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Anaemia in the Elderly IBD Patient

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Abbreviations *ACD* Anaemia of chronic disease · *CD* Crohn's disease · *CHr* Reticulocyte haemoglobin content · *ESA* Erythropoiesis-stimulating agent · *Hb* Haemoglobin · *%HYPO* Hypochromic red cells · *IBD* Inflammatory bowel disease · *TfS* Transferrin saturation · *TIBC* Total iron binding capacity · *UC* Ulcerative colitis · *ZPP* Zinc protoporphyrin

Opinion statement

Anaemia is a common multifactorial extraintestinal manifestation in IBD patients. Moreover, anaemia represents an important health problem among the elderly population and has a significant impact on healthcare utilisation and costs. Data on the prevalence, diagnosis and management of anaemia in elderly IBD patients are scarce, since clinical trials have largely excluded this population. In this review, we reconsider anaemia in older IBD patients in the light of new diagnostic and therapeutic tools.

Introduction

Anaemia is the most common systemic complication and extraintestinal manifestation of inflammatory bowel disease (IBD) [1••, 2]. In the majority of cases, IBD-associated anaemia is a prime example of the combination of chronic iron deficiency and anaemia of chronic disease (ACD) [2]. Less frequent causes of anaemia in IBD include vitamin deficiency (vitamin B_{12}, Vitamin D, folic acid) and toxic effects of medications (e.g. azathioprine). Anaemia has a substantial impact on quality of life in IBD patients, affecting physical, emotional and cognitive functions, ability to

work, rate and duration of hospitalisation and healthcare costs [3]. Anaemia in IBD is not just a laboratory marker; it is a disease complication that demands appropriate diagnostic and therapeutic management [1••, 4, 5••, 6].

Several publications have suggested that IBD in older patients, typically defined as those aged over 65 years (also referred to as geriatric), is different from the disease seen in younger individuals, arguing for different disease phenotypes [7•, 8•]. Lower requirements for immunosuppression in elderly IBD patients have also been reported, suggesting a milder disease course [3]. On the other hand, the rate of postoperative complications is increased, and hospital stays and operation times are prolonged, even if adjusted for comorbidity and immunosuppressive therapy.

Comorbid disease is frequently encountered in geriatric medicine, posing major challenges for management. Data from a geriatric IBD cohort indicate that the majority of patients suffered from multiple comorbid illness, most commonly cardiovascular illness, pulmonary disease and diabetes mellitus [9]. However, the impact of ageing on anaemia, and more specifically in IBD patients over 65 years of age, is not yet defined.

Prevalence and definition

Anaemia is a common, multifaceted condition which is common in the elderly population. In elderly IBD patients, it has been shown to be the most frequent extraintestinal disease manifestation [10]. Based on the WHO definition (Table 1) [11], large community studies from both the USA and Europe have reported prevalences of 8 to 25 % in individuals >65 years of age [12, 13]. These fractions rose to 26.1 and 20.1 % in subjects older than 85 years, in males and females, respectively [13]. Since normal haemoglobin levels vary with age, gender and ethnicity, there is increasing debate as to the exact haemoglobin (Hb) levels which should be applied to define anaemia in general, and particularly in the elderly population [14]. For example, the lower limits of normal haemoglobin concentration in African Americans are lower (11.5 g/dL for women, 12.9 g/dL for men) and likewise in the elderly. Interpretation of haemoglobin and haematocrit levels needs to take account of such modulating factors [1••].

While two thirds of IBD patients have anaemia at diagnosis, the prevalence and causes of anaemia may change during follow-up [13]. In children, anaemia is even more common (approx. 70 %) than in adults (30–40 %) [15]. Data describing the prevalence of anaemia in the elderly IBD population are scarce. Based on European studies published between January 2007 and May 2012 including 2192 patients, Filmann et al. calculated the overall prevalence of anaemia in patients with Crohn's disease (CD) to be 27 %, compared with 21 % in patients with ulcerative colitis (UC). Fifty-seven percent of anaemic patients were iron deficient. Age and gender-stratified basis prevalence showed that whereas male patients aged 30–64 years have a significantly lower risk for anaemia than younger patients (<30 years) or men older than 65 years, the prevalence in women is almost entirely independent of age (Table 2). Gender was not significantly associated with the existence of anaemia [16•].

Older age-associated deficiencies of *micronutrients* involved in haemoglobin synthesis primarily include iron, vitamin B_{12} (cyanocobalamin) and vitamin D deficiencies [15, 17, 18]. The same deficiencies, in vitamin B_{12}, iron and vitamin D, are also common in patients with IBD [2, 19–23]. The impact of advanced age on these nutritional parameters in the geriatric IBD population has been elucidated by Juneja et al. Using data extracted from electronic medical records based on ICD-9 coding for CD and UC, the authors identified a total of 393

Table 1. Minimum haemoglobin and haematocrit levels used to define anaemia in people living at sea level [11]

Age or sex group	Haemoglobin [g/dL]	[mmol/dL]	Haematocrit [%]
Children 1/2 to 5 years	11.0	6.83	33
Children 5 to 11 years	11.5	7.14	34
Children 12 to 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

elderly IBD patients (49.1 % male, 50.9 % female; 61.8 % UC, 38.2 % CD; mean age 73.4±6.6 years). Of these, 17.6 % (18 % CD, 17.3 % UC) were deficient in vitamin B_{12}, consistent with rates identified in the tertiary referral adult IBD population [20, 24].

In addition, iron deficiency was found in 17.6 % of the cohort (13.3 % CD, 20.2 % UC), while 15.3 % (11.3 % CD, 17.7 % UC) had a vitamin D deficiency. Surprisingly, the identified prevalence of vitamin D deficiencies was lower than reported in other studies of adults with IBD, although this may be due to the use of different cut-offs [24, 25].

The authors also examined nutritional deficiencies in elderly IBD patients in the context of disease duration. Disease duration was shown to be significantly longer in geriatric CD patients with vitamin B_{12} deficiency (22.6±14.1 years) than without (12.5±14.4 years). Likewise, duration of CD was significantly longer in those with iron deficiency (21.9±16.9 years) compared with non-deficient subjects (12.8±13.9 years). The same pattern held true for vitamin D-deficient subjects (28.9±14.0 years) compared to those without deficiency (12.8 ±14.1 years). The effect of disease duration on vitamin B_{12}, iron and vitamin D deficiency remains unclear. It is conceivable that micronutrient deficiencies result from the development of dietary aversions in patients with a longer duration of CD. Furthermore, these patients are probably more likely to have undergone (multiple) surgical procedures, leading to absorptive insufficiency. Similar correlations were not observed in geriatric patients with UC.

Pathogenesis

The cause of anaemia in patients with IBD is multifactorial (Table 3). The two most frequent aetiological forms by far are iron deficiency anaemia (IDA), resulting from iron deficiency secondary to blood loss through ulcerations of the intestinal mucosa, decreased iron absorption and reduced intake, and anaemia of chronic disease (ACD), described for the first time by Cartwright in 1946. ACD is characterised by normal or reduced mean corpuscular volume (MCV), reduced serum iron, reduced total iron binding capacity (TIBC), normal to elevated serum ferritin and reticuloendothelial system (RES) stores that are elevated relative to total body iron. While vitamin B_{12} and folate deficiency and drug-induced anaemia (sulfasalazine, thiopurines, methotrexate,

Table 2. Prevalence of anaemia in IBD patients, stratified by age and gender (Filmann et al. [16•])

Age (years)	Male %	Female %
18–29	31	26
30–39	18	25
40–49	19	25
50–64	21	24
65–74	28	23
>74	35	24

calcineurin inhibitors) are less widespread, these possibilities should also be considered [2, 26••]

In the context of the high prevalence of vitamin D deficiency in the elderly population, new insights into the pathogenesis of anaemia have been gained from studies in patients with chronic kidney disease: Vitamin D status (serum concentration of the prohormone 25-hydroxyvitamin D [25D]) correlates inversely with the prevalence of anaemia and resistance to erythropoiesis-stimulating agents (ESAs) and directly with blood haemoglobin levels. In addition, vitamin D repletion in anaemic haemodialysis patients has been shown to correlate with lower ESA requirements [27, 28]. More recently, in a pilot study of healthy volunteers, Bachetta et al. demonstrated that oral vitamin D supplementation resulted in a significant decrease in circulating levels of hepcidin within 24 h after vitamin D supplementation [29].

Anaemia workup

Several guidelines and recommendations have been proposed for anaemia diagnostics in IBD patients [1••, 14, 20, 30]. However, there are no recommendations for diagnosis and management of anaemia in the elderly IBD population. Anaemia workup should be performed if haemoglobin is below normal. At a minimum, workup should include red blood cell indices such as red cell distribution width (RDW) and mean corpuscular volume (MCV), reticulocyte count, differential blood cell count, serum ferritin, transferrin saturation (TfS) and CRP concentration. More extensive workup includes serum concentrations of vitamin B12, folic acid, haptoglobin, the percentage of hypochromic red cells, reticulocyte haemoglobin, lactate dehydrogenase, soluble transferrin receptor, creatinine and blood urea nitrogen

Because the interpretation of traditional biomarkers is frequently complicated by concomitant chronic diseases and polypharmacy, the accurate diagnosis of IDA in elderly patients with IBD is often challenging. Although MCV and mean corpuscular haemoglobin (MCH) have been recommended as useful variables and are routinely determined in IBD patients within the complete blood count, MCV reduction in older persons is often lacking in the early stages of anaemia and/or blunted by other concomitant nutritional deficiencies, e.g. folic acid or vitamin B_{12} [31]. Similarly, the other common laboratory markers of 'absolute' iron deficiency (ID), i.e. low serum ferritin and transferrin saturation, have been demonstrated to have low sensitivity in an elderly population

Table 3. Causes of non-iron deficiency anaemia in IBD [adapted from reference 1••]

Common	Anaemia of chronic disease
Occasional	Cobalamin deficiency
	Folate deficiency
	Drug-induced [sulphasalazine, 5-ASA, 6-MP, azathioprine]
Exceptional	Haemolysis
	Myelodysplastic syndrome
	Aplastic anaemia
	Glucose-6-phosphate dehydrogenase deficiency
Probable	Vitamin D deficiency
	Vitamin B6 deficiency

5-ASA 5-aminosalicylic acid, *6-MP* 6-mercaptopurine

[32]. For example, serum ferritin ≤30 μg/L, the classical cut-off value to define ID in younger IBD patients (if CRP <5 mg/dL), has been claimed to be too stringent in elderly patients. Indeed, in the elderly population, true ID often occurs at higher ferritin values since ferritin per se rises with age [33]. In a study carried out in hospitalised older patients, serum ferritin <50 μg/L was found to be a more reliable indicator of ID than other traditional cut-off values [34]. The low sensitivity of traditional iron biomarkers is also demonstrated by the fact that anaemic elderly patients sometimes respond to iron supplementation despite normal iron indices at baseline [35].

Reticulocytes

Reticulocytes are those immature erythrocytes which still contain sufficient RNA to be microscopically detectable using specific alkaline stains. This blood count parameter (%) is obtained by flow cytometry and is available in all larger laboratories at a reasonable cost.

In chronic anaemia that has reached a steady state, relative reticulocyte count correlates inversely, though non-linearly, with the shortening of the erythrocyte lifespan. The absolute reticulocyte count, on the other hand, is a gauge for effective erythrocyte production by the bone marrow [36]. Therefore, anaemia can be effectively classified using a combination of MCV and reticulocytes (Table 4).

Soluble transferrin receptor

An up-regulation of the number of soluble transferrin receptors (sTfR) on cellular membranes continuously moving into the plasma reflects erythropoietic activity and inversely correlates with the amount of iron available for erythropoiesis. Thus, the determination of sTfR has been reported to be a reliable indicator of iron deficiency [37, 38]. In the past, some evidence supported sTfR measurement as a novel marker of ID in older people, since its concentration neither increases with age nor is it affected by the presence of inflammation [22, 39].

However, sTfR concentrations are also increased in every expansion of erythropoiesis (i.e. haemolytic anaemia, thalassaemia or polycythaemia) and reduced in aplastic anaemia and other conditions with hypoproliferative erythropoiesis (e.g. renal anaemia).

Disadvantages for the routine diagnostic use of the TfR-F (sTfR-ferritin) index are its lack of uniform reference range (the reference ranges of the individual components are assay-dependent) and its relatively high cost. It may be hypothesised that the combination of haematologic markers such as reticulocyte haemoglobin content (see below) which decreases with iron deficiency and TfR/F ratio may allow for a more precise classification of anaemias [23].

Hypochromic erythrocytes and reticulocyte haemoglobin content

Recent research by Thomas et al. has confirmed cytometry of the reticulocyte haemoglobin content (CHr) and the percentage of hypochromic red cells (%HYPO) to have a high predictive value in the differential diagnosis of IDA even when inflammation and ACD are present. While a reduction in %HYPO (mean lifetime, 120 days) denotes a longer-term deficiency in iron supply, reduced CHr (mean lifetime, 48 h) is an indicator of current iron deficiency providing an accurate measurement of bioavailable iron over the previous 3–4 days (Table 3). In haemodialysis patients, CHr <29 pg has been demonstrated to be a more accurate measure of functional iron deficiency than the combined use of ferritin and transferrin saturation (TfS). Furthermore, CHr measurement may serve to predict the response to intravenous (IV) iron therapy [40, 41]. One study in patients with rheumatoid arthritis and IDA showed that an increase of CHr predicts response to oral iron supplementation 1 week after onset [42]. However, no data are available from IBD patients.

Zinc protoporphyrin

Zinc protoporphyrin (ZPP) was pinpointed by Dagg and colleagues as early as 1966 as a potential indicator of ID [24]. A reduction in iron supply for erythropoiesis to a suboptimal level results in the production of ZPP instead of haem, with zinc, instead of iron, being incorporated into protoporphyrin IX. Thus, ZPP levels are a direct marker of iron status in the bone marrow during erythropoiesis. ZPP production is entirely unaffected by ACD or other chronic inflammation and is therefore an effective indicator of ID even in the presence of inflammation. The onset of iron-deficient erythropoiesis triggers continuously increasing ZPP concentrations. Concentrations <40 μmol/mol haem are considered normal. Values of 40–80 μmol/mol haem represent latent iron deficiency (haemoglobin normal); >80 μmol/mol haem are associated with manifest iron deficiency. In severe cases, values of up to 1000 μmol/mol haem have been reported [43, 44].

Treatment of anaemia in the elderly IBD patient

Treatment of iron deficiency anaemia

Currently, no specific guidelines exist for the management of anaemia in elderly persons with IBD. Nevertheless, it is clear that, alongside adequate micronutrient

Table 4. Classification of anaemia by MCV and reticulocytes [adapted from reference 1••]

Microcytic anaemia with normal or low reticulocytes
Iron deficiency
Anaemia of chronic disease [cancer, infection…]
Lead poisoning [very rare]
Hereditary microcytic anaemia [rare]
Microcytic anaemia with elevated reticulocytes
Haemoglobinopathies [thalassaemia…]
Normocytic anaemia with normal or low reticulocytes
Acute haemorrhage [may initially have elevated reticulocytes]
Renal anaemia [endogenous erythropoietin levels=inappropriately low]
Severe aplastic anaemia [SAA], pure red cell aplasia [PRCA]
Primary bone marrow diseases [leukaemias, MDS diseases]
Bone marrow infiltration by cancer [prostate, breast…]
Combination of iron deficiency and B_{12}/folate deficiency [very rare, usually in malabsorption]
Normocytic anaemia with elevated reticulocytes
Haemolytic anaemia
Macrocytic anaemia with normal or low reticulocytes
Myelodysplastic syndrome [MDS]
Vitamin B_{12} deficiency [pernicious anaemia, H. pylori gastritis, antacids, vegans]
Folate deficiency [increased requirement in pregnancy, haemolysis, chronic myeloid leukaemia]
Long-term cytostatic medication [hydroxy-urea, methotrexate, azathioprine…]
Hypothyroidism
Alcoholism [isolated macrocytosis without anaemia]
Thiamine-responsive megaloblastic anaemia syndrome [very rare]
Macrocytic anaemia with elevated reticulocytes
Haemolytic anaemia [false macrocytosis]
Myelodysplastic syndrome with haemolysis

supplementation (iron, vitamin B_6, B_{12}, D and folate), therapy should focus on the identification and treatment of the underlying causes of anaemia.

Once IDA is clearly ascertained or deemed likely (because of ambiguous results of iron markers, as discussed above), iron replacement should be initiated. In cases of iron deficiency without manifest anaemia, an individualised approach is required [1••, 45]. The major goal of therapy for IDA is to increase haemoglobin levels by >2 g/dL or to normal values within 4 weeks, to replenish iron stores (TfS >30 %), relieve anaemia-related symptoms and thereby improve quality of life.

Iron supplementation can be administered orally or intravenously. The choice of route is determined by the symptoms, aetiology and severity of the condition, the dynamics of the haemoglobin decrease, comorbidities and individual risks of therapy. Because oral iron is convenient, inexpensive and effective for the treatment of stable patients, oral supplementation has been the preferred therapy for many years. The recommended daily dose for adults is 100–200 mg elementary iron and 3–6 mg/kg body weight (divided into two doses) for children [26••]. In contrast, there are no clear dose recommendations for elderly people.

Oral iron is associated with gastrointestinal adverse effects, including nausea, flatulence, diarrhoea and gastric erosions [46]. Furthermore, emerging data suggest that non-absorbed iron can cause potentially harmful modification of

the gut microbiota, increasing the concentration of intestinal pathogens in both children and adults [47, 48].

Although oral iron replacement is widely used in older people (including IBD patients), evidence concerning its efficacy in this population has been discussed controversially for many years. Tay and Soiza's most recently published systematic review and meta-analysis demonstrated that oral iron raises Hb levels in elderly persons with IDA by only 0.35 g/dL after 4–6 weeks, possibly due to a slower bone marrow response [21]. Moreover, orally administered iron is often poorly absorbed because of the relatively high prevalence of malabsorptive conditions and concomitant polypharmacy in the elderly population [49]. It remains questionable whether this small increase in Hb level results in tangible health benefits [21]. Normally, Hb levels are expected to rise approximately 1–2 g/dL every couple of weeks after starting oral iron therapy. Since the mean total iron dose generally required to correct anaemia and replenish iron stores in IBD patients is 1000–1500 mg, national and international guidelines recommend intravenous iron supplementation for the correction of IBD-associated IDA [1••, 14, 20, 30].

Intravenous iron has been demonstrated to be safe, effective and well tolerated in both the correction of IDA and the maintenance of iron stores in patients with IBD [50, 51]. Several intravenous iron preparations are currently available for treatment of IDA. Such formulations differ by complex chemistry and can be grouped into labile, semi-labile and stable iron complexes [52]. Large trials in IBD patients have been published for iron sucrose, ferric carboxymaltose and iron isomaltoside 1000, demonstrating efficacy and safety in terms of dose (1000 mg or ≤20 mg/kg body weight) and therapy duration [1••, 50].

Only limited data are available on high-dose intravenous iron supplementation in elderly patients (>65 years). Röhrig et al. collected data describing the efficacy and tolerance of ferric carboxymaltose (Ferinject) in geriatric patients (>70 year), including IBD patients. High-dose ferric carboxymaltose (746–1575 mg) was well tolerated and effective as a treatment option in functional iron deficiency [53].

Vitamin supplementation

In the case of existing vitamin B_{12} deficiency, parenteral (intramuscular or subcutaneous) administration remains the preferred route. Unfortunately, therapy recommendations regarding dosage and timing of vitamin B_{12} supplementation are largely inconsistent. However, the given dose must be calculated to take account of the fact that clinical symptoms only begin to be manifest when body vitamin B_{12} stores (3–5 mg) are depleted to as little as 5–10 % [54]. The aim of therapy must be to fully compensate the deficit and the dosage chosen accordingly. Standard initial therapy for patients without neurological involvement is 1000 μg i.m./s.c. three times a week for 2 weeks [55] or daily for 5 days, followed by five further weekly injections of 1000 μg [56]. Maintenance treatment for patients presenting without neurological deficits is hydroxocobalamin 1000 μg i.m./s.c. every 3 months [55].

Evidence-based recommendations for effective vitamin D substitution in IBD are also currently lacking, but targeting serum 25-hydroxy vitamin D [25(OH)D] levels between 30 and 50 ng/mL appears safe and may have also benefits for IBD disease activity. Depending on baseline vitamin D serum concentration, ileal

involvement in CD, body mass index and perhaps smoking status, daily vitamin D doses of 1800–10,000 IU/day are probably necessary [57].

Erythropoiesis-stimulating agents and blood transfusion

In most IBD patients, treatment of the underlying disease in conjunction with iron and vitamin replacement is sufficient to effectively correct anaemia. In patients with ACD showing insufficient response to supplementation, despite optimal IBD therapy and intravenous iron supplementation, treatment with ESAs is an option. To minimise adverse events (venous thrombosis and/or cardiovascular events), maximal target haemoglobin value should be limited to 12 g/dL in cancer or renal insufficiency [1••].

As in the younger IBD population, red blood cell transfusion should only be considered when haemoglobin concentration is below 7 g/dL or if symptoms or particular risk factors like severe comorbidities are present. Blood transfusion should be followed by intravenous iron supplementation to replenish the deficient iron stores [1••].

Compliance with Ethics Guidelines

Conflict of Interest

Jürgen Stein has received consultancy fees from Abbvie, Fresenius-Kabi, Immundiagnostik, MSD, Pharmacosmos, Takeda, and Vifor. Dr. Stein has also received payment for lectures from Abbvie, Falk Foundation, Ferring, Immundiagnostik, MSD, Pharmacosmos, Takeda, Thermofischer and Vifor. Additionally, Dr. Stein has received payment for manuscript preparation from Abbvie, Falk Foundation and MSD.

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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