Viewpoint

Practical Guideline for Fatigue Management in Inflammatory Bowel Disease


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Abstract

During active inflammatory bowel disease (IBD) fatigue is a common symptom, which seems related to active gut inflammation. However, even in remission many patients suffer from fatigue that negatively affects quality of life and work productivity. Currently, robust knowledge on the pathogenesis and treatment of IBD-related fatigue is lacking. In order to alleviate the burden of IBD-related fatigue, a systematic approach is mandatory. We propose a fatigue attention cycle to enhance identification, evaluation and management of fatigued IBD patients. The benefits of the cycle are twofold. Firstly, it allows the systematic and uniform identification of patients with severe fatigue, in turn allowing tailored non-pharmacological and pharmacological interventions. Secondly, uniform identification of such patients creates a well-defined patient base to investigate the underlying pathogenesis of fatigue, resulting in a greater understanding of this debilitating phenomenon and possibly resulting in the discovery of predictive factors and new treatment interventions.

Key Words: Inflammatory bowel disease; fatigue; identification; management; quality of life

1. Introduction

Fatigue is a common and aggravating symptom in patients with inflammatory bowel disease (IBD). IBD is characterized by chronic inflammation of the gastrointestinal tract with alternating periods of disease activity and remission, and mainly comprises two diseases: Crohn’s disease (CD) and ulcerative colitis (UC). Many IBD patients suffer from additional symptoms that negatively affect their quality of life (QoL) and physical well-being, fatigue being an important contributor.1-3 Fatigue is a common health problem in IBD, as illustrated by Cohen et al.,4 who showed that 25% of newly diagnosed IBD patients (n = 220) suffered from fatigue. Recently a pan-European online survey showed that over 80% of IBD patients suffered from debilitating fatigue.5 Although fatigue understandably increases during periods of active gut inflammation, it nevertheless persists in half of the patients in whom sustained clinical and endoscopic remission is achieved and this ongoing fatigue affects both direct and indirect health costs.6-11 In a systematic review, van Langenberg and Gibson12 concluded that treatment of gastrointestinal symptoms has been extensively researched but subjective complaints, such as fatigue, have been ignored. Although patients highlight fatigue as a major concern, current literature on treatment strategies remains scarce. The causal relationship between fatigue and diminished QoL is not completely understood, though an intricate interaction of several factors, such as pain, psychological distress, sleep difficulties and ongoing inflammation, seems to be involved.15,16 Consensus on the standard care for IBD-related fatigue, particularly regarding screening and management, is nonexistent. Previous research by our study group has proved that psychotherapy has a positive effect on fatigue and QoL in patients with IBD, and, moreover, focuses on (existing) adequate coping strategies in these patients.17 Following a pilot study, we performed a randomized controlled trial in fatigued IBD patients and showed that solution-focused therapy (SFT) significantly reduced fatigue. However, after stopping the therapy the fatigue seemed to reoccur. Our inability to adequately manage fatigue seems to be related to our limited knowledge of the pathogenesis of IBD-related fatigue.18 In recent studies it has been hypothesized that upregulation of pro-inflammatory cytokines contributes to fatigue by directly inducing
sickness behaviour, affecting muscle performance and indirectly affecting physical activity through sickness behaviour. Moreover, different domains strongly associated with fatigue can be affected, such as physical, cognitive and emotional fatigue, and different, personalized strategies might be mandatory for accurate treatment of these different types of fatigue. We sought to review available evidence in order to develop a clinically useful ‘fatigue attention cycle’ (Figure 1) regarding the evaluation and management of IBD-related fatigue with the aim of optimizing fatigue care. The goal of the attention cycle is to identify patients suffering from fatigue and associated distress or interference with daily activities, in order to apply a systematic management strategy to alleviate fatigue and improve QoL.

2. The fatigue attention cycle

The fatigue attention cycle is designed to aid clinicians in identifying and managing IBD-related fatigue. The cycle consists of 7 steps, elaborated in more detail below.

2.1. Screening

Screening for IBD-related fatigue is the primary step in the fatigue attention cycle. We propose the use of a visual analogue scale (VAS) with a score from 0 to 10 covering the severity of fatigue, with 10 representing severe fatigue and 0 representing no fatigue. Because of the simplicity of the VAS, this first step should be easy to perform during routine outpatient visits. The purpose of this short screening method is to distinguish patients with mild fatigue (score 0–3), who require only basic education and counselling, from patients suffering from more severe fatigue (score 4–10), in whom a thorough and more focused fatigue evaluation is appropriate. These cut-off values are in line with the scores used in cancer-related fatigue.

