Chronic abdominal pain, fatigue and inflammatory bowel disease in children

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CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal tract with two distinct phenotypes: Crohn's disease (CD) and ulcerative colitis (UC). Approximately 10% of all patients with IBD manifestations in the colon have overlapping features of both phenotypes and are categorized as 'IBD unclassified' (IBDU).(1)

CD has a classic triad of presenting symptoms: abdominal pain, weight loss and diarrhoea. In contrast, weight loss is relatively rare as presenting symptom in patients with UC, in which rectal bleeding tends to be more prominent at the time of diagnosis. Clinical presentation of either of the two types of IBD varies according to the location, severity and chronicity of inflammation.(2) About 10% of all new patients with IBD are younger than 19 years of age at the time of diagnosis.(3) Compared to adults, children are more likely to present with extensive disease and to be at greater risk of complications.(2)

Strategies for diagnosing IBD, alleviating symptoms and improving well-being have been subjects of intensive research. Nevertheless, conclusive answers have yet to be provided regarding important research questions concerning the management of paediatric IBD (see **Table 1** for current knowledge gaps).

Table 1: Knowledge gaps concerning paediatric IBD

Diagnostics
Appropriate triage for patients with gastrointestinal complaints for endoscopic evaluation
Reliable monitoring of disease activity in ambulatory patients
Treatment
Understanding the effect of enteral nutrition on inflammation (and predicting success/failure)
Comparison between novel and currently available medication for children: long-term safety and efficacy
Use of genetic profiling to develop precision medicine
Effect of altering the gut microbiome with anti/pro/prebiotics
Education of patients
Optimizing drug adherence
Achieving treatment self-competence and autonomy in adolescents
Improving quality of life
Supporting psychological growth
Physical and psychological impact of lifelong therapy
Quantification and characterisation of fatigue in IBD
Identifying factors associated with fatigue

Inflammatory bowel disease is a chronic illness that is frequently characterized by periods of exacerbation and remission, and that often follows a progressive course. Unpredictable flares, frequent hospitalizations and chronic medication use affect psychosocial functioning and limit social activities.(4) Early recognition of IBD can reduce the inflammation in an early

phase of the disease, what could subsequently alter the course of the disease and prevent long-term complications.

In the absence of full curative treatment, the current ultimate goal of paediatric IBD care is to minimize the burden of disease for patients. This thesis focuses on the triage of children with abdominal complaints with regard to endoscopic evaluation, as well as on recognizing fatigue in IBD patients. In the first part of this thesis, we investigate strategies to improve the diagnostic pathway to identify children with gastrointestinal complaints due to IBD for whom endoscopic evaluation is indicated. In the second part, we address quality-of-life issues following the diagnosis of IBD and, more specifically, persistent fatigue in clinically inactive or mild/moderate IBD.

Part I **- Triage for endoscopy**

Endoscopy of the upper and lower gastrointestinal tract with biopsies is the reference standard for diagnosing IBD.(1) At the same time however, many patients with gastrointestinal complaints do not appear to have IBD. Since endoscopy is an invasive diagnostic procedure with the possibility of harmful complications, only patients with the highest risk of inflammatory disorders should be exposed to endoscopy. For general paediatricians who see many patients with gastrointestinal complaints (e.g. recurrent abdominal pain, diarrhoea), it may be a challenge to decide which child should be referred for endoscopy. A non-invasive test could enhance the process of triage for children with regard to referral for endoscopy. This triage test could be very helpful if it would be reliable in preventing children at low risk of IBD from undergoing endoscopy.

As stated above, IBD is characterized by chronic inflammation of parts of the intestine. For this reason, blood and urine markers have traditionally been assessed as indicators of intestinal inflammation in patients suspected of having IBD.(5) In current practice, C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR) continue to be the most frequently used blood markers for inflammation. Despite the common use of such blood markers, their specificities and sensitivities for IBD are low, making them less suitable for decision making regarding which patients with gastrointestinal complaints should or should not be referred for endoscopy.(6) Substances that are excreted in urine (e.g. neopterin,

leukotriene E-4 and prostaglandine E metabolite) have also been investigated as markers of inflammation. To date, however, none of these markers has been validated for clinical use.(5)

Faecal markers

Before a biomarker can be safely used as a clinical triage test, its discriminatory power must be defined upon the intended patient population and in a specific clinical setting within the current diagnostic pathway. This is because the sensitivity and specificity of a test can vary according to the patient population and clinical setting.(7)

