Pediatric Inflammatory Bowel Disease:

from diagnosis to transition

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Inflammatoire darmziekten bij kinderen:
van diagnose tot en met transitie

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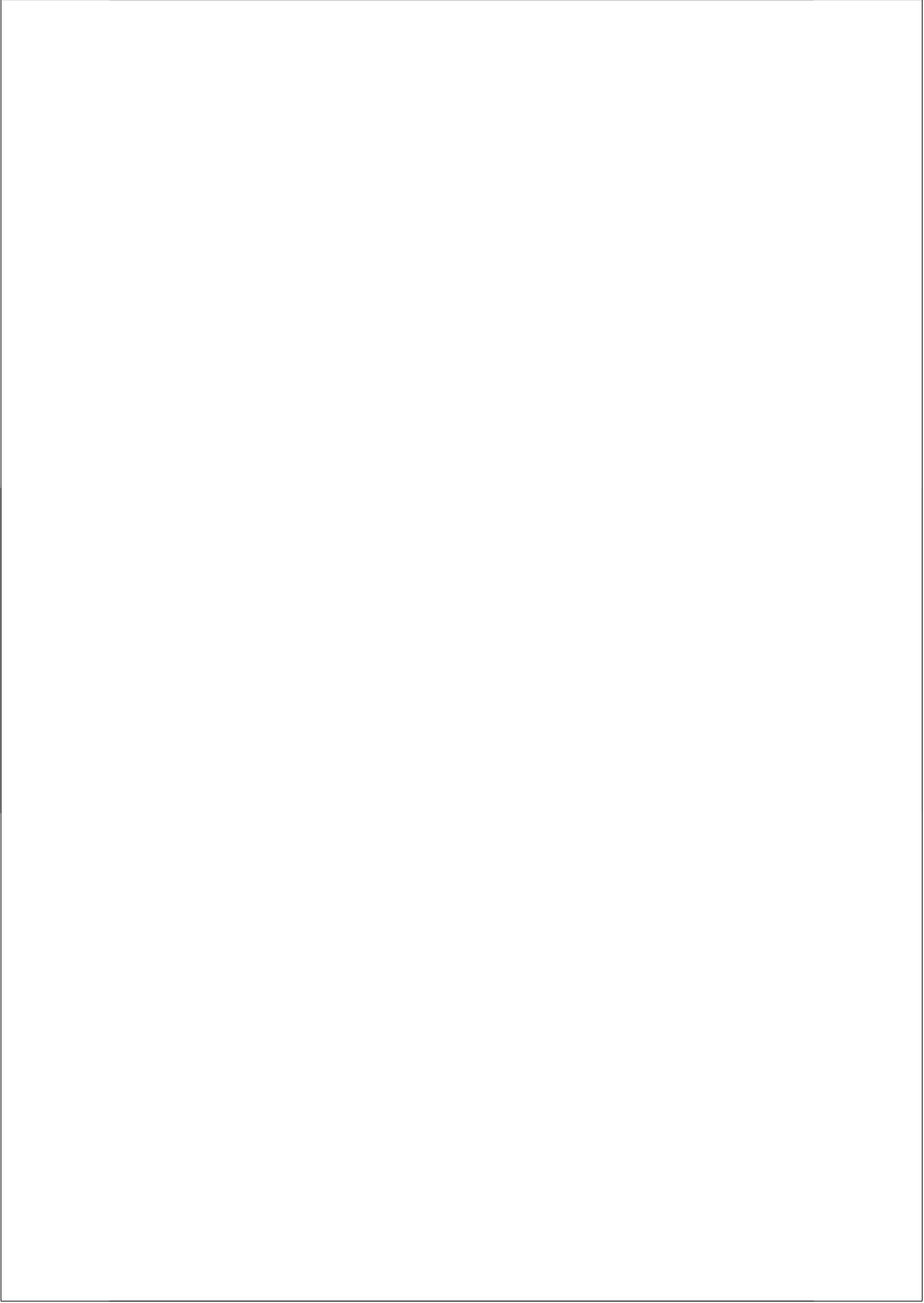
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Introduction