2.2. Assessment of concurrent symptoms

In order to select an optimal treatment strategy, assessment of concurrent (treatable) symptoms is mandatory. Many factors are known to contribute to fatigue, such as inflammation, pain, emotional distress, sleep disturbance, anaemia, alterations in nutrition and overall nutritional status, and a diminished activity level. The presence of any of these conditions should be treated in accordance with practice guidelines and with referral to other (health-)care professionals as appropriate. Furthermore, medication side effects as well as alcohol and/or drug abuse should be taken into account, as should other comorbidities.

2.2.1. Inflammation

During periods of active gut inflammation, fatigue rates understandably increase. Fatigue, on the other hand, is a highly reported symptom and a major concern in IBD patients and (chronic) fatigue can be a concealed indication of active disease. Disease activity should be ascertained by the usual clinical, radiological and endoscopic assessments in order to optimize treatment.

2.2.2. Anaemia

Studies have shown anaemia to be a common problem associated with fatigue in IBD patients. Anaemia can result from several deficiencies through several conditions, such as malabsorption, impaired dietary intake, suppression of iron binding and erythropoiesis or a combination of these factors. Other causes of anaemia, specifically in IBD patients, include chronic intestinal bleeding, inflammation and certain types of medication. A systematic review performed by Goldenberg et al. showed that isolated iron deficiency without the presence of anaemia is not a clinically relevant contributor to fatigue in IBD patients. Patients with established anaemia, regardless of the cause, should be thoroughly investigated and treated accordingly.

2.2.3. Nutrition

Various nutrient deficiencies have been associated with fatigue in the general population. IBD subjects are at risk of nutrient deficiencies due to chronic inflammation, impaired muscle strength and malabsorption. Even IBD patients that appear well nourished may actually harbour vitamin and/or mineral deficiencies. Vagianos et al. showed a high prevalence of inadequate dietary intake of nutrients and biochemical deficiencies, such as vitamin B6 and B12, folate, ferritin and zinc, mainly in patients with active disease and vitamin D deficiency in both active disease and remission. Nutrient status (ferritin, copper, zinc, folate, phosphate, magnesium, vitamin B6 and B12, calcium, vitamin D) should be restored if necessary, with referral to a dietitian when appropriate.

2.2.4. Sleep disturbance

There seems to be a strong correlation between fatigue and sleep disorders, and problematic sleep quality seems common in active

![Figure 1. The fatigue attention cycle. All steps are explained in more detail in the corresponding paragraph in the text.](image-url)
disease and also in non-active disease. Sleep disturbances have been associated with increased fatigue scores as well as deterioration of the inflammatory disease course, possibly through altered immune–endocrine factors associated with inflammation.14,31,33 Although separate experiences, there is a strong correlation between fatigue and sleep, and diminished sleep quality should be considered and investigated in clinical practice, for instance using the validated Pittsburgh Sleep Quality Index (PSQI) questionnaire.16,34 Cognitive behavioural therapy is considered the treatment of choice in adults with insomnia and has been proved effective in the long term.35–38

2.2.5. Emotional distress
Psychological factors such as a depressive mood, stress, anxiety and impaired QoL are associated with fatigue.19,20 Moreover, these psychological factors and diminished QoL are capable of negatively influencing the disease course of IBD.21,40,48 It is difficult to measure the influence of psychological factors such as depression on IBD-related fatigue, since invalidating fatigue symptoms could be a cause of depressive symptoms as well.42 Nonetheless, depression, anxiety and other psychological symptoms should be considered as part of this systematic approach to fatigue, as well as referral to a psychologist or psychiatrist.

2.2.6. Pain
In IBD, functional symptoms, including abdominal pain, have been shown to be associated with psychological dysfunction, even in quiescent disease.43–45 Psychological factors may affect sensory processing and thus lead to variations in abdominal pain perception.46 A simple VAS score can be used to determine the presence and severity of pain. Accurate assessment of the severity and origin of pain can contribute to appropriate diagnostic work-up and treatment.

2.2.7. Medication side effects
Although fatigue is noted as a possible side effect of practically all registered pharmacological drugs, review of current medication and recent changes in medication is still important in the assessment of IBD-related fatigue. Of note, it has to be taken into account that fatigue has frequently been reported in pharmacological therapy for IBD, especially in those receiving anti-tumour necrosis factor α (anti-TNF) agents.24,47

2.2.8. Activity level
Impaired muscle strength was seen in IBD patients compared with healthy controls.48–51 Additionally, IBD-related fatigue was associated with a reduced physical activity level and decreased muscle strength.52 Impaired physical activity and fitness must be considered in the assessment of fatigue-associated factors and insights into the activity level can contribute to the development of specific non-pharmacological treatment targets.

2.2.9. Comorbidities
Fatigue can be caused by a considerable number of other diseases. For instance, fatigue is associated with endocrine, renal, cardiac, respiratory and infectious diseases, amongst many others.49 Specifically, other autoimmune diseases, such as rheumatoid arthritis, diabetes mellitus, coeliac disease, asthma and primary sclerosing cholangitis, should be taken into account, as IBD is associated with an increased risk of these autoimmune diseases. Comorbidities should therefore be considered as potential causes of fatigue.