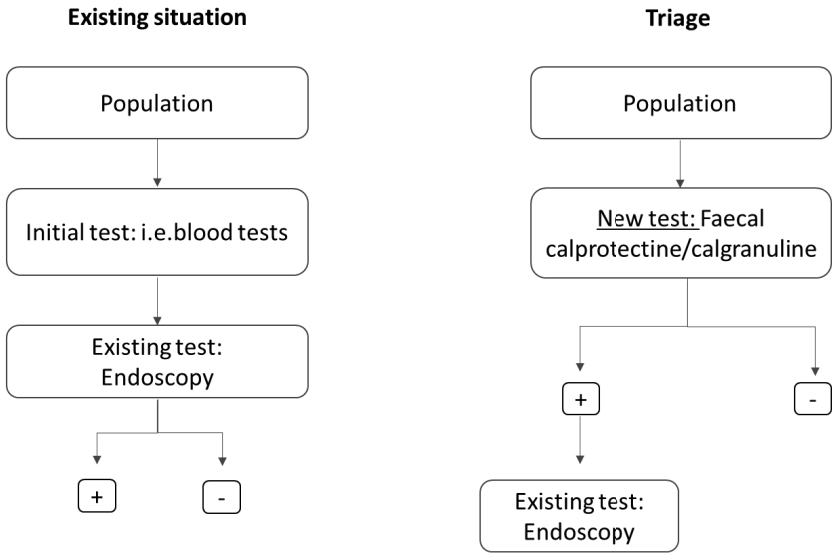

Figure 1 l Roles of tests and positions in existing diagnostic pathways. Figure adapted from (7)

Given that the inflammation in IBD is an intestinal process, it is logical that faecal parameters have also been suggested as being valuable for the assessment of intestinal inflammation. In practice, faecal markers have indeed become very popular for assessing the presence of inflammation in the bowel. During mucosal inflammation, various substances are actively released or passively leaked into the intestinal lumen, and they are subsequently excreted in the stool. An overview of the faecal parameters that have been evaluated is presented in **Table 2**.(8, 9)

Table 2: Faecal markers of inflammation (8, 9)

Faecal marker	**Molecular function/cellular source**	**Number of articles in paediatric literature (1990 - June 2019)**
Lysozyme	Released with degranulation of Paneth cells, macrophages and granulomas	20
Polymorphonuclear elastase	Released with degranulation of polymorfonuclear granulocytes; plays a role in the first-line host defence	43
Myeloperoxidase	Cytotoxic lysosomal protein released with degranulation of activated neutrophils	47
Metalloproteinase-9	Protein involved in neutrophil migration process, released by a variety of cell types, including activated neutrophils	3
Neopterin	Synthesized by activated macrophages; serves as marker of cellular immune-system activator	23
Lactoferrin	Cytoplasmic iron binding glycoprotein secreted by neutrophils and mucosal epithelial cells	21
Calprotectin (S100A8/S100A9)	Cytoplasmic calcium binding protein released by neutrophils, monocytes and epithelial cells	154

All substances listed in **Table 2** are found in abundance in the faeces of patients with active IBD, and concentrations are significantly lower in patients in remission.(5, 10) Calprotectin has been studied more extensively in children than any other faecal marker, and this biomarker test is now readily available in clinical laboratories.

Evaluating the accuracy of the calprotectin stool test

In 2010, we wrote a diagnostic meta-analysis (11) on the applicability of calprotectin as a triage test. All the articles included in that meta-analysis were based on the fully paired design that is typical of Phase II diagnostic accuracy studies. In these studies, a group of patients suspected of having IBD underwent faecal calprotectin testing followed by the reference standard: endoscopy. These studies estimated the diagnostic accuracy of faecal calprotectin under ideal experimental conditions.

In the next phase, a triage test (e.g. faecal calprotectin) needs to be used as means of triage before performing the existing diagnostic test (i.e. endoscopy), and only patients with positive results on the triage test will continue along the diagnostic pathway (see **Figure 1**). In 'Phase III' diagnostic accuracy studies, accordingly, not all suspected patients would need to undergo the reference standard.(12) To date, no Phase III diagnostic accuracy studies have been performed with regard to the potential value of faecal calprotectin. Therefore, we set ourselves to test the accuracy of faecal calprotectin with respect to the identification of patients with gastrointestinal complaints that should be referred for endoscopy because of IBD.

In **Chapter 2** we assess the role of faecal calprotectin as a triage test in the diagnostic work-up of children with gastrointestinal complaints (such as chronic abdominal pain, diarrhoea) in a Phase III diagnostic accuracy study. All children will have a faecal calprotectin test, but not all suspected patients will undergo endoscopy. The decision to expose a patient to endoscopy will be based on the physicians' clinical gut feeling. They are blinded to the FC result and consequently cannot take this result into account.

Faecal calprotectin is not the only marker for intestinal inflammation. Another candidate marker that could aid in differentiating IBD from IBS is Calgranulin-C (S100A12). Calgranulin-C is released almost exclusively by activated granulocytes, and has hardly been investigated as a marker of intestinal inflammation.(13) In previous case control studies, calgranulin-C showed diagnostic promise, exhibiting better specificity for intestinal inflammation relative to calprotectin.(14-16) In **Chapter 3**, we investigate the use of calgranulin-C to predict IBD in children and teenagers with chronic abdominal pain and diarrhoea, and we compare its accuracy to that of the calprotectin stool test.

Chapter 4 describes a further refinement of the formulated diagnostic test strategy of chapter 2, based on repeating the study in a separate and large validation cohort. We use an optimized cut off for calprotectin in combination with blood markers, and modify the inclusion criteria of the study cohort.

Part II - **Quality of life beyond clinical remission: Fatigue in paediatric IBD**

Treatment goals in IBD have changed considerably over the years. In the past, treatment was limited to controlling exacerbation, and it was aimed at alleviating clinical symptoms. The introduction of biological agents as anti-inflammatory therapy marked the beginning of a new era. Mucosal healing became the primary goal of treatment. The use of these agents have decreased rates of surgery and hospitalization.(17) In current practice, the focus of IBD treatment is typically on anti-inflammatory agents and therapies that modulate the immune system. However, many symptoms may not be directly caused by active inflammation, but may involve other mechanisms, including disease-associated symptom experience and psychological processes.(18) Moreover, the increasing recognition of, and appreciation for, the importance of health-related quality-of-life has spurred the use of such patient-important outcomes in clinical trials.

Quality of life in IBD

The World Health Organization defines quality of life as 'an individual's perception of their position in life, in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns'.(19) In IBD, stress and psychological health are likely to play an important role in symptom experience. For this reason, an exclusive focus on anti-inflammatory therapies is not expected to fully serve the needs of the patient. One important symptom that is frequently reported by IBD patients is fatigue.

Fatigue

Fatigue refers to a subjectively overwhelming sense of tiredness, lack of energy and a feeling of exhaustion that decreases an individual's capacity for physical and mental activity.(20) It is

a common, independent and nonspecific symptom that has been identified in numerous chronic health conditions in childhood, including IBD.(21)

Fatigue can be a major source of disablement in patients with a chronic disease, and it is often reported as being amongst the most severe and distressing symptoms.(22) Fatigue affects physical, emotional, cognitive and social functioning, and it has an impact on the quality of life. Despite its importance, researchers have rarely included and quantified fatigue in assessments of symptom severity or outcomes of chronic diseases in which it is observed, including chronic obstructive pulmonary disease, cystic fibrosis, chronic renal disease, cancer and heart failure.(22)

The quantification of fatigue poses several challenges, due to the lack of a consensus framework, vague terminology and a multidimensional nature of symptoms. Although subjective methods (e.g. self-reported or parent-reported surveys)(23, 24) are commonly used, they can be distorted by response and recall bias. More objective methods (e.g. polysomnography and performance tests)(25-27) are expensive and time-consuming, and the prevalence of fatigue varies by age group. For example, it is common in infancy, early childhood and late adolescence, while being less frequently observed in mid-childhood, and it is more common in girls than it is in boys.(26) Such variations in fatigue amongst healthy children makes it difficult to quantify fatigue in patients.

Fatigue is determined by a variety of factors. In adult studies, active inflammation, depression and other factors are implied in fatigue. A recent review on fatigue in IBD patients classifies factors into two categories: modifiable and non-modifiable.(28) The modifiable factors include physical factors (e.g. disease activity, anaemia, physical functioning and fitness), as well as psychosocial factors (e.g. anxiety, depression and self-directed personality). Non-modifiable factors include disease duration, gender and extra-intestinal manifestations. All studies in the review describe adult patients, and it is unclear whether a similar classification would apply to children with IBD. For this reason, we performed a systematic review of the existing literature aimed at exploring the prevalence of fatigue in paediatric IBD and identifying elements that contribute to fatigue (**Chapter 5**). Several studies have suggested that disease activity, anaemia and physical functioning affect the experience of fatigue.(24, 29-31)

In **Chapter 6**, we evaluate the effect of anaemia, subclinical inflammation and physical fitness on the sense of fatigue. For that, we conducted a cross-sectional observational study in children and adolescents with IBD. This study is based on validated questionnaires for fatigue and quality of life, endurance testing, blood testing and stool analysis to delineate fatigue in IBD. The study is intended to assess the extent to which the severity of fatigue is correlated with disease-related factors and biochemical parameters.

In **Chapter 7**, we discuss the implications of our different studies for clinical practice, a few remaining unresolved issues and we present suggestions for future research.

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