.</i> ¹¹⁷	IL-10-/- mice	500 mg/kg diet 1 mM enema			+† +†		2000

DSS colitis, dextran sulphate sodium-induced colitis in rats; TNBS colitis, trinitrobenzene sulfonic acid induced-colitis in rats; BW, body weight; i.p., intraperitoneal iron; ±, no difference to controls.

* iNOS and COX-2 expression.

† Proinflammatory cytokines produced by colonic tissue.

Empty fields: test not done.

marrow.¹⁴⁰ Within clinical trials such effects have not been observed.¹⁴¹

DISCUSSION

The variation in prevalence data as summarized in Table 1 of this systematic review indicates that anaemia is more prevalent in in-patients than in out-patients. If anaemia is a trigger for hospitalization, it should be recognized early, diagnosed fast and treated effectively preferably in the ambulant setting. For in-patients, anaemia may prevent doctors from discharging patients. Again, early and effective measures to counteract this condition may reduce the time of hospitalization and prevent the use of blood transfusions. Not only economic reasons should lead to early diagnosis and treatment, but also lower quality of life

should sensitize doctor's perception of the magnitude of this problem. Although reliable (population-based) data are not available, the prevalence of anaemia seems to decrease with time. The same was also observed in a recent original analysis.¹⁰ As anaemia is related to disease activity, it is likely that the introduction of effective treatment options at the end of the 20th century has changed the natural course.

From the data extracted from Tables 2–4, the most fundamental cause of anaemia in CD is iron deficiency. Although this has been identified as the overwhelming causative factor, little is known on iron absorption in CD. The available studies^{33, 36} used different absorption tests and came to contradictory results. No data are available for upper GI CD (the L4 phenotype of the Vienna Classification).⁴ Although most of the laboratory tests have been used for over 30 years, the diag-

Table 7. EPO therapy in patients with CD

Study	Design	n	Phenotype	Dose	Compound	Duration (weeks)	Response	Hb change (g/dL)	Adverse events	Publication
Koutroubakis <i>et al.</i> ¹³⁰	Refractory anaemia	20	IBD	0.9 µg/kg BW once/week, 1300 mg iron total	Darbepoetin-α iron sucrose	4	75	9.5–12.7	0%	2006
Dohil <i>et al.</i> ¹³¹	CD	3	CD	150 U/kg BW 3×/week	Epoetin-α	12	100	10.9–13.8	1 AE	1998
Gasche <i>et al.</i> ¹²⁶	Randomized double-blind (EPO)	40 (20)	CD	150 U/kg BW 3×/week, 200–400 mg iron/week	Epoetin-α iron sucrose	8	95	8.7–13.6	5 AE	1997
Schreiber <i>et al.</i> ¹⁶	Randomized double-blind (EPO)	34 (17)	IBD	150 U/kg BW 2×/week, 100 mg iron/day	Epoetin-α iron-glycin-sulphate	12	82*	8.8–10.5	Not specified	1996
Gasche <i>et al.</i> ¹⁷	Open	2	CD	150 U/kg BW 3×/week, 200 mg iron /week	Epoetin-α iron sucrose	5	100	9.1–14.1	0%	1994
Horina <i>et al.</i> ¹⁸	Open	3	IBD	200–300 U/kg BW 3×/week, 100 mg iron/day	Epoetin-β oral iron	8–14	100	8.6–12.8	Not specified	1993

* 1 g/dL increases.

IBD, inflammatory bowel disease; CD, Crohn's disease; EPO, erythropoietin.

Response is defined as increase of haemoglobin of ≥ 2 g/dL.

nostic criteria of iron deficiency are still vague. In a recent review on ACD,³⁸ the presence of iron deficiency was considered when ferritin levels drop below 100 µg/L and the transferrin saturation is below 16%.³⁸ The clinical dilemma of diagnosing iron deficiency in CD becomes even bigger as azathioprine and MP are now commonly used for CD therapy. Both drugs increase the MCV and thereby obstruct one of the most sensitive measures of iron deficiency. On the other hand, the MCV increase is considered a good marker for azathioprine drug monitoring.^{78, 79} In the presence of iron deficiency this marker cannot be used as well.

As iron deficiency is the most prevalent cause of anaemia, iron supplementation is the most relevant therapeutic intervention. In general, oral iron preparations are inexpensive, partially (temporarily) efficient, but are commonly associated with GI side effects (abdominal pain, increase in diarrhoea) that limit their use and compliance. The overwhelming evidence from iron treatment in animal IBD models (as summarized in Table 6) question the safety of ferrous salts in IBD. This is particularly true for the carcinogenic properties of ferrous iron¹⁰⁹ as colitis patients *per se* are already at a higher risk to develop colorectal cancer.¹⁴² As ferrous salts are continuously prescribed for these conditions, after marketing safety trials are warranted. Upon these considerations we like to adjust our previous recommendation for using ferrous salts in patients with mild iron deficiency and IBD.⁹ As long as the safety of ferrous salts is questionable, IBD patients should rely on iron sucrose, currently the only iron compound with sufficient available safety data. This recommendation is mainly based on the dogma: 'safety first'. As intravenous iron sucrose is more costly (also highly varying from country to country),

long-term cost-effectiveness needs to be addressed in future trials. However, apart from IBD (and chronic renal failure) the oral route remains the cornerstone of iron replacement therapy.

Both the clinical trials in IBD and the data from animal models would rather suggest the use of parenteral iron supplementation. The cumulative data on over 250 Crohn's patients who received iron sucrose within clinical trials (Table 5) together with the huge experience in non-IBD patients (over 1 million applications) establish iron sucrose as a safe alternative to iron dextran. As opposed to 9% with iron dextran,¹²⁹ no allergic reactions were reported with iron sucrose. The only disadvantage of iron sucrose is the need for repeated infusions as a single dose should not exceed 500 mg (or 7 mg/kg body weight).¹²⁷ The common dose for single infusions seems to be 200 mg iron sucrose in 100 mL sodium chloride.

For the treatment of anaemia, the most important measure is the treatment of the underlying disease. This even holds true for drugs (such as purine analogues) that have adverse effects on erythropoiesis. As effective therapy may cause mucosal healing^{143, 144} we may expect a lower incidence of anaemia.¹⁰ It is unlikely, however, that anaemia will completely disappear in the near future.

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As it is out of the question to absolutely identify all related articles, we like to apologize if we missed important work on this subject and encourage authors to communicate such to us.

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