2.2.10. Substance abuse
Alcohol and/or drug abuse are associated with emotional distress, poor sleep quality and anxiety, and should always be assessed in the work-up of IBD-related fatigue.53–55

2.3. Thorough fatigue evaluation
Fatigue related to IBD is typically chronic and characterized by irreversibility.56,57 It is not alleviated by rest and not related to exertion, and the compensation mechanisms that are useful in reducing acute fatigue are not effective in IBD-related fatigue. Screening for fatigue using the VAS described above will distinguish those patients with mild fatigue from patients suffering from moderate to severe fatigue. Since the latter group could benefit from a (non)-pharmacological intervention, a more elaborate assessment of the different areas of fatigue should take place. Multiple questionnaires have been used to assess fatigue in the literature. In a previous study by Tinsley et al.,3 the FACT-F questionnaire, comprising 13 questions, was validated for IBD. Recently, the intricate concept of fatigue has called for a multidimensional assessment scale designed to address the different domains of fatigue. The Multidimensional Fatigue Inventory (MFI-20)58 and the Checklist Individual Strength (CIS) are 20-question, patient-reported, validated instruments for measuring motivation, activity level, concentration and, with the subscale CIS-fatigue, the severity of fatigue.57 Similarly, Czuber-Dochan et al.59 developed a questionnaire in collaboration with IBD patients for the assessment of fatigue and QoL, comprising 41 questions. Several studies report that the domains most strongly associated with fatigue are physical (functional, reduced activity), cognitive (mental, sensory) and emotional (affective, motivational, mood).15,19,60 Therefore, it is important to assess these domains with a questionnaire that reflects the multidimensional character of fatigue, in order to define specific treatment targets and their appropriate therapies.

2.4. General anti-fatigue strategies
Before proceeding to specific targeted interventions, more general anti-fatigue strategies should be employed. In particular, teaching patients how to plan their days seems to be the keystone in anti-fatigue strategies. Specifically, patients should be advised to distribute their energy throughout the whole day, to prioritize important events, to alternate their activities and to plan structured rests and breaks. Furthermore, relatives play an important role in the process of acceptance of fatigue, as their acceptance of and their support in managing disease-related symptoms, such as fatigue, are highly valued by IBD patients.61

2.5. Non-pharmacological interventions
Non-pharmacological interventions, such as physical activity and psychosocial interventions, have been shown to help patients with a range of other chronic conditions to manage fatigue.59,60,62 Several non-pharmacological interventions have been applied in IBD populations, mainly focused on mental health symptoms or overall QoL. However, literature on these interventions is conflicting. Some studies show beneficial effects of these interventions, such as stress management and cognitive behavioural therapy, mainly in the short term.62–66 Unfortunately, evidence on non-pharmacological interventions in the treatment of IBD-related fatigue remains scarce. Garcia-Vega et al.67 reported that adequate management of stress through stress-management techniques, had a beneficial effect on tiredness compared with treatment as usual in CD patients. Vogelaar et al.68 showed that SFT, focusing on existing adequate coping abilities of patients for fatigue, had a positive effect on fatigue and QoL in IBD.
patients, but the effect diminished during follow up. Reduced activity and muscle strength was reported in fatigued IBD patients, with supporting evidence showing that physical activity was beneficial for individuals with IBD by improving bone health, increasing muscle mass and function, increasing energy intake and possibly improving nutritional status. Additionally, QoL and fatigue were improved by exercise interventions in IBD patients. 

Interestingly, studies in animal models have suggested that exercise may reduce the inflammatory response, thus providing benefits additional to those given by exercise. However, it is challenging to specify guidance on the appropriate activity level or develop a practical physical activity protocol as the literature on these subjects in chronically ill patients is scarce. Whether specific treatment combinations exist for specific types of fatigue, related to the various domains of fatigue (i.e. physical, cognitive, emotional), remains to be elucidated.

### 2.6. Pharmacological interventions

Currently, all pharmacological treatments for fatigue remain in the investigational stage. For instance, psychostimulants such as methylphenidate and dexamethasone have shown promising results in severe cancer-related fatigue. However, these agents should be used cautiously and a specific treatment schedule has not yet been established, nor have these agents been investigated in IBD-related fatigue. Additionally, the randomized trials that have been performed in fatigued cancer patients have shown a significant placebo response. Regarding IBD-related fatigue, few randomized trials have been performed. In a pilot study in 12 IBD patients, high-dose thiamine decreased overall fatigue scores. However, the included patients were poorly defined and did not have thiamine deficiency. Other studies showed that the anti-TNF agents infliximab and adalimumab reduced fatigue, but these placebo-controlled studies were performed in patients with active disease. Consequently, there is a clear necessity for studies on pharmacological interventions for the treatment of IBD-related fatigue in patients with quiescent disease.