1

INFLAMMATORY BOWEL DISEASE

The inflammatory bowel diseases (IBD) are chronic relapsing inflammatory disorders of the gastrointestinal tract, comprising Crohn's disease (CD), ulcerative colitis (UC), and IBD-unclassified (IBD-U). CD is characterized by a transmural and often granulomatous inflammation that can involve any part of the gastrointestinal tract in a discontinuous manner[1], while UC is defined as a chronic inflammatory condition causing continuous mucosal inflammation of the colon, without granulomas on biopsy, affecting the rectum and a variable extent of the colon in continuity.[2] The term IBD-U is used for patients presenting with IBD restricted to the colon without the specific features of either CD or UC.[2] Early-onset IBD represents a distinct disease entity with differences in disease type, disease location, disease behavior, gender preponderance, and genetically attributable risk compared with late-onset IBD.[3] As in adults, treatment of early-onset IBD is aimed at inducing and maintaining remission, but special considerations are needed regarding optimal growth, pubertal development, and the transition period to adult care. A better understanding of the differences between early-onset and late-onset IBD will eventually lead to a better understanding of the pathogenesis of the disease. One of the limitations of studying pediatric IBD is however that a relatively small number of patients is available for study at one institution, which requires ongoing collaborations between many institutions. This thesis will present six (inter)national multicenter studies, a single-center pilot study and a review, which all focus on the unique clinical aspects of pediatric IBD, thereby complementing the relatively small body of literature on the diagnosis and treatment of children with IBD.

Epidemiology

IBD is often diagnosed in late childhood and early adulthood, but can also occur in very young children.[4-5] Approximately 10 – 20% of IBD patients are diagnosed during childhood[6-7], and the rest occurs throughout adulthood, peaking in the second and third decades of life.[8] The incidence and prevalence of IBD varies greatly worldwide, with the highest disease incidence rates occurring in the Western countries.[9] In the Netherlands, the incidence of pediatric IBD between 1999 and 2001 was 2.1 per 100,000 children per year for CD, and 1.6 for UC[10], which is comparable with the rates reported in other European countries. These studies have shown incidence rates of 0.6 to 6.8 per 100,000 children per year for CD, and 0.8 to 3.6 for UC.[6, 11-19] Incidence rates of pediatric CD are usually higher than those for UC[6, 11-13, 15-16, 18-19], although data from Finland and Poland have shown the opposite.[14, 17] Part of the variation in incidence rates may be due to heterogeneity of data collection, differences in disease classification, and differences in the age limit used for pediatric patients, but also geographical differences may play a role.[20]

In the last five decades, the incidence rates of pediatric IBD seem to be increasing, especially of pediatric CD.[20] Reasons for this increase are unknown, but may be associated with yet undetermined environmental factors.

Pathogenesis

IBD is a complex disorder that is thought to be the result of an aberrant immune response to commensal bacteria in a genetically susceptible host.[21] The importance of genetic factors in the development of IBD has first been demonstrated by epidemiological studies. Approximately 25 – 30% of pediatric IBD patients has a positive family history for IBD[5, 22], and first-degree relatives of IBD patients carry a 10-fold increased risk of developing the disease.[23] Today, genetic studies and genome-wide association (GWAS) studies have identified almost 100 susceptibility genes that are associated with an increased risk of developing IBD.[24-26] Most of these genes code for molecules of the innate or adaptive immune system. However, concordance rates in monozygotic twins are only 35 – 63% for CD and 16 – 18% for UC[27-28], illustrating that genetic factors alone are not sufficient to cause IBD. The importance of intestinal microbiota is supported by the observations that surgical deviation of inflamed intestine ameliorates inflammation[29], and that antibiotic treatment can be effective in at least a subset of IBD patients.[30-31] Other environmental factors that are believed to be associated with the etiology of IBD are smoking, perinatal events, childhood infections, diet, and domestic hygiene.[32]

Clinical presentation

A clinical suspicion of IBD is raised in children with persistent (≥ 4 weeks) or recurrent symptoms (≥ 2 episodes in 6 months), such as abdominal pain, diarrhea, rectal bleeding, and weight loss.[33] Other gastrointestinal symptoms may include decreased appetite, nausea, and vomiting. Only 25% of pediatric CD patients presents with the 'classic triad' of abdominal pain, diarrhea, and weight loss, as was demonstrated by Sawczenko et al.[34] Approximately 25% of children with CD presents with non-specific symptoms such as lethargy and anorexia, which may be associated with only mild abdominal discomfort. In contrast to the diverse symptomatology in pediatric CD, the clinical presentation of pediatric UC is almost uniformly bloody diarrhea (84 – 94% of children).[35] Clinical presentation alone is however not sufficient to make a reliable distinction between UC and CD.[36]

