

Fatigue and acute/chronic anaemia

Acute upper gastrointestinal bleeding/chronic inflammatory bowel disease used as a model

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THE 4 ORIGINAL PAPERS ARE

1. Bager P, Dahlerup JF. Randomised clinical trial: oral versus intravenous iron after upper gastrointestinal haemorrhage - a placebo-controlled study. *Aliment Pharmacol Ther.* 2014;39:176-87.
2. Bager P, Dahlerup JF. Patient-reported outcomes after acute nonvariceal upper gastrointestinal haemorrhage. Submitted.
3. Bager P, Befrits R, Wikman O, Lindgren S, Moum B, Hjortswang H, Dahlerup JF. The prevalence of anaemia and iron deficiency in IBD outpatients in Scandinavia. *Scand J Gastroenterol.* 2011;46:304-9.
4. Bager P, Befrits R, Wikman O, Lindgren S, Moum B, Hjortswang H, Hjøllund NH, Dahlerup JF. Fatigue in outpatients with inflammatory bowel disease is common and multifactorial. *Aliment Pharmacol Ther.* 2012;35:133-41.

INTRODUCTION

Fatigue is generally known to accompany many chronic diseases. For patients with inflammatory bowel diseases (IBD), it has been found that 40% suffered from fatigue, even with the disease in remission (1). Fatigue has not yet been measured in patients with acute upper gastrointestinal bleeding (AUGIB).

Gastroenterological diseases cover a wide range of specific diagnoses. Some of them are accompanied by acute or chronic anaemia. Both the symptoms of the disease itself and the symptoms of anaemia can cause the patients to experience fatigue, and it can be difficult to distinguish between the causes of increased fatigue.

Anaemia is a huge global problem, affecting approximately 25% of the world's population (2). There are large variations between subgroups (age, gender, geographic region). The background

population in Scandinavia is estimated to have a lower prevalence of anaemia (5-20%) than the world in general (3).

Acute anaemia can be treated with blood transfusions with good instant effect, although it is an expensive and sometimes risky solution (4,5). The use of blood transfusions in Denmark is high and alternatives would be welcomed (6,7). An alternative might be intravenous iron. New formulations allow doses of more than 1000 mg intravenous iron in a single dose. The dose of 1000 mg is equivalent to the iron uptake after 3 months' therapy with oral iron supplementation.

Chronic anaemia in gastroenterological diseases can occur due to different conditions of deficiency, with iron deficiency (ID) as the most frequent. Furthermore, inflammatory conditions can cause anaemia of chronic disease (ACD). Combinations of these causes are common.

BACKGROUND

'The disease is better, but I feel worn out'.

Health professionals often hear such a statement from their patients. How can the relationship between fatigue and disease be determined?

In gastroenterological diseases, anaemia is a known companion to the disease itself. This dissertation will focus on fatigue and anaemia in patients with IBD or AUGIB. Fatigue can originate from both the disease and the anaemia or be caused by a combination of both. A simple illustration of the relationship is shown in Figure 1.

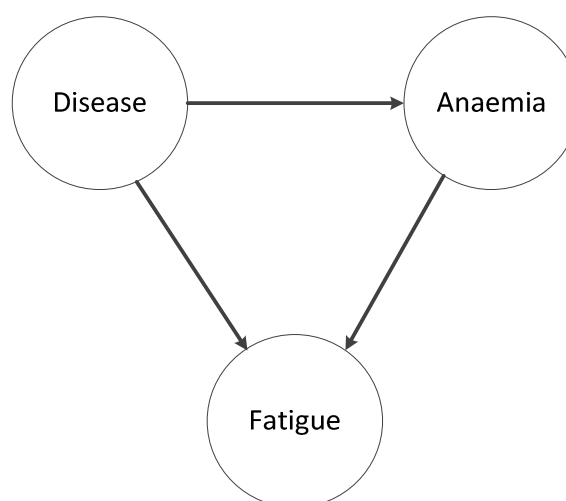


Figure 1:

Relationship between disease, anaemia and fatigue

Acute upper gastrointestinal bleeding

Upper gastrointestinal bleeding is defined as bleeding that originates proximal to the ligament of Treitz; in practice from the oesophagus, stomach and duodenum (8).

It is a common disorder that is associated with a high mortality rate (3-15%) (9-15). Causes can vary, but upper gastrointestinal bleeding is often due to gastric ulcers caused by non-steroidal anti-inflammatory drugs or *Helicobacter pylori* (16). Symptoms like haematemesis and/or melaena are often seen. This can lead to circulatory insufficiency, and sometimes the patients can develop shock. The volume of blood loss can be serious and an extreme drop in haemoglobin (Hb) levels can be seen. A variant of AUGIB is bleeding from varices (abnormally distended veins) in the oesophagus or gastric varices. Oesophageal and gastric varices are caused by portal hypertension due to liver diseases (8). Our focus was research in patients with nonvariceal AUGIB. The pre-endoscopic management and the endoscopic treatment of nonvariceal AUGIB has been well characterised and standardised (8,17-19). Most patients with nonvariceal AUGIB experience significant blood loss prior to endoscopic therapy. The use of blood transfusions prior (and after) endoscopic intervention has been described as well. Still, guidelines are generally lacking for the monitoring and treatment of anaemia in patients after treatment of a nonvariceal AUGIB.

The lack of standardisation in the management of post-discharge anaemia is probably due to a limited focus on the post-discharge phase of patient management. Follow-up studies of patients admitted with nonvariceal AUGIB reveal that more than two-thirds of the patients diagnosed with anaemia prior to discharge recovered from the anaemia after a period of 2 to 144 months (20-23). Recently, a retrospective study showed that more than 80% of patients admitted to hospital with nonvariceal AUGIB were anaemic at discharge from a semi-intensive-care unit. However, oral iron supplementation was recommended by the physicians to only 16% of the anaemic patients (24).

The level of Hb after AUGIB matters. A risk score for mortality after AUGIB has been developed (Rockall Risk Score). The score was developed using stepwise logistic regression analysis. The risk of mortality owing to Hb < 10 g/dl was increased, with an odds ratio of 1.94 (confidence interval (CI): 1.61–2.33) (25). Unfortunately, the Hb variable was not included in the final risk score. An inclusion of Hb levels would have highlighted the topic of anaemia.

Inflammatory bowel diseases

The term IBD is used for the diagnoses ulcerative colitis (UC) and Crohn's disease (CD). Both are chronic diseases with a pattern of relapse. In UC, the mucosa is affected, and UC is located in the rectum and the colon. While UC has a continuous pattern from rectum and upwards, CD has a transmural and often a segmental pattern and can affect any part of the gastrointestinal (GI) tract — from mouth to anus (26,27).

The disease prevalence and incidence vary across the globe and are highest in the industrialised world (28,29). In Denmark, the annual incidence of CD and UC has been estimated to be 10 per 100,000 and 17 per 100,000, respectively, and the prevalence to be 151 per 100,000 and 294 per 100,000, respectively (30).

IBD can be accompanied by extraintestinal manifestations, e.g. arthritis, erythema nodosum, pyoderma gangrenosum, uveitis and anaemia (31).

At the time the study was planned, the prevalence of anaemia in patients with IBD was described with very wide prevalence estimates [6.2%-73.7%] (32,33).

A majority of the publications used in the reviews originate from periods prior to the introduction of biological therapy and high dose intravenous iron supplementations. This fact makes it difficult to use the results in a clinical setting of today.

Patients with IBD can also develop different conditions related to deficiency, e.g. vitamin B12 deficiency, folic acid deficiency or ID. Having IBD can lead to several disadvantages and concerns. One of the main concerns of patients is "lack of energy"; this is also the case if the disease is in a quiet phase (34,35).

Anaemia in gastrointestinal diseases

According to the World Health Organization (WHO), anaemia is present if Hb levels are < 12 g/dl (< 7.5 mmol/l) in non-pregnant women and < 13 g/dl (< 8.1 mmol/l) in men (36). Globally, anaemia can have many causes. In gastroenterology, the main causes are blood loss (acute or chronic), decreased uptake of essential components in the GI tract and inflammatory activity. The causes can occur isolated or combined.

Apart from the physiological symptoms of anaemia, e.g. tachycardia, shortness of breath, paleness, fainting and headache, anaemia can also lead to impaired quality of life (37).

Anaemia due to blood loss

Acute blood loss without a precondition of anaemia or iron deficiency will lead to an acutely reduced blood volume. The iron stores in the body will probably be full initially, but can be expected to be reduced or even depleted when erythropoiesis increases due to the low level of Hb. The condition AUGIB is a good example of acute blood loss. Acute blood loss can also be seen in cases of active IBD.

Chronic blood loss occurs in IBD in the inflamed mucosa, with diffuse bleeding or bleeding from erosions/ulcers. As the bleeding is microscopic, the patients might not notice it. Chronic bleeding will lead to iron deficiency and anaemia. If the blood loss is due to inflammatory activity, a combined anaemia can occur.

Anaemia due deficiency conditions

The GI tract is responsible for uptake of essential vitamins and minerals. In gastrointestinal diseases, the risk of reduced uptake should always be considered. Macrocytic anaemia can occur due to vitamin B12 (cobalamine) or folic acid deficiency (38). These conditions can be easily diagnosed and treated.

Iron is, along with a healthy bone marrow and erythropoietin, essential for the erythropoiesis. ID will lead to iron deficiency anaemia (IDA), if untreated. Several blood tests can be used to diagnose ID. Serum ferritin levels are the most powerful indicator of the level of stored iron in the macrophage system and in the hepatocytes. Reduced concentrations can indicate ID (39,40). A drawback is that serum ferritin is an acute-phase reactant and can be elevated if an inflammation or infection is present. Transferrin saturation (TSAT) can be used as a measure of the iron content of circulating transferrin and is stated as a percentage. A TSAT less than 16% indicates a suboptimal supply of iron for use in erythropoiesis and is suggested as the cut-off point of sufficient iron stores. TSAT has a high specificity but a low sensitivity (41). Finally, soluble transferrin receptors (sTfRs) indicate the iron requirement, as an increased number of receptors will occur in functional ID. The concentration of sTfR is found to be of less accurate than serum ferritin (42).

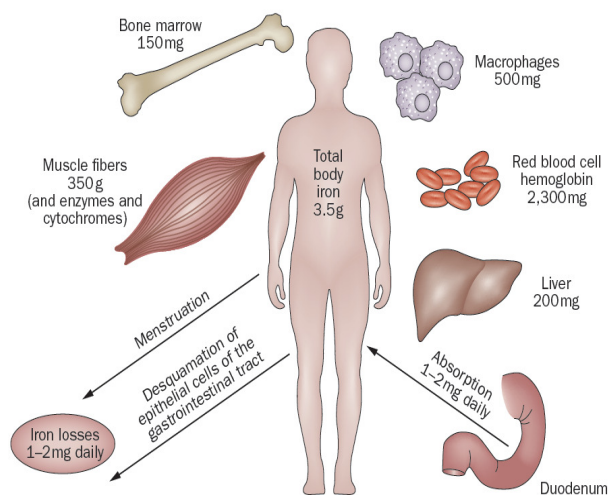


Figure 2:

Iron homeostasis in healthy man (90-100 kg). A total of 3.5 g of iron is stored in the body. In the body, 2300 mg are distributed in the red cell haemoglobin, 500 mg are stored in the macrophages, 350 mg in muscle fibres, 200 mg in the liver and 150 mg in the bone marrow. The size of the iron stores depends of the individual body weight. On a daily basis, approximately 1 to 2 mg is lost. Iron absorption from the GI tract is equivalent to the losses, and homeostasis is maintained. The figure used with permission from Prof. Stein (40).

Iron absorption occurs only in the duodenum and the upper jejunum. The daily absorption is estimated to be 1 to 2 mg per day (Figure 2) (38,40).

Absorption is promoted by the presence of nutrition elements, e.g. ascorbic acid and fatty acids, and inhibited by coffee/tea or increased levels of hepcidin (see below) (38,40,43).

But also treatment with proton pump inhibitors or the presence of *Helicobacter pylori* in the stomach has been suggested to inhibit iron absorption (44-46). These conditions are most relevant for patients with AUGIB.

In patients with inflammatory conditions (e.g. patients with IBD), the iron absorption in the GI tract can be inhibited by an increased level of hepcidin. Hepcidin is a regulator of systemic iron homeostasis. During an inflammation, the hepcidin level increases and leads to an internalisation of ferroportin in the enterocytes in the duodenum, decreasing iron uptake. Furthermore, hepcidin blocks iron release from the iron store cells. Both mechanisms can contribute to the development of ACD (38,40).

Anaemia of chronic disease

An inflammation activates the cytokine IL-6, which causes an elevated level of hepcidin. Apart from blocking the iron absorption, hepcidin can also trap iron in the macrophages, leading to functional ID. This can lead to ACD (38,47). No simple diagnostic algorithm to distinguish between IDA and ACD has yet been introduced. Although, there is international consensus regarding the cut-off levels of ferritin in relation to the two conditions (47).

- Anaemia without an inflammation and a ferritin level below 30 µg/l is interpreted as 'pure' IDA.
- Anaemia and an inflammation and a ferritin level above 100 µg/l is interpreted as 'pure' ACD.

- Anaemia and an inflammation and a ferritin level between 30 – 100 µg/l is a combination of IDA and ACD.

An overview of selected laboratory findings in IDA, ACD and the combination of IDA and ACD is given in Table I.

Serum iron just shows the actual level of circulating iron and can not be used as a measure for available body iron stores.

Serum iron is included in Table I, as a blood-test-panel for anaemia or ID often includes serum iron. Still, serum iron alone is useless when diagnosing anaemia or ID.

Treatment of anaemia

When anaemia is diagnosed and characterised, treatment may also depend on the treatment goal and the time frame.

Blood transfusions might be necessary after acute blood loss.

However, a recent study on transfusions after AUGIB suggests that a restrictive transfusion strategy would be appropriate (48).

In IBD, blood transfusions are not recommended for treatment of IDA (49).

Table I:

An overview of selected laboratory findings in IDA, ACD and the combination of IDA and ACD. Inspired from (38,40).

Laboratory measures	IDA	ACD	IDA and ACD
Serum ferritin	↓	↑	↑ or normal
Serum transferrin	↑	↓ or normal	↓
TSAT	↓	↓	↓
sTfR	↑	↓ or normal	↑ or normal
CRP	Normal	↑	↑
Haemoglobin	↓	↓	↓
Serum iron	↓	↓	↓

IDA: iron deficiency anaemia; ACD: anaemia of chronic disease; TSAT: transferrin saturation; sTfR: soluble transferrin receptor; CRP: C-reactive protein

Oral iron supplementations are inexpensive and can be absorbed from the duodenum if no inflammation is present. But a maximum of 10% (10–15 mg/day) of the oral iron taken will be absorbed. Ninety percent will pass through the rest of the GI tract and straight in the toilet bowl.

In patients with anaemia, depleted iron stores and no inflammation, it will take at least 2 to 3 months just to fill the iron stores (estimated to be 1000 mg for a body weight > 80 kg) if oral iron is chosen, depending on the patient's body weight. In addition to this, the anaemia itself needs correction. Depending on the severity, this could add another 2 to 3 months to the total period of oral iron treatment.

Oral iron has many side effects. The most common are gastrointestinal symptoms (nausea, diarrhoea, constipation and abdominal pain). Furthermore, as 90% of the iron taken passes per rectum, many treated patients have "black stool" (50). This can confuse signs of GI bleeding. Adherence to oral iron treatment is known to be rather poor; this might be due to the side effects mentioned above (51-54). Finally, it has been hypothesized that the generation of reactive oxygen species by the non-absorbed iron could potentially re-activate IBD (55).

Intravenous iron therapy might be an alternative. In the last few years, new preparations allowing doses of (and above) 1000 mg iron without a test dose have been marketed. The most used high-dose preparations in Europe are iron carboxymaltose (Ferinject®) and iron isomaltoside 1000 (Monofer®). Low-dose preparations (200 mg) are still available (iron sucrose and iron dextran). Low-dose preparations are cheaper, but if several infusions are to be given, the total cost is higher for low-dose preparations than for high-dose preparations (56).

High-dose preparations can be given at 2-week intervals. This means that 2000 mg iron can be loaded into patients at least eight times faster than if oral iron was chosen (see the example above). This leads to a much more rapid availability of iron in the body. Side effects of intravenous iron are primarily infusion reactions (rare). Furthermore, a temporary drop in serum phosphate level has been suggested to be linked to intravenous iron infusions (57,58).

In the European guidelines on anaemia in IBD, intravenous iron is recommended to treat ACD in IBD (49). As mentioned, there are no guidelines for treating anaemia in patients after AUGIB.

Earlier, the cumulative dose of iron needed was calculated using the Ganzoni formula published in German in 1970 (59):

$$\text{Iron deficit (mg)} = \text{body weight (kg)} \times [\text{target Hb} - \text{actual Hb (g/l)}] \times 0.24 + \text{stored iron (500 mg)}$$

It has later been demonstrated that the formula underestimates the iron needed (at least in patients with IBD) and the current practice is to use 1, 2 or even 3 g iron as the cumulative target dose, using a more simple algorithm (60,61).

Finally, intravenous iron has lately been demonstrated to have a positive effect on the level of fatigue in non-anaemic women with ID (62).

Fatigue

Fatigue has been known in the scientific community for a long time:

"It is suggested that the term fatigue be absolutely banished from precise scientific discussions."

B. Muscio, 1921, (63).

Fatigue may be a normal feature of human life, but increased fatigue is associated with many medical conditions. A interview-based study has revealed that patients label their sensation of fatigue in a qualitatively very different way from the way they experienced fatigue before they became ill (64).

While there is no generally accepted definition of fatigue, it is often described as:

"A persistent, overwhelming sense of tiredness, weakness or exhaustion resulting in a decreased capacity for physical and/or mental work" (65,66).

In published studies, fatigue is mostly described as a multicausal, multidimensional and complex concept in which psychological, biochemical and physiological mechanisms play a role. As fatigue is subjective, multidimensional and complex, a multidimensional scale must be preferable for measurement. So far, there are no specific tests for fatigue, and the measurement of fatigue symptoms is usually done using self-reported questionnaires.

The methods for measuring fatigue in chronic diseases are numerous. A review published in 2007 presented 252 different ways to measure fatigue, and more than half of these tools have been

used only once (67). The majority of the scales are disease-specific. Generic instruments must be used if the differences in fatigue levels between ill people and the general population (GP) are to be compared. Most of the fatigue scales distinguish between *physical fatigue* and *mental fatigue*. Some scales measure chronic fatigue (fatigue lasting more than 6 months); some measure real-time fatigue (68-71). Furthermore, many scales were developed for a certain disease category and later on expanded to include other diseases. When choosing a generic fatigue scale, it should be considered whether normative data have been published, making it possible to compare the levels of fatigue in the investigated group with the GP.

The experience of being anaemic after AUGIB has not been investigated in patients. However, a small study monitoring patient-reported outcomes at baseline and 1 month after the bleeding found an improvement in the physical components of the patients' health-related quality of life (HRQoL) (49,72).

Fatigue is a frequent complaint and is one of several concerns among patients with IBD (35,73). When planning the studies in this dissertation, publications regarding fatigue in IBD patients were sparse and mostly based on single-centre or national studies. Only a few studies have investigated fatigue as their primary endpoint, as noted by Langenberg and Gibson in a systematic review in 2010 (66). Lately, two publications from Norway found that chronic fatigue was more prevalent in a Norwegian IBD population than in healthy controls, and fatigue in IBD was associated with a reduced HRQoL (74,75). A Dutch paper reported similar results using data from a large IBD cohort (76). Furthermore, fatigue was found to be more severe in patients with ongoing disease activity than in patients with disease in remission. Still, 40% of the IBD patients with quiescent disease were found to be fatigued when the 95th percentile of the score for the healthy controls was used as the cut-off point for *general fatigue* (1,76). This could call for the development of normative values for patients with IBD.

Fatigue in the GP has been measured in population-based studies. Two Scandinavian studies found that women had higher fatigue scores than men (77,78). A large German study reported similar findings (79). These studies suggested different cut-off points for fatigue based on gender and age. No fatigue studies in patients with IBD have yet used gender- and age-specific cut-off points when comparing fatigue in IBD with the GP.

HYPOTHESES AND AIMS

For patients with AUGIB, any data on post-discharge anaemia, the effect of iron supplementation and HRQoL, will be new. There is good evidence for the use of intravenous iron in other diseases to treat both chronic and acute anaemia. The question was, whether iron supplementation given to anaemic AUGIB patients could have an effect.

In the Scandinavian countries, we have similar health care systems, e.g. with regard to organisation, economic resources and level of services. Furthermore, almost all patients with IBD are monitored in hospital settings. The question was, whether updated and valid data on anaemia and fatigue in IBD outpatients could be emerged from an international study.

On this basis, the following hypotheses were proposed:

1. Iron supplementation given to anaemic AUGIB patients after stabilisation of the bleeding source will have a significant impact on the patients' levels of Hb.

- Intravenous iron supplementation given to anaemic AUGIB patients as a single dose will appear to be more effective than oral iron treatment.
- AUGIB patients will have a decreased HRQoL when anaemic. Furthermore, they will have increased levels of fatigue.
- The prevalence and type of anaemia in outpatients with IBD can be estimated in an unselected sample of patients from tertiary hospitals in Scandinavia.
- Different dimensions of fatigue in outpatients with IBD can be derived from an unselected sample of patients from tertiary hospitals in Scandinavia.
- Anaemic outpatients with IBD will have increased fatigue, and so will those with ID.

The aims were to investigate whether iron would have a significant effect in anaemic patients after AUGIB and to describe the prevalence and type of anaemia and fatigue in IBD outpatients in an international cross-sectional study.

METHODOLOGICAL ASPECTS

The dissertation is based on two studies with different designs. One study was in patients with acute anaemia (patients with AUGIB); one was in patients with chronic anaemia (patients with IBD). In the following, the studies will be named *the AUGIB study* or *the IBD study*.

Study designs

The AUGIB study

The AUGIB study was a double-blind, placebo-controlled, randomised trial. The study was conducted as a mono-centre study at Aarhus University Hospital. All included patients were initially followed up for 13 weeks after baseline. Patients still anaemic at week 13 were offered rescue therapy with intravenous iron immediately after week 13. Those receiving rescue therapy were followed up for an additional 13 weeks. Evaluations were performed at weeks 1, 2, 4, 8 and 13. In addition, all patients were asked to answer a questionnaire regarding HRQoL and fatigue at 6 months and 12 months after baseline. Data on re-admission to hospital or death were also collected at months 6 and 12.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) Guidelines and was monitored continuously by the GCP unit at Aarhus University, Denmark. The study was approved by all relevant authorities and registered in the ClinicalTrials.gov database.

Participants

The eligible patients were men and women older than 18 years old who had been admitted to hospital with nonvariceal AUGIB. The patients were included approximately 48 hours after stabilisation of the bleeding source and endoscopic evaluation. All of the patients were anaemic at inclusion according to the anaemia definitions of the WHO: Hb levels < 12 g/dl for women and < 13 g/dl for men (36). Patients were excluded if they had oesophageal variceal bleeding, liver disease (including haemochromatosis), kidney disease, cancer or were pregnant. Furthermore, the included patients had to have been able to follow verbal and written instructions. Known hypersensitivity to any of the treatment drugs excluded patients from participation.

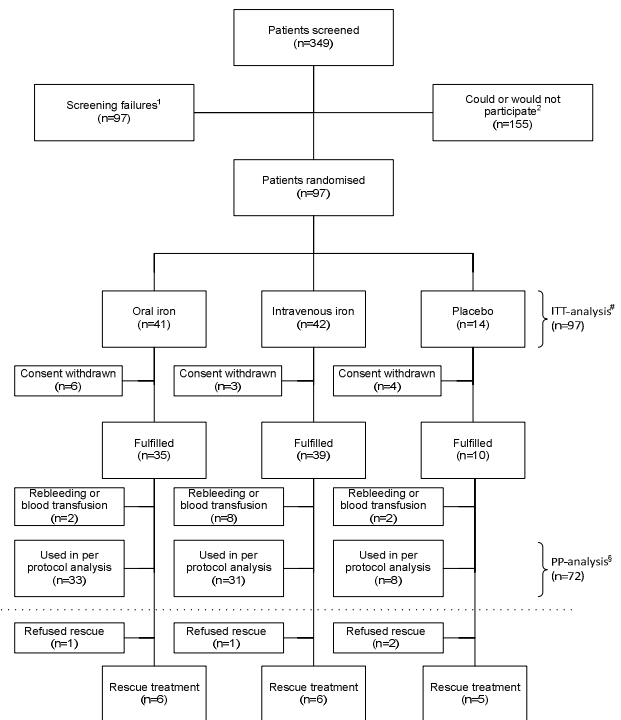


Figure 3:

Patient flow, randomisation, withdrawals, and rescue treatment. ¹ Mainly due to cancer or liver or kidney diseases; ² Mainly due to geography or reduced mental function; ³ Intention-to-treat analysis; ⁴ Per protocol analysis.

Ninety-seven patients with nonvariceal AUGIB were included in the trial. The patient flow, treatments and rescue treatments are illustrated in Figure 3.

After 42 patients were included and randomised, a protocol amendment was approved and implemented. An unexpectedly large number of patients required rescue treatment (25%), and for ethical reasons, the placebo group was excluded when allocating the remaining patients to the treatment arms. The amendments were approved by all of the relevant authorities, and the study remained blinded until the end of the study period.

Interventions

The included patients were randomised to one of three treatment arms. They were assigned in a block-randomised design with a block size of 9 and randomised in a 1:1:1 ratio to three groups: oral group, IV group or placebo group.

Randomisation and treatment blinding were performed by the Hospital Pharmacy at Aarhus University Hospital and were monitored by the GCP unit at Aarhus University.

- The oral group received ferrous sulphate tablets (Recipharm AB, Solna, Sweden), 100 mg twice per day, for 3 months and an intravenous saline infusion at baseline.
- The IV group received intravenous ferric carboxymaltose (FCM) (Vifor Pharma Ltd., Glattbrugg, Switzerland) 1000 mg in a saline solution at baseline (for patients with a bodyweight < 65 kg, the dose was 750 mg; for patients with a bodyweight < 50 kg, the dose was 500 mg) and two placebo tablets (Recipharm AB, Solna, Sweden) per day for 12 weeks.

- The placebo group received an intravenous saline infusion at baseline and two placebo tablets per day for 12 weeks.

Participants were not allowed to take any other iron supplementation during the study period. The intake of multivitamin pills containing a small dose (often < 20 mg) of iron was allowed. Both the participants and the investigators were blinded to the intravenous study drug using dark non-transparent bags and black infusion lines (Figure 4).



Figure 4:
Black infusion bag and line used for the AUGIB study drug.

Unblinded nurses administered the intravenous study drug. The oral study drugs were blinded, packed and labelled by the Hospital Pharmacy and administered by investigators. At weeks 4, 8 and 13, the distributed tablets were collected and counted to monitor the intake.

If the patients still were still anaemic at week 13, they were offered unblinded rescue treatment with intravenous FCM (1000 mg) in a saline solution at baseline (for patients with a body-weight < 65 kg, the dose was 750 mg; for patients with a body-weight < 50 kg, the dose was 500 mg). This treatment was administered regardless of treatment allocation because the allocation remained blinded until the end of the trial.

The IBD study

The IBD study was an international cross-sectional study including outpatients with IBD from six centres in Scandinavia. To estimate the point prevalences of anaemia and ID, all of the centres contributed approximately 5% of their existing IBD cases. The study was initiated and coordinated from Aarhus University Hospital and was approved by the Ethics Committees of Denmark, Norway and Sweden and by the Danish Data Protection Agency.

All data were collected locally and each hospital sent de-identified data to Aarhus University Hospital, where the data analyses were performed.

Participants

Outpatients diagnosed with CD or UC were enrolled consecutively as they attended the outpatient clinics, regardless of whether visits were scheduled or acute and regardless of the level of disease activity. Enrolment took place during 1-week periods in June, October, and November–December of 2009.

The study included 437 patients with IBD patients from the six centres. Six pregnant patients and two patients with no available blood samples were excluded from the analysis, leaving 429 patients to be included in the anaemia and ID analysis.

Another four patients did not complete the fatigue questionnaire and were excluded in the fatigue analysis, leaving 425 patients for analysis.

Measurements

The AUGIB study

Blood samples

Blood samples were collected at baseline and at all of the follow-up visits, and the samples were tested for the following: haematology (incl. Hb), ferritin, transferrin, iron, white blood cells, platelets, phosphate and C-reactive protein (CRP). TSAT was used as a measurement for the iron content of circulating transferrin and was stated as a percentage (quotient of plasma iron concentration [$\mu\text{mol/l}$]/2 x transferrin concentration [$\mu\text{mol/l}$]). In this study, full iron stores were defined as serum ferritin > 100 $\mu\text{g/l}$ and CRP less than the upper limit of the normal range (< 8 mg/l).

Some follow-up samples were drawn in the participants' homes by the hospitals' mobile laboratory units or by the investigator because of the immobility of some participants. All of the blood samples were analysed in the Department of Clinical Biochemistry at Aarhus University Hospital.

Sociodemographics and disease related data

At baseline, information was collected on the patients' genders, ages, diagnoses, co-morbidities, bleeding sources, the presence of *Helicobacter pylori*, numbers of blood transfusions, endoscopic interventions and concomitant medication. At each follow-up visit, re-bleeding, blood transfusions, re-admission to the hospital and death were registered. The co-morbidities were classified, and a total score was calculated using the Charlson Co-morbidity Index (80).

Patient reported outcomes

At all visits the participants were asked to complete the following questionnaires:

- EuroQol, five dimensions, three levels (EQ-5D-3L)
- The Multidimensional Fatigue Inventory (MFI-20)

At every visit, the patients were asked about potential side effects to the study drug taken.

The EQ-5D-3L questionnaire is a generic instrument for measuring HRQOL and has been validated in a variety of international settings in both GP and patient studies (see also www.euroqol.org). The EQ-5D-3L classification system comprises five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each of which has three levels (no problems, moderate problems and extreme problems)(81). A single index score can be derived by combining the levels of each dimension, allowing 243 (= 3⁵) health states and by applying a preference weight obtained from the GP in Denmark, using the time trade-off method (82). The health stage 11111 will indicate full health (= index 1.0).

In addition to the five dimensions, the EQ-5D-3L instrument also measure a single overall health index score (scale 0–100). *High scores indicate high level of HRQOL.*

The Danish norms for EQ-5D-3L-values were estimated in a population-based study, and the age- and gender-specific scores were used as the reference values in this study (83). The Danish norms are calculated up to an age of 79 years. The reference norms for age-group 70–79 years were used as reference for the patients older than 79 years. The EQ-5D-3L was chosen because it is a generic instrument and it covers the main perspectives of HRQOL.

But most important, the questionnaire is short. This was supposed to be an advantage for the target group and should ensure a high completion rate.

The MFI-20 questionnaire consists of 20 self-rated statements and is designed to measure five dimensions of fatigue (*general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue*) (70). Each dimension contains four questions and scores range from 4 to 20 (*a higher score indicates greater fatigue*). The norms for fatigue in the GP have been calculated according to gender and age groups in a German population, and these values were used for reference in this study (79). Fatigue was defined as the 95th percentile of the fatigue score for a healthy control group and stratified by age and gender. The instrument was originally developed for cancer patients and has since been used and validated in many other diseases. However, the MFI-20 has neither been specifically validated in an IBD population nor in an AUGIB population.

The questionnaires were mainly answered by self-completion, but in a few cases during a telephone interview or by self-completion in the presence of an interviewer.

The EQ-5D-3L relates to the respondent's situation at the time of completion, while the MFI-20 asks the responder how he or she felt lately. None of the instruments were specifically validated to measure individual changes over time. Consequently, the repeated measurements were calculated as group means or percentages.

Patients with missing forms were not included in the analysis. Due to the relative small sample size, missing items were imputed as the mean of the observed patients.

The IBD study

Blood samples

The following blood samples (collected at the visit or within a 2-week period from the visit) Hb, CRP, transferrin, ferritin, iron, folic acid and vitamin B12 were analysed locally and the results were sent to Aarhus University Hospital. The reference range and the units at each centre were used. The WHO limits were used to define anaemia, while the upper limit for the normal reference value at each centre was used to define an elevated CRP value. As ferritin is an acute-phase reactant, patients with an inflammation were classified to have ID if CRP was elevated and the ferritin value was less than 100 µg/l. For patients without an inflammation, ID was defined if CRP was within the normal range and the ferritin value was less than 30 µg/l (47). CRP as a marker for an inflammation was chosen to be the most relevant marker owing to the fact that CRP, like ferritin, is an acute-phase reactant.

Sociodemographics and disease related data

Data on age, gender, height, weight, type of IBD disease, duration of IBD, concomitant medication, localisation and behaviour of the disease were collected. The classification and extent of the patients' IBD disease were monitored using the Vienna classification for CD patients and Montreal classification for UC patients. Disease activity was assessed using the Harvey-Bradshaw activity index (HBAI) for CD and a simple clinical colitis activity index (SCCAI) for UC (84,85).

Patient-reported outcomes

The MFI-20 was used to measure fatigue (please see section 4.2.1.3). In addition, it should be mentioned that the MFI-20 has

been translated into Danish, Swedish and Norwegian. The instrument has been validated in both Denmark and Sweden (78,86,87). As in the AUGIB study, fatigue was defined as the 95th percentile of the fatigue score for a healthy control group and stratified by age and gender. All participants answered the questionnaire on location at the day of attendance.

Statistics

In the AUGIB study, the primary statistical analysis was performed according to the intention-to-treat (ITT) principle. In addition, per protocol analyses were performed, omitting patients who had re-bleeding, who received blood transfusions and withdrawals. For both studies, summary statistics were used to describe the different groups. Continuous variables were expressed as the medians and interquartile ranges or the means and standard deviations. Categorical variables were expressed as a percentage and as exact numbers. Comparison of frequencies was made by chi-square test or Fisher's exact test. Outcome measures were analysed using Student's t-test, the chi-square test, ANOVA and non-parametric tests. A stepwise multiple regression model was used to identify the determinants of fatigue in the IBD study. A statistic significance level of 95% were used. The software programs Epidata and Stata 11 or 12 were used for the analyses.

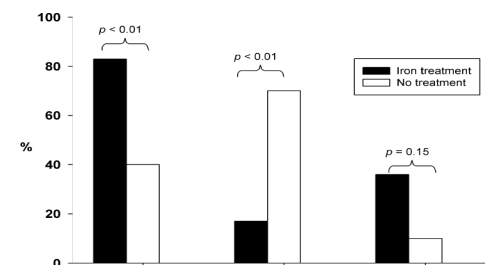
MAIN RESULTS

Paper 1

Randomised clinical trial: oral versus intravenous iron after upper gastrointestinal haemorrhage - a placebo-controlled study

Compared to placebo, iron supplementation after AUGIB was shown to have a significant positive effect on patients' Hb levels, (Figure 5).

A: Iron treatment vs. placebo



B: Oral iron treatment vs. intravenous iron treatment

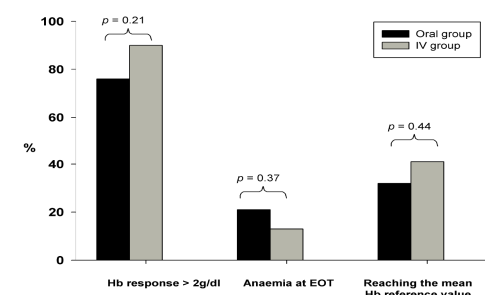


Figure 5:

Proportions of patients with Hb levels > 2 g/dl, anaemia at the EOT, and achievement of the gender-specific mean Hb reference values for a healthy population. Intention-to-treat analysis comparing iron treatment with no treatment (A) and oral iron with intravenous iron (B). Hb, haemoglobin; EOT, end of treatment.

For both treatment groups, the percentage of patients with full iron stores was higher at all times during follow-up than it was in the placebo group (Table II).

In the IV group, the percentage of patients with ferritin > 100 µg/l and normal levels of CRP was higher than in the oral group.

No serious adverse events related to the study drug were identified in any of the groups. Four patients in the oral group had to reduce dose or discontinue treatment due to GI side effects. The overall adherence to treatment in the oral group was 56%.

A few patients withdrew their consent, and 35, 39 and 10 patients from the oral, intravenous and placebo groups, respectively, fulfilled the study. At the EOT, seven patients in each treatment group were still anaemic, as illustrated in Figure 3. At the EOT, Hb levels in both treatment groups were significantly lower than in those in the placebo group ($p < 0.01$).

Table II:
Laboratory data during study period

	Oral group 41	IV group 42	Placebo group 14	P value ^a
Mean Hb, g/dl, (95% CI)				
Baseline	10.1 (9.8–10.4)	9.7 (9.4–10.0)	10.1 (9.5–10.7)	0.20
Week 1	11.1 (10.8–11.4)	11.0 (10.6–11.4)	10.6 (9.5–11.7)	0.50
Week 4	12.5 (11.9–13.1)	12.9 (12.5–13.2)	11.4 (10.3–12.5)	< 0.05
Week 13 (EOT)	13.5 (12.9–14.1)	13.9 (13.4–14.3)	11.5 (10.3–12.9)	< 0.01
Mean ferritin, µg/l, (95% CI)				
Baseline	174 (113–235)	161 (64–259)	257 (14–500)	0.54
Week 1	181 (27–335)	874 (767–980)	149 (40–259)	< 0.01
Week 4	84 (62–107)	319 (232–407)	300 (0–765)	< 0.01
Week 13 (EOT)	88 (66–110)	188 (116–259)	75 (9–141)	< 0.05
Proportion with ferritin > 100 µg/l & CRP < 8 mg/l^b, n (%)				
Baseline	10 (24.4)	13 (31.0)	1 (7.1)	0.20
Week 13 (EOT)	8 (23.5)	16 (41.0)	1 (10.0)	0.11
Mean CRP, mg/l (95% CI)				
Baseline	10.9 (4.7–16.9)	14.6 (8.5–20.6)	44.4 (9.6–79.1)	< 0.01
Week 1	13.9 (5.6–22.1)	9.9 (4.8–15.1)	9.4 (1.0–14.8)	0.64
Week 4	7.6 (0.1–15.2)	6.4 (2.4–10.4)	28.1 (0.9–66.2)	< 0.05
Week 13 (EOT)	3.7 (2.0–5.4)	4.0 (1.2–6.4)	6.9 (1.2–12.6)	0.44
Proportion with CRP > 8 mg/l^b, n (%)				
Baseline	16 (39.0)	20 (47.6)	11 (78.6)	< 0.05
Week 13 (EOT)	3 (8.8)	4 (10.6)	3 (30.0)	0.20
Mean TSAT, % (95% CI)				
Baseline	21 (15–25)	20 (17–25)	27 (15–39)	0.37
Week 1	24 (19–29)	24 (21–28)	13 (10–16)	< 0.05
Week 4	25 (19–30)	26 (21–31)	17 (11–23)	0.18
Week 13 (EOT)	26 (21–30)	24 (20–28)	17 (11–22)	0.13

^a One-way ANOVA test over the groups or Fisher's exact test

^b An expression of full iron stores

^c An expression of an inflammation

CI, Confidence Interval; EOT, end of treatment; Hb, haemoglobin; CRP, C-reactive protein; TSAT, transferrin saturation

Paper 2

Patient-reported outcomes after nonvariceal acute upper gastrointestinal haemorrhage

Anaemia did not seem to influence either HRQoL or fatigue in the AUGIB population studied. All dimensions of fatigue decreased (indicating reduced fatigue) and most dimensions of HRQoL increased (indicating improved HRQoL) from baseline to the EOT. The HRQoL mean index was higher in those patients who were not anaemic than in those who were anaemic at the EOT. However, statistical differences could not be demonstrated at any time point (Figure 6).

Fatigue was found in 1% to 7% of patients at the EOT. This finding was regardless of whether anaemia was present at the EOT.

In addition, no differences at any time points were identified in the HRQoL or in the five dimensions of fatigue after stratifying for gender, age and co-morbidity.

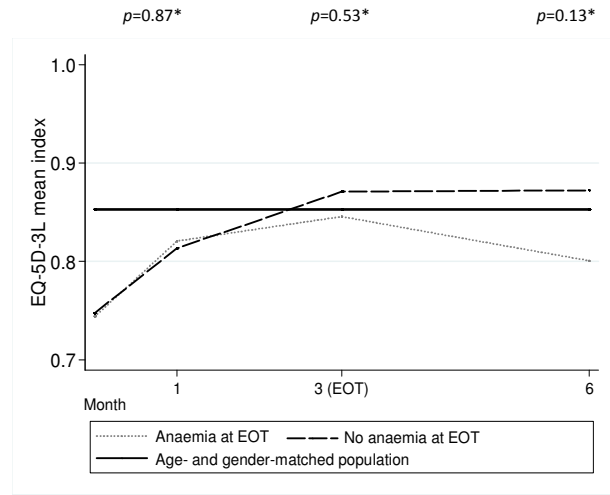


Figure 6:

Mean health-related quality-of-life (EQ-5D-3L) at four time points stratified for anaemia at the EOT and compared to the general population.

Anaemia, haemoglobin < 12 g/dl for non-pregnant women and haemoglobin < 13 g/dl for men; EOT, end of treatment; *Student's t-test.

Paper 3

The prevalence of anaemia and iron deficiency in IBD outpatients in Scandinavia

Anaemia was found in 83 of 429 patients, 19% (CI: 16–23%). Two-thirds ($n = 56$) of patients with anaemia had a combination of ACD and IDA, while 17 (20%) had pure IDA and 10 (12%) pure ACD. Anaemia was more frequent among patients with CD than in patients with UC: 23% vs. 14% (Table III). ID was found in 152 patients, 35% (CI: 31–40%).

Table III:
Prevalence of anaemia and iron deficiency: laboratory values of 429 IBD outpatients in Scandinavia

	All 429	Ulcerative colitis 176	Crohn's disease 253	p value
Gender, male/female %, (n)	55 % / 45 % (235 / 194)	60 % / 40 % (106 / 70)	51 % / 49 % (129 / 124)	
B-haemoglobin (g/L), median (IQR)	136 (126–145)	138 (129–148)	133 (123–144)	
Patients with anaemia¹ %, (n), (CI)	19 % (83) (16–23 %)	14 % (24) (9–19 %)	23 % (59) (18–29 %)	$p = 0.01$
Anaemia, male/female %, (n)	21 % / 17 % (50 / 33)	16 % / 10 % (17 / 7)	26 % / 21 % (33 / 26)	$p = 0.21$
Patients with iron deficiency², %, (n), (CI)	35 % (152) (31–40 %)	32 % (56) (25–39 %)	38 % (96) (32–44 %)	$p = 0.19$

IQR, Interquartile range ; CI, 95% confidence Interval

¹Anaemia: haemoglobin < 120 g/L for non-pregnant women, haemoglobin < 130 g/L for men

²Iron deficiency: ferritin < 30 µg/L & CRP ≤ upper reference limit for each site or ferritin < 100 µg/L & CRP > upper reference limit for each site

In the patients with anaemia, only a few had folic acid deficiency or vitamin B12 deficiency.

Paper 4

Fatigue in outpatients with inflammatory bowel disease is common and multifactorial

Women with IBD express more fatigue than men, and the difference in *general fatigue* was statistically significant ($p < 0.01$), and subsequently the analyses were stratified by gender.

Approximately 44% of the IBD cohort had *general fatigue* (Table IV). The percentage of patients with *physical fatigue* was higher than the percentage of patients with *reduced motivation* and *mental fatigue*. This tendency was the same for both women and men.

Table IV: Fatigue (MFI-20): percentage of patients with over 95% of normal fatigue levels[#] in 425 IBD outpatients in Scandinavia

	IBD diagnosis		Disease activity [*]		Anaemia		Total
	Ulcerative colitis	Crohn's disease	No	Yes	No	Yes	
Women	N = 70	N = 124	N = 98	N = 96	N = 161	N = 33	N = 194
Dimensions of fatigue							
General fatigue	39 %	44 %	26 %	59 %	40 %	52 %	43 %
Physical fatigue	29 %	40 %	19 %	53 %	36 %	36 %	36 %
Reduced activity	30 %	32 %	18 %	45 %	28 %	48 %	31 %
Reduced motivation	21 %	9 %	9 %	18 %	12 %	21 %	13 %
Mental fatigue	24 %	13 %	8 %	26 %	16 %	24 %	17 %
Men	N = 104	N = 127	N = 149	N = 82	N = 182	N = 49	N = 231
Dimensions of fatigue							
General fatigue	38 %	50 %	34 %	65 %	43 %	49 %	45 %
Physical fatigue	25 %	40 %	21 %	56 %	31 %	43 %	33 %
Reduced activity	18 %	28 %	15 %	39 %	23 %	27 %	23 %
Reduced motivation	11 %	21 %	13 %	23 %	16 %	16 %	17 %
Mental fatigue	14 %	27 %	14 %	34 %	20 %	24 %	21 %

MFI-20: Multidimensional Fatigue Inventory (range 4-20, a high score is worse)

[#]95% cut-off points for fatigue according to gender and age group in the general population

^{*}Disease activity: Harvey-Bradshaw Activity Index > 4 for CD patients and Simple Clinical Colitis Activity Index > 4 for UC patients

As IBD patients became older, *general fatigue* tended to differ less between men and women and be less related to disease activity (or not) and tended to approach the level of *general fatigue* in the GP (Figure 7).

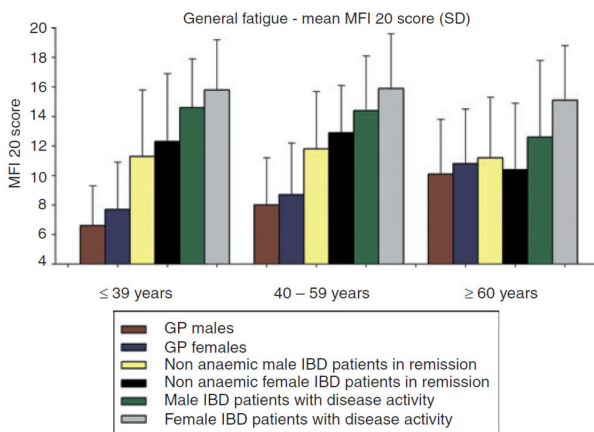


Figure 7: The mean fatigue for the general population (GP) and IBD patients (non-anaemic and in remission vs. with disease activity) by gender and age group.

The exact fatigue scores were not significantly different between the UC and CD patients, except for the men with CD, who had a significantly higher reduction in activity score than did men with UC. The scores for all the fatigue dimensions were significantly higher in the patients with disease activity than in patients with disease in remission.

In contrast, statistically significant differences between the patients with and without anaemia could not be demonstrated. However, anaemia was found to be a minor determinant of fatigue in men with CD. Similarly, no fatigue scores differed significantly between the patients with and without ID.

Based on data from non-anaemic patients with disease in remission, normative scales for the different dimensions of fatigue in IBD were derived. The scales were stratified for gender and age groups.

DISCUSSION

Iron supplementation given to anaemic AUGIB patients

Iron supplementation for anaemia following AUGIB was shown to be essential for normalising Hb and the body's iron stores. Despite implementation of the protocol amendment, in which the placebo group was reduced to one third of the originally planned number, we demonstrated clear statistically significant differences between the patients treated with iron and those given placebo.

The flowchart (Figure 3) illustrates a very dynamic study population. Patients withdrew their consent, had re-bleedings, and/or additional blood transfusions. Furthermore, many patients were not included in the study for different reasons. These circumstances were expected to some degree and were incorporated into the design of the study and the intervention chosen. The dosage schemes for both oral and the intravenous iron were as simple as possible in order to be easy to implement in clinical practice, i.e. a single intravenous infusion with only three dose options.

Oral iron was shown to be as effective as intravenous iron in raising the levels of Hb. This finding occurred despite a treatment adherence of only 56%. Still the percentage of patients that adhered to treatment in our study was similar to that in other studies (51-54). In general, participating in a study may even increase adherence to treatment. Because adherence to oral iron treatment has generally seemed to be low, we found that it would be most pragmatic to compare the IV group (with 100% adherence) with the entire oral group, regardless of adherence or dose reductions.

As mentioned, the study population was quite dynamic. This is also illustrated by the number of patients with an elevated CRP levels. Elevated CRP levels challenges the assessment of iron stores. We chose to measure both TSAT and serum ferritin levels. The TSAT as a marker is not influenced by increased CRP levels, but it gives a less precise estimate than does ferritin. On the other hand, ferritin is precise but will be influenced by an elevated CRP levels. We chose to use the internationally recommended cut-off points for CRP and ferritin levels. At the EOT, most patients' CRP levels had normalised and ferritin levels could be used as the most precise marker for adequate iron stores.

As our AUGIB study was the first of its kind, we decided to design the study in order to generate the best evidence. The study was calculated to include 42 patients in each of the three groups. In the sample size calculations, we expected a dropout rate of 15%. For ethical reasons, we had to drop the placebo group after 42 patients had been included and randomised. With just one-third of the planned patients included in the placebo group, we managed to demonstrate significant results. Afterwards it could be asked whether we were too pessimistic when calculating the sample size. Naturally, we did not want to include more patients than needed, but on the other hand, we had to ensure that the study had enough power to avoid type II errors.

Intravenous iron is a black fluid, and oral iron is known to give black stool. Both facts are challenges when conducting a double-blinded trial and no absolute blinding guarantee could be achieved.

We chose to let unblinded nurses administer the intravenous drug (iron or saline) in a black coloured line and to cover the infusion bag with a black plastic bag. As the patients were constantly observed by the unblinded nurses, the patients had only a limited chance of discovering the colour of the fluid.

The oral placebo and the oral iron tablets were manufactured by the same pharmaceutical company, and the tablets had an absolutely identical appearance.

Black stool cannot be caused by placebo tablets, but can be expected in up to two-thirds of patients treated with oral iron (50). Black stool can also be caused by GI re-bleeding. There was a risk that patients treated with oral iron could unmask the blinding. On the other hand, the patients who believed they were receiving oral iron could be expected to stick to the treatment until the EOT, as this would be the best alternative for them. Still, the primary outcome measures (Hb) were not influenced by the unmasking by some patients of their treatment allocation. The design prescribed five follow-up visits. We expected the patients to come to the hospital for blood samples and for a consultation. In practice, this was too ambitious, and many patients had to drop some visits. We considered weeks 1, 4 and 13 to be of most importance for the study outcome and encouraged the patients to complete these visits. The completion rates in week 2 and week 8 were so low that we subsequently decided to delete the results obtained at these two visits from the final analysis.

Furthermore, the number of geriatric patients came as a surprise. Some of these could not come to the hospital for follow-up visits unless they were transported by ambulance. This led to a time-consuming extra activity because the investigator often had to complete the follow-up visits in the patients' homes.

As our study was the first of its kind, we are not able to compare our results with those obtained by others, but just conclude that our results support hypothesis 1.

Hypothesis 2 could only be partly verified. Intravenous iron could fill the patients iron stores most effectively, but was not superior to oral iron in elevating the patients Hb level.

HRQoL and fatigue in AUGIB patients

We expected the patients' HRQoL and fatigue to be influenced by whether they had anaemia or not. This was not the case. There were overall significant improvements from baseline to the EOT. Furthermore, the percentage of patients having full health at the EOT was the same as in the GP. This indicates that the bleeding episode itself and the recovery afterwards had a huge impact on the patients' HRQoL and that the anaemia itself might have had less impact on HRQoL.

The study design did not allow us to compare HRQoL data with the individual norms, as we did not have individual HRQoL data prior to the acute bleeding episode. Furthermore, baseline-data collected approximately 48 hours after endoscopy might be influenced by a turbulent course of events. It was no surprise that HRQoL and fatigue were affected at baseline. The focus in our study was therefore on measurements in the follow-up period. In the analysis, we chose to stratify the patients according to anaemia at the EOT. This was a pragmatic choice. We did not have Hb values for all patients at month 6 and were therefore not able to relate the HRQoL data from month 6 with a real-time state of anaemia. However the aim of our sub-study was to investigate the HRQoL and fatigue in anaemic nonvariceal AUGIB patients. Assessment of Hb level after 6 months would be difficult to relate to the initial bleeding episode.

The same limitations could be stated regarding HRQoL and fatigue assessments at month 6. However, measuring HRQoL and fatigue at month 6 could illustrate the long-term impact of being anaemic 3 months after the initial AUGIB.

The assessment tools were not validated in the study population, but they proved to be adequate. Both the EQ-5D-3L and the MFI-

20 questionnaire managed to identify significant differences in the whole study sample between baseline and the EOT. Furthermore, the most marked differences were in the physical dimensions. This indicates that the changes identified by the tools used were changes that could be expected. Having the study population in mind, we chose a simple HRQoL questionnaire with only five dimensions and three levels.

The MFI-20 turned out to have some validity problems. Some patients had difficulties filling in the MFI-20, as some statements in the 20-item questionnaire are much like each other. This confused especially older patients. Furthermore, the composition of the questionnaire was commented on. Some patients found that there were too many items and the typing was too small. We could have chosen a simpler tool to avoid this, but the price would be less detailed information.

As mentioned, the number of geriatric patients came as a surprise, and from a retrospective point of view, a simpler questionnaire would have been preferable.

Excluding older patients from study participation would not have been correct, because they represent a crucial percentage of the patient population studied.

Measuring PRO in patients after AUGIB has only been done by one other group. Our findings are in accordance with their results (72). Any clear correlations between anaemia and fatigue in other gastrointestinal diseases have been difficult to achieve. Contradictory results have been found in IBD and celiac disease (74,76,88,89). In nonvariceal AUGIB, as in other diseases in gastroenterology, anaemia seems to influence the patients HRQoL and fatigue, but the association seems to be difficult to separate from the disease/condition as such. Hypothesis 3 could not be verified in our study.

Prevalence of anaemia and ID in IBD outpatients

Both the prevalence and type of anaemia were estimated with narrow CIs in the IBD outpatient population, as was the prevalence of ID.

Our investigation challenges the former systematic reviews on the topic. One of the most cited reviews uses results from original papers that would be excluded if the review should be relevant to current practice (33). Many studies were small and many were old (before 1980). Both the treatment options and the organisation of follow-up for patients with IBD have been optimised during the last decade.

A possible drawback of our study could be that the participating centres were all university hospitals and all investigators were especially focused on anaemia and ID. It is therefore to be expected that the prevalence of anaemia and ID found in our study was underestimated compared to the IBD outpatient population in general. On the other hand some patients were referrals and therefore more complicated patients than IBD outpatients seen at general hospitals. This might bias the results towards higher prevalence's than in the IBD outpatient population in general. This factor was evaluated not to be enough to neutralise the potential overall underestimation of anaemia and ID.

Our results reveal that in 80% of cases with anaemia, an inflammation was involved. This finding is in contradiction with other findings where "pure" IDA was found to be the dominant type of anaemia (40,49). Our findings could be explained by several factors: i) the participating centres treated ID in IBD outpatients before anaemia developed, ii) a majority of outpatients seen in the clinics had more disease activity than patients in other studies, iii) the patients accessibility to the clinics and to have blood samples drawn might also have influenced the number of patients

with ACD because iron treatment could have been initiated earlier in patients with pure IDA.

We used CRP levels as a marker for an inflammation. While there is consensus regarding the use of ferritin levels to classify the types of anaemia, the correct marker for an inflammation can be discussed. Some would say that an elevated faeces calprotectin is the best marker; others prefer clinical scores (HBAI or SCCAI). A weakness in the clinical scores is that some of the factors are subjective (general well-being and abdominal pain). Furthermore, the score includes "number of stools". For patients, the meaning of "stool" can vary. It could be each toilet visit or every time stool was actually present.

Faeces calprotectin was chosen as an optional marker in the study but due to too few measurements, we chose to keep CRP levels as the most relevant marker. In addition, we re-calculated the data using clinical scores as a marker of disease activity and found exactly the same prevalence of anaemia. These calculations were not mentioned in the publication (Paper C), but were done as a response to reviewers.

The cross-sectional design was an ideal and a cost-saving way to collect data for estimates of point prevalence. The way the samples were selected could be questioned. It was of importance that the patients were not disturbed unnecessarily. In the design, we consecutively included outpatients as they attended the clinic. Many of the blood samples drawn for this study were supposed to be drawn anyway.

The study comprised a broad spectrum of IBD patients and must be seen as representative for an outpatient IBD population. The patients were unselected, included consecutively, and the same percentage was included at each centre.

The number of patients was enough to stratify the data collected in relevant strata and give valid estimates for both anaemia and ID. Still a cross-sectional study is limited by the static design. A longitudinal design would cover the transition between the stages of ID and anaemia, the time to recurrence of anaemia (or ID) when treated, and it could estimate the burden of anaemia.

As ACD was involved in most explanations of the anaemia findings in IBD outpatients, anaemia could be used as a predictor of an inflammation.

Hb could therefore be suggested to be a simple benchmark for the total quality of IBD patient care. This would cover treatment (both of inflammation and of anaemia/ID), organisation of care, accessibility, patients' knowledge and behaviour, the level of information/education given to the patients, and patients' adherence to treatment.

Fatigue in IBD outpatients

Fatigue in patients with IBD is dominant, even with disease in remission. Our study has confirmed the findings in other studies and confirmed the comments from many patients with IBD.

As in the GP, women IBD outpatients experienced more fatigue than men (79). This finding led us to stratify our analysis for gender.

Not surprisingly, we found increased values for all the dimensions of fatigue when disease activity was present. We did expect anaemia or ID to have significant influence on the level of fatigue. This was not the case. It was also remarkable that anaemia was a negative determinant for *general fatigue* and *mental fatigue* among the women with UC; this finding could be due to the limitations of a single measurement, where inter-individual differences dominate. Measuring chronic fatigue (fatigue lasting more than 6 months) might have eliminated this limitation, but the measurement would then have been unsuitable to link fatigue to

an actual IBD condition. Our findings on anaemia, ID and fatigue were recently confirmed in a Canadian study (90).

When fatigue is defined as the 95th percentile of the fatigue scores for a healthy control group and stratified by age and gender, almost half of the outpatients had *general fatigue*. Furthermore, the physical dimensions (*general fatigue*, *physical fatigue* & *reduced activity*) were the most dominant. These findings illustrate how the physical burden of IBD was of importance to the patients. There were only slight differences in the percentages having fatigue, between those being anaemic when compared to those being non-anaemic.

Whether the exact fatigue score differs a few points might not matter to the individual patient and could be clinically irrelevant. The most conservative and relevant differences will be the percentage of patients suffering from fatigue in comparison with the percentage suffering from fatigue in the GP:

After completion of our study, results from a longitudinal study on fatigue in IBD were published (91). The group found that fatigue can decrease over time, even for patients with disease in remission. It is notable that the MFI-20 scale was used to measure fatigue, regardless of its non-validated responsiveness.

It is known that depression is correlated to fatigue and the prevalence of in-patients with IBD is higher than that in the GP (89,92). A limitation in our study could be that we did not measure depression.

In contrast to the AUGIB study, we experienced no difficulties with the MFI-20 in the IBD study. It was an advantage that the MFI-20 was available in Norwegian, Swedish and Danish. We did not receive any comments on the design of the MFI-20 from the participants and only four patients from the initial cohort did not complete the MFI-20. The high response rate might be due to the design, which meant that the patients in the outpatient clinic answered the questionnaires in the presence of a study nurse. Our study managed to describe the prevalence of fatigue and the dimensions of fatigue in IBD outpatients, but anaemia and ID could not be demonstrated as determinates of fatigue. This means that hypothesis 6 could not be verified in our study.

Additional limitations

An overall bias in the studies could be the gender-specific definition of anaemia. WHO has chosen to suggest a lower Hb cut-off point for women than for men. Background data used for the definition might be lower due to because women lose blood during menstruation. Still it is controversial why a lower value for Hb in women should be accepted. For pragmatic reasons, we chose to use the WHO definitions.

Implementation of the protocol amendment in the AUGIB study turned out to be the right decision for ethical reasons. But reducing one of the groups to one-third its proposed size could have jeopardised the results. If we had chosen not to drop the placebo group, they would have received "treatment as usual", because iron supplementation is only sporadically recommended in practice (24).

The AUGIB study could be biased by being a single centre study. Local routines could bias the results, but the primary endpoint was evaluated by Hb values that are absolute measurements. Conducting a single centre study also had clear logistic advantages.

The normative scales we used for fatigue reference in the GP were German. There are normative scales for MFI-20 available in Danish, but the scale does not include the 95th percentile of the fatigue scores, which has been used as the cut-off point for fatigue in other studies.

CONCLUSIONS AND PERSPECTIVES

The AUGIB study:

- Iron supplementation is effective and essential when treating anaemia after nonvariceal AUGIB.
- Intravenous iron supplementation is the most effective way to fill the patients' iron stores and will guarantee full adherence to treatment.
- The percentage of completely healthy patients 3 months after nonvariceal AUGIB was the same as in the GP.
- Anaemia after nonvariceal AUGIB could not be shown to influence fatigue or HRQoL.

The IBD study

- Anaemia was found in 19% of Scandinavian outpatients with IBD.
 - Inflammation was involved in 80% of those having anaemia.
- ID was found in 35% of Scandinavian outpatients with IBD.
- Fatigue was present in 44% of Scandinavian outpatients with IBD.
 - *Physical fatigue* was the most dominant type.
 - Neither anaemia nor ID was a clear determinant of fatigue.

The studies conducted in this dissertation have contributed new knowledge on the topics studied. But they have also generated new questions to be answered.

None of the studies could clearly identify a tool to distinguish fatigue from the disease itself and as a condition of anaemia. Patients who complain of fatigue should still be evaluated for anaemia and/or deficiency conditions.

In patients with AUGIB, a simple tool to recommend the best iron supplementation (oral or intravenous) is still to be generated. Important factors could be an inflammation (or infection) and presumed adherence to oral treatment. Iron absorption is related to the patients' inflammatory activity, with no or severely reduced absorption when an inflammation is present. It could be interesting to investigate whether the CRP level alone could predict the oral iron absorption or whether markers like IL-6 or hepcidin are needed.

Intravenous iron is much more expensive than oral iron. It could be interesting to do health economic estimates on the differences, both as a budget impact analysis and as a cost-benefit analysis (including the patient and the society costs).

The IBD study added a prevalence estimate of anaemia and ID to those already existing. When anaemia or ID has been diagnosed and treated, it is not known at what time points to monitor signs of recurrence and when to re-treat. A longitudinal study including unselected cohorts of patients with anaemia and IBD could contribute to new knowledge on recurrence after iron treatment and/or recurrence in relation to disease flare.

It is evident that fatigue is present in many patients, even if they have disease in remission and are non-anaemic.

Interventional studies on fatigue in this group of patients with IBD are needed. Physical exercise has positive effects on fatigue in patients with other diseases and should be investigated in patients with IBD. Furthermore, additional longitudinal studies on fatigue in IBD are needed.

SUMMARY

Fatigue in patients with gastrointestinal (GI) diseases can be caused by several conditions and anaemia is one of them. Anaemia can be caused by acute GI bleeding, or it can appear in relation to more chronic conditions: iron deficiency anaemia (IDA) and/or anaemia of chronic disease (ACD).

Acute anaemia due to acute upper GI bleedings (AUGIB) is often treated with blood transfusions and/or oral iron supplementations. The need for blood transfusions prior to endoscopic intervention has been well described in guidelines. However, guidelines for the monitoring and treatment of anaemia in patients after nonvariceal AUGIB are generally lacking. A retrospective study showed that more than 80% of patients were discharged from hospital with anaemia and less than 20% of them were recommended iron supplementations.

Chronic anaemia in inflammatory bowel diseases (IBD) is well known. Anaemia can be caused by deficiency conditions (iron, folic acid or vitamin B12); chronic bleeding; inflammation or medication (or a combination of these). Fatigue in IBD is found in 40% of IBD patients, even with disease in remission.

The PhD dissertation is based on two studies.

1. A randomised placebo controlled trial where patients were allocated to iron supplementation (oral or intravenous) or placebo. Patients with nonvariceal AUGIB and anaemia were included in the study ($N = 97$). The primary follow-up time was 13 weeks, followed by additional 3 months follow-up.
2. A cross-sectional study including Scandinavian outpatients with IBD. Five hospitals in Denmark, Norway and Sweden included consecutively 5% of their cohort of patients with IBD ($N = 429$).

The aims were:

1. To investigate the effect of iron supplementation in patients who had anaemia after endoscopic intervention for AUGIB. Furthermore, to investigate the Health-related quality of life (HRQoL) and fatigue in these patients.
2. To determine the prevalence and type of anaemia, iron deficiency (ID) and fatigue in an unselected group of Scandinavian IBD outpatients.

Results:

1. Using haemoglobin (Hb) as a marker, the results of the intervention study on anaemic AUGIB patients showed that iron supplementations were superior to no treatment and intravenous iron was more effective to fill the patients iron stores than was oral iron. No differences in the Hb levels were found between the oral and intravenous iron groups after 13 weeks. Data on HRQoL and fatigue showed in general an improvement during the follow-up period. The improvement was not solely linked to treatment of anaemia.
2. The overall prevalence of anaemia in the Scandinavian population of IBD outpatients was 19%. Most patients had both IDA and ACD. The prevalence of ID was 35%. Fatigue was found in 44% of patients, and the physical dimensions of fatigue were the most marked. Anaemia and/or ID were not associated with increased fatigue.

Conclusions:

1. Treatment with iron supplementations of post-discharge anaemia after AUGIB had significant effect on Hb levels. Intravenous iron supplementation should be chosen if adherence to treatment is essential. The patients' HRQoL was not affected by anaemia.

- Anaemia in IBD outpatients was present in one of five patients and only 20% had pure IDA. The remains had pure 'ACD' or a combination between ACD and IDA. Fatigue was present in nearly half of the patients and was not associated with anaemia, but was related to gender and age. *Physical fatigue* was the most affected dimension of fatigue.

ABBREVIATIONS

ACD	Anaemia of chronic disease
AUGIB	Acute upper gastrointestinal bleeding
CD	Crohn's disease
CI	Confidence interval
CRP	C-reactive protein
EQ-5D-3L	European quality of life questionnaire with 5 dimensions and 3 levels
EOT	End of treatment
FCM	Ferric carboxymaltose
GCP	Good Clinical Practice
GI	Gastrointestinal
GP	General population
Hb	Haemoglobin
HBAI	Harvey-Bradshaw activity index
HRQoL	Health-related quality of life
IBD	Inflammatory bowel disease
ID	Iron deficiency
IDA	Iron deficiency anaemia
IQR	Interquartile range
ITT	Intention to treat
MFI-20	The Multidimensional Fatigue Inventory
PP	Per protocol
SCCAI	Simple clinical colitis activity index
sTfR	Soluble transferrin receptors
TSAT	Transferrin saturation
UC	Ulcerative colitis
WHO	World Health Organization

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