### 2.7. Re-assessment

Given the fact that multiple factors influence (the severity of) IBD-related fatigue and that disease activity itself tends to fluctuate, the level of IBD-related fatigue is expected to change over time. Therefore, re-evaluating the presence and severity of fatigue is essential in optimal fatigue management.

### 3. Discussion

IBD-related fatigue is an underdiagnosed and undertreated phenomenon in current clinical practice with a severe negative effect on QoL, accompanied by high costs. At present, consensus on management of IBD-related fatigue has not been developed. A systematic approach to the assessment of IBD-related fatigue is of great importance in identifying and understanding this debilitating phenomenon and should start at the time of diagnosis of IBD.

The fatigue attention cycle as proposed ought to serve as an important tool for uniformly identifying severely fatigued patients and will aid in thoroughly evaluating and managing these patients. It is essential to consider these perspectives when engaging in strategies to optimize IBD care. Unfortunately, proper implementation of this cycle in clinical practice is hampered by lack of knowledge concerning the pathogenesis of IBD-related fatigue, making an effective treatment strategy very difficult to define. Currently, a non-pharmacological intervention (i.e. SFT), although not widely used, seems effective, although the effect diminished over time. Several studies on the effect of non-pharmacological interventions on overall QoL have been conducted, but their results are conflicting. Furthermore, the duration of the beneficial effects of these interventions is generally limited. Consequently, there is a clear need for long-term studies involving well-defined non-pharmacological treatment interventions. Such studies would assess not only the short-term effects but also the long-term effects of these interventions, and eventually allow tailored management of fatigue. Pharmacological interventions are still in a premature state, and the lack of knowledge regarding the underlying mechanism of IBD-related fatigue makes the development of novel interventions complex. In order to discover important clues in the identification, prediction and treatment of IBD-related fatigue, the underlying biological mechanisms involved need to be unravelled. As proposed by van Langenberg and Gibson, pathogenic pathways involved in muscle fatigue and the contribution of disease-related psychological and neurobiological processes to fatigue genesis in IBD should be explored.

Uniform identification of patients with fatigue, via the proposed assessments, will be key in profiling patients in whom to study the pathogenesis of IBD. In these patients, it is important to focus on mediators of inflammation, but also on the keystones in the immunological response. In previous studies, differences in immune parameters (i.e. pro-inflammatory cytokines) between fatigued and non-fatigued patients were observed. Studies on cancer-related fatigue have identified several pro-inflammatory cytokines as being associated with the severity of fatigue. Yet the exact mechanism by which fatigue is linked to the immune system and the reason why some patients but not others show such altered pro-inflammatory cytokine patterns during remission of disease remain obscure. As with other diseases, such as chronic fatigue syndrome (CFS) and multiple sclerosis (MS), the brain–gut axis is assumed to play a key role in the pathogenesis of IBD-related fatigue. However, IBD is a chronic autoimmune disease affecting the gut, and therefore the effects of the brain–gut axis could be considerably different in IBD compared with CFS or MS. A combination of altered microbiota, pro-inflammatory cytokine levels, increased stress (both hormonal and psychological) and a genetic predisposition may jointly underlie the mechanism of IBD-related fatigue. There is increasing evidence that the microbiota functions as a mediator in the bidirectional communication between the nervous system and the gut, though much remains to be discovered in this field. Consequently, a ‘back to basics’ approach is required in order to identify mechanisms of this assumed multifactorial phenomenon of IBD-related fatigue. These insights may lead to the discovery of biomarkers to identify patients at risk of fatigue, and may eventually result in the development of an effective and efficient treatment strategy.

The recommendations presented here are largely based on expert experience and pragmatism and are supported where possible by published evidence. Key points include the need for the development of a well-defined fatigue attention cycle and structured support for IBD patients suffering from fatigue. We recognize that there may be large discrepancies between the recommendations presented here and those of allied healthcare professionals or IBD patients. However, these irregularities should not interfere with implementing a systematic diagnostic approach in clinical practice as a preliminary step towards proper identification and management of IBD-related fatigue.

### 4. Conclusion

IBD-related fatigue is a multifactorial debilitating phenomenon in need of a multidisciplinary approach. Current knowledge on the pathogenesis of IBD-related fatigue is severely lacking, resulting in
sub-optimal identification and management of these patients. Uniform identification of fatigued patients will create a patient base in whom to study the underlying mechanisms of IBD-related fatigue. Research on the pathogenesis of IBD-related fatigue will allow the discovery of predictors of severe fatigue and the development of well-defined fatigue treatment algorithms and structured support for IBD patients.

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**Conflicts of Interest**

None of the authors have financial interests or potential conflicts of interest to declare.

**Author Contributions**

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