Extraintestinal manifestations may be a presenting sign in 6 – 17% of pediatric IBD patients, with joint inflammation, skin manifestations, and aphthous stomatitis being most frequently reported.[37-38]

Perianal lesions can be present in CD, but are not a common feature of UC. These lesions can range from single simple skin tags to complex networks of fistulas and abscesses. Fistulas and abscesses have been reported in 7 – 10% of newly diagnosed pediatric CD patients, while skin tags and fissures can be present in 5 – 20% of patients.[39-41]

Unique to pediatric-onset IBD is the occurrence of linear growth impairment and pubertal delay.[3] Impaired growth velocity may be the first sign of IBD, and may start several years before the onset of gastrointestinal symptoms.[42-43] Growth failure at diagnosis is reported in 10 to 20% of pediatric CD patients[34, 44-47], and to a much lesser extent in pediatric UC patients.[34, 43, 48-49]

Diagnosis

The diagnosis of IBD is based on a combination of clinical presentation, physical examination, endoscopic appearance, histologic findings, and small bowel imaging studies. In 2005, the IBD Working Group of ESPGHAN (European Society for Pediatric Gastroenterology, Hepatology and Nutrition) published consensus-based criteria for the diagnostic workup of pediatric IBD, the Porto criteria.[33]

First of all, infectious causes of diarrhea need to be excluded by stool cultures, and laboratory screening tests should be performed. Anemia, increased inflammatory markers (erythrocyte sedimentation rate, C-reactive protein), trombocytosis, and hypoalbuminemia are suggestive of IBD[50], but normal laboratory screening tests may be present in 21% of children with mild CD, and in 54% with mild UC.[51] Serologic markers have been introduced as a possible tool to help diagnose IBD. These markers are antibodies against microbial products that have been found in the blood of IBD patients. Antibodies to anti-Saccharomyces cerevisiae (ASCA) are associated with CD, and are found in approximately 60% of CD patients, 10% of UC patients, and <5% of non-IBD patients. In addition, perinuclear antineutrophil cytoplasmic antibodies (pANCA) are associated with UC, and are present in approximately 60% of UC patients, 20% of CD patients, and <5% of non-IBD patients.[52] Other markers that have been studied, are: anti-E. coli outer-membrane porin C antibodies (anti-OmpC), antibodies to bacterial flagellin (anti-CBir1), antibodies to a bacterial sequence from Pseudomonas fluorescens (anti-I2), and antiglycan antibodies. As the diagnostic accuracy of serologic markers is still limited, results of an antibody screen alone are not sufficient to confirm or exclude a diagnosis of IBD.[53] Non-invasive stool tests, such as fecal calprotectin and lactoferrin, may become increasingly important as a screening tool in order to avoid more invasive investigations.[54]

Secondly, endoscopy and histology are of key importance to establish a diagnosis of the type of disease, as well as disease severity, localization, and extent of disease. All children suspected of IBD should undergo a complete endoscopic evaluation (ileocolonoscopy and upper gastrointestinal endoscopy) with multiple biopsies taken from each segment of the gastrointestinal tract.[33] Table 1 summarizes endoscopic and histologic features of CD and UC.[33, 36, 55] The routine use of upper gastrointestinal endoscopy at diagnosis is not recommended in all guidelines on pediatric IBD. According to The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN), upper gastrointestinal endoscopy with biopsies should be 'considered' in children suspected of having IBD[36], and

the ECCO (European Crohn's and Colitis Organization) guidelines on UC recommend upper gastrointestinal endoscopy in children and adolescents when ileocolonoscopy does not confirm a diagnosis of UC .[35] It is therefore important to evaluate the diagnostic yield of this endoscopic procedure in the initial workup of a child suspected of IBD.

Table 1 | Endoscopic and histologic features of Crohn's disease and ulcerative colitis.[33, 36, 55]

		Typical	Less common, but compatible	Incompatible
CD	*Endoscopy*	Discontinuous inflammation with intervening zones of normal mucosa Extracolonic inflammation (ileum, upper GI tract) Ulceration, stricture, and fistula formation Cobblestoning		None
	Histology	Submucosal or transmural involvement Chronic (active) ileitis/colitis Granulomas (nonpericrypt) Focal changes within a biopsy Patchy distribution Crypt distortion, crypt abscess	Inflammation limited to the mucosa	None
UC	*Endoscopy*	Continuous inflammation with variable proximal extension from the rectum No extracolonic inflammation Erythema, friability Ulceration Spontaneous bleeding Pseudopolyps Loss of vascular pattern	Rectal sparing Discontinuous inflammation in cecum or appendix Backwash ileitis Nonspecific gastritis/duodenitis	Ileal involvement not consistent with backwash ileitis (e.g. stenosis, cobblestoning, linear ulcerations) Macroscopic ileitis in the presence of a normally looking cecum Extensive inflammation of the upper GI tract (e.g. serpentine ulcers and cobblestoning)
	Histology	Inflammation limited to the mucosa Chronic (active) colitis with crypt distortion, crypt abscess, goblet cell depletion, basal lymphoplasmacytosis, distal Paneth cell metaplasia	Deeper or transmural inflammation in fulminant colitis	True (nonpericrypt) granulomas Transmural lymphoid aggregates Perianal granulomatous inflammation within skintags Absolute rectal sparing Normal appearing skip lesions

CD: Crohn's disease. UC: ulcerative colitis. GI: gastrointestinal.

Thirdly, small bowel investigation is indicated in all patients at diagnosis (except in definitive cases of UC) to guide therapeutic management and to detect strictures that may need surgical resection.[33] The Porto criteria recommended small bowel follow-through (SBFT) or enteroclysis as the preferred imaging modality. However, children with IBD carry an increased risk of high radiation exposure[56-57], which mandates the use of alternative imaging techniques where possible. The resolution of magnetic resonance imaging (MRI) techniques has markedly improved during the years, and is therefore increasingly being used for diagnosing small bowel CD in children. Capsule endoscopy is another imaging modality that allows endoluminal examination of the small bowel using a wireless capsule-shaped tool that is usually swallowed and then propelled through the gastrointestinal tract by gut motility.[58] The current preference for one technique over another often depends on the availability of local expertise.

Classification of IBD disease phenotype
Accurate phenotype classification is important for choosing the most appropriate therapy, assessing disease prognosis, and for a better understanding of the pathofysiology of the different manifestations of IBD. Adult gastroenterologists have therefore developed the Vienna classification for CD[59], which was revised and extended to UC in the subsequent Montreal classification.[60] As the Montreal classification did not sufficiently capture the dynamic features of pediatric IBD and had only moderate interrater reliability when utilized in pediatric IBD, an international group of pediatric IBD experts has recently developed a pediatric modification of the Montreal classification: the Paris classification.[55] The differences between the Paris and Montreal classification for CD and UC are displayed in Tables 2A and 2B.

Treatment
Induction and maintenance of remission are the main goals of treatment in IBD. As pediatric IBD occurs during a critical period of growth and development, special considerations in treatment are needed to reverse linear growth failure, malnutrition, delayed puberty, and deficits of bone mineralization.
High quality evidence from clinical trials in children with IBD is still scarce, and treatment decisions are often based on extrapolations from the adult literature.[61] In 2008 and 2010, European consensus-based guidelines for the treatment of IBD were published, which also contained brief sections on the treatment of pediatric CD and UC.[35, 62] Currently, the ESPGHAN/ECCO is preparing guidelines on diagnosis and treatment of pediatric UC, which are expected to be published soon. The current approach to the treatment of pediatric IBD is based on a step-up strategy, indicating that more aggressive immunosuppressive treatment is only prescribed after milder/less toxic treatment has failed.

Table 2A | Paris and Montreal classification for Crohn's disease.[55, 60]

		Paris classification		Montreal classification
Age at diagnosis	A1a	< 10 years	A1	< 17 years
	A1b	10-16 years	A2	17-40 years
	A2	17-40 years	A3	> 40 years
	A3	> 40 years		
Location	L1	Distal 1/3 ileum ± limited cecal disease	L1	Ileal disease
	L2	Colonic disease	L2	Colonic disease
	L3	Ileocolonic disease	L3	Ileocolonic disease
	L4	Isolated upper disease*	L4	Isolated upper disease*
	L4a	Upper disease proximal to ligament of Treitz		
	L4b	Upper disease distal to ligament of Treitz and proximal to distal 1/3 ileum		
Behavior	B1	Non-stricturing, non-penetrating	B1	Non-stricturing, non-penetrating
	B2	Stricturing	B2	Stricturing
	B3	Penetrating	B3	Penetrating
	B2B3	Both stricturing and penetrating		
	p	Perianal disease modifier	p	Perianal disease modifier
Growth	G0	No evidence of growth delay	not applicable	
	G1	Growth delay		

* L4A/B and L4 may coexist with L1, L2, L3.

Table 2B | Paris and Montreal classification for ulcerative colitis.[55, 60]

		Paris classification		Montreal classification
Extent	E1	Ulcerative proctitis	E1	Ulcerative proctitis
	E2	Leftsided colitis distal to splenic flexure	E2	Leftsided colitis distal to splenic flexure
	E3	Extensive colitis distal to hepatic flexure	E3	Extensive colitis proximal to splenic flexure
	E4	Pancolitis, proximal to hepatic flexure		
Severity	S0	Never severe*	S0	Clinical remission
	S1	Ever severe*	S1	Mild ulcerative colitis
			S2	Moderate ulcerative colitis
			S3	Severe ulcerative colitis

* Severe is defined by a Pediatric Ulcerative Colitis Activity Index (PUCAI) ≥ 65.

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Consensus-based Guidelines on the Treatment of Pediatric CD[63-64]

Induction of remission can be achieved by exclusive enteral nutrition (EEN) or corticosteroids. These treatment modalities have been demonstrated to be equally effective in children with CD[65-66], but EEN has significant advantages over steroids due to its beneficial effect on growth, and lack of serious side effects. Thiopurines, such as azathioprine and 6-mercaptopurine, are used for maintenance of remission, and are often introduced at the time of remission induction with either EEN or corticosteroids. Thiopurines have a very slow onset of action and may take 3 – 6 months to reach maximal effect. Methotrexate, another immunomodulator, is an alternative to thiopurines when these drugs are ineffective or not tolerated. The onset of action seems to be more rapid for methotrexate than for thiopurines. When patients are refractory to or intolerant of these conventional treatment regimens, infliximab therapy can be effective.[67] Infliximab is a chimeric monoclonal antibody against TNFα[68], a proinflammatory cytokine with an increased expression in the inflamed tissues of IBD patients.[69] Other anti-TNF drugs, i.e. adalimumab and certolizumab, have also been used off-label to treat refractory pediatric CD.[70] The current knowledge on the use of anti-TNF drugs in pediatric IBD has been reviewed and is presented in **Chapter 8**. Elective surgery should be considered in children with refractory CD or strictures, especially in pre-pubertal or early pubertal children with growth failure and localized CD.

Consensus-based Guidelines on the Treatment of Pediatric UC [63-64, 71]

Treatment of pediatric UC depends on disease extent and severity. Mild or left-sided colitis is usually managed with oral and/or topical aminosalicylates. Oral (and topical) amino-salicylates are also recommended as first line therapy for mild to moderate (pan)colitis, while corticosteroids are used in case of an insufficient treatment response or severe disease (see below). Maintenance treatment consists of aminosalicylates, or thiopurines for patients with relapsing disease. After its recent registration for treatment of pediatric UC, infliximab is increasingly used in children with refractory UC.[72] Colectomy may be indicated in patients with persistently active disease with corticosteroid dependency despite concomitant immunosuppression, or growth retardation despite apparently adequate maintenance therapy.

Children with acute severe colitis should be admitted to the hospital for intravenous corticosteroid therapy. Approximately 30 – 40% of children will not respond to steroid therapy and will require second-line therapy or colectomy. The pediatric UC disease activity index (PUCAI) can assist in determining the need and timing of alternative treatments early during the admission.[73] Second-line treatment options include cyclosporine, tacrolimus, or infliximab, which all seem to have similar short-term response rates. Colectomy is indicated in case a patient is refractory to one salvage therapy or in case of toxic megacolon.

Transition

Transition is defined as the purposeful, planned movement of adolescents and young adults with long-term physical conditions from child-centered to adult-orientated health care.[74] Research from other disciplines taking care of pediatric patients with chronic diseases provides evidence that the transition period into adult care is associated with poorer medical adherence resulting in insufficient disease control.[75] These outcomes may be improved by a structured transition program. In IBD, research on transitional care has been scarce.

There are several differences between pediatric and adult IBD health care.[76] Pediatric care tends to be more focused on growth and development, whereas adult gastroenterologists are faced with health issues such as pregnancy, fertility, and cancer surveillance. Additionally, pediatric care requires parental direction and consent, while the adult gastroenterologist expects his patient to be autonomous and independent. There are also significant differences regarding use of sedation during diagnostic procedures. Transfer to the adult gastroenterologist requires anticipation of this changing role for the patient and his parents. Knowledge of the disease and medication regimens are considered first steps in the process by which patients become independent.[77] Nevertheless, a survey of 363 adult gastroenterologists showed that young adult IBD patients transferred to their practice often had significant deficits in knowledge of their medical history and medication regimens.[78]

Other important components of the transition process are self-reliance and independent behavior.[79] A recent study in adolescents with somatic chronic conditions demonstrated that their perception of readiness for transfer was associated with the level of self-efficacy in managing day-to-day self-care and hospital consultations.[80] A novel disease-specific tool to assess self-efficacy in adolescents with IBD has been developed and evaluated, which is described in **Chapter 9** of this thesis.

Existing IBD transition programs and clinics are highly variable, ranging from primarily educational didactic modules, joint visits with both pediatric and adult physicians, alternating visits between the pediatric and adult sites, or a having a dedicated nurse transition coordinator.[75] Currently, there are no data on the most successful way to transition adolescents and young adults to adult care.

Pediatric IBD registries

Accurate epidemiological data are one of the most important tools to elucidate disease etiology and natural history.[81] During recent years, pediatric IBD studies have improved in quality and quantity due to more extensive use of multicenter national and international collaborations, such as:

– Pediatric IBD Consortium Registry, USA[5, 37]
– Pediatric IBD Collaborative Research Group Registry, USA and Canada[38, 40, 51]
– EPIMAD Registry, France[6, 82]

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– CEDATA-GPGE Registry, Germany and Austria[83]
– The Register of Pediatric IBD, United Kingdom[84]
– Italian Pediatric IBD Registry, Italy[85]
– Danish Crohn Colitis Database, Denmark[18]

In this thesis, we will report 5-year data from a novel multinational pediatric IBD registry, established by the IBD Working Group of ESPGHAN: the EUROKIDS registry (**Chapters 2 – 5**). This is a prospective, web-based registry of newly diagnosed pediatric IBD patients in Europe and Israel, initiated in May 2004 by 20 pediatric centers in 11 European countries and Israel. Today, more than 3000 pediatric IBD patients have been registered by 55 centers in 19 countries.

In the EUROKIDS registry, data on newly diagnosed children or adolescents with IBD (aged 0 – 18 years) are collected at baseline only (i.e. diagnosis of IBD). Recorded parameters are age at first symptoms, age at diagnosis, gender, ethnicity, family history of IBD, type of IBD, presenting symptoms, and height and weight. All diagnostic procedures performed at and within 3 months of diagnosis are recorded, as well as disease extent and localization. Each segment of the gastrointestinal tract (esophagus, stomach, duodenum, jejunum, proximal ileum, terminal ileum, ascending colon, transverse colon, descending colon, sigmoid, rectum) can be registered as 'normal' or 'abnormal', as assessed by endoscopy, histology, and radiology. An Excel-database can easily be generated from the web-based registry.

Data from another registry will be used in **Chapter 7** of this thesis: a national database on the use of infliximab in children with refractory CD treated by pediatric gastroenterologists. After the appearance of a national consensus guideline on the indications and use of infliximab in children with refractory CD, a national database was initiated in 2002. All pediatric gastroenterology units were solicited yearly to report data retrieved from the medical records. As the number of pediatric gastroenterologists in the Netherlands is limited, all pediatric CD patients treated with infliximab by pediatric gastroenterologists are included in this database.

OUTLINE OF THIS THESIS

In this thesis, a series of studies is presented that concern diagnostics (part I), clinical presentation (part II), treatment (part III), and transition (part IV) of pediatric IBD patients.

Part I | Diagnosis of pediatric IBD in Europe
In **Chapter 2**, we evaluate the adherence to European consensus-based criteria (i.e. the Porto criteria) for the diagnostic workup in children suspected of having IBD. Additionally, we aim to determine the diagnostic yield of upper gastrointestinal endoscopy and ileal intubation during colonoscopy, and the additional value of small bowel imaging. For this purpose, 5-year data from the EUROKIDS registry have been analyzed.

Part II | Disease phenotype of newly diagnosed pediatric IBD patients in Europe
In **Chapters 3** and **4**, 5-year data from the EUROKIDS registry are used to describe the unique disease phenotype of pediatric CD and UC patients at diagnosis. **Chapter 5** aims to assess the incidence of growth retardation and malnutrition in newly diagnosed pediatric CD and UC patients across Europe by using different growth references. Additionally, associations between disease location and height and body mass index will be evaluated.

Part III | Treatment of pediatric IBD
Chapter 6 describes the experience of treating newly diagnosed pediatric CD patients with a course of EEN in two tertiary referral centers in the Netherlands. Variation in EEN protocols and treatment outcome are discussed. In **Chapter 7**, data from a national database on the use of infliximab in children with refractory CD are used to evaluate the long-term efficacy of infliximab treatment in the Netherlands. **Chapter 8** gives an overview on the current literature on anti-TNF treatment in children with IBD.

Part IV | Transition from the pediatric to the adult gastroenterologist
An IBD-specific questionnaire was developed to assess the self-efficacy of adolescents visiting the transitional IBD clinic of the Erasmus MC – Sophia Children's Hospital. In **Chapter 9**, the reliability of this questionnaire, and the level of self-efficacy of adolescents with IBD are evaluated.

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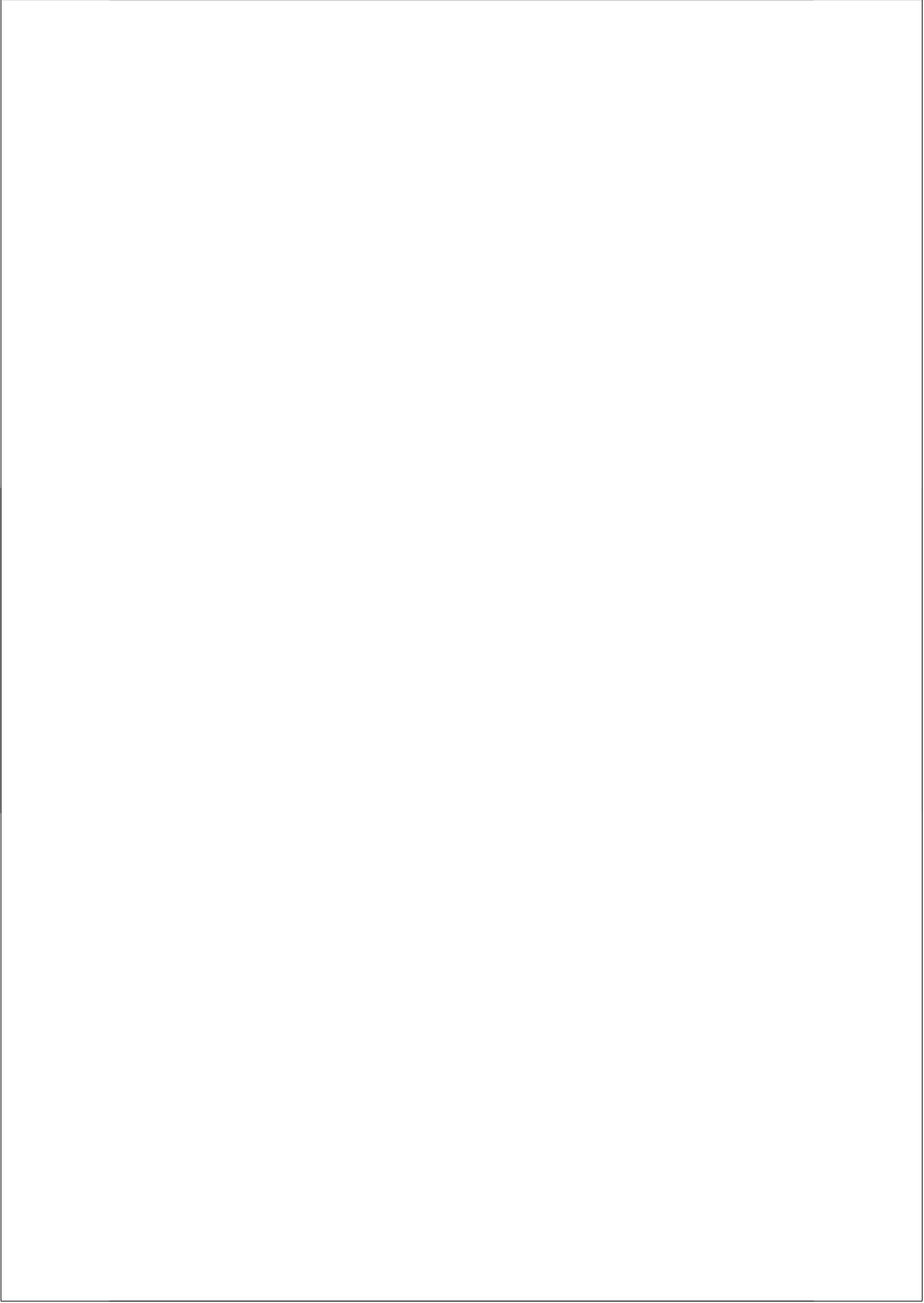
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Part I

Diagnosis of pediatric IBD in Europe

Chapter

2

Diagnostic workup of pediatric inflammatory bowel disease patients in Europe: results of a 5-year audit of the EUROKIDS registry

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ABSTRACT

Objectives

In 2005, the Inflammatory Bowel Disease (IBD) Working Group of ESPGHAN published consensus guidelines on the diagnostic workup of pediatric IBD, the Porto criteria. According to these guidelines, children suspected of IBD should have an esophagogastroduodenoscopy (EGD), ileocolonoscopy, and (except in cases of definitive ulcerative colitis (UC)) adequate imaging of the small bowel. To audit and evaluate the diagnostic workup of pediatric IBD patients in Europe, the Working Group created EUROKIDS, a prospective, web-based registry of newly diagnosed pediatric IBD patients.

Methods

IBD patients (aged 0 – 18 years) were registered in 44 centers in 18 countries. Data on diagnostic workup were analyzed according to year of diagnosis, type of IBD, and center size. Diagnostic yield of EGD and ileal intubation was evaluated.

Results

Between 2004 and 2009, 2087 newly diagnosed patients were correctly registered. Both EGD and ileocolonoscopy had been performed in 64% of all patients, and increased significantly from year 1 (52%) to year 5 (71%, $p<0.001$). Small bowel follow-through (SBFT) use decreased during the years (year 1: n=213; year 5: n=108; $p<0.001$), whereas MRI use increased (year 1: n=25; year 5: n=171; $p<0.001$). Patients diagnosed with Crohn's disease (CD, 59%) and UC (58%) were more likely to have had a complete diagnostic workup than patients diagnosed with IBD-unclassified (45%). In CD, the diagnostic yield of EGD was 7.5%, and the yield of ileal intubation was 13%.

Conclusions

The quality of diagnostic workup in pediatric IBD patients increased steadily during 2004 and 2009. Small bowel imaging by MRI superseded the use of SBFT. EGD and ileal intubation contributed to a definitive diagnosis of CD.

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INTRODUCTION

Large scale national epidemiology studies of inflammatory bowel disease (IBD) in children have documented a rising incidence of pediatric IBD[1-5], and have identified that certain features of IBD presenting in childhood are unique to children as compared with adults.[6] The IBD Working Group of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recognized 10 years ago that at the time there were no agreed criteria for diagnosing pediatric IBD. The Working Group agreed that collaboration on a multinational level was needed. In order to have consistent and reliable data, the essential first step was to ensure an optimal and uniform workup, and use of agreed criteria to diagnose IBD. The group then held a number of meetings in Porto, looked at the evidence, and in 2005 published the 'Porto diagnostic criteria', a consensus guideline for diagnosis of IBD in children.[7] It was agreed that diagnosis of Crohn's disease (CD), ulcerative colitis (UC), and IBD-unclassified (IBD-U) should be based on clinical signs and symptoms, endoscopy with histology, and radiology. Every child suspected of IBD should undergo a complete diagnostic program consisting of colonoscopy with ileal intubation, esophagogastroduodenoscopy (EGD) and in all cases, except in definitive UC, radiologic contrast imaging of the small bowel. Additionally, multiple biopsies from all segments of the gastrointestinal (GI) tract are needed for a complete histologic evaluation. It was also agreed that a diagnosis of IBD-U is acceptable only when the diagnostic program has been fully completed.

In order to audit the Porto criteria, the group started to prospectively collect anonymous data on new pediatric IBD patients from May 2004, using an agreed database (EUROKIDS registry). The primary aim of this study was therefore to evaluate adherence to the Porto criteria in the first 5 years of the EUROKIDS registry (May 2004 – April 2009). Secondly, we aimed to evaluate the diagnostic yield of EGD and ileal intubation during colonoscopy, and the additional value of small bowel imaging.

MATERIALS AND METHODS

EUROKIDS registry

The EUROKIDS registry is a prospective, web-based registry of newly diagnosed pediatric IBD patients in Europe and Israel, established by the IBD Working Group of ESPGHAN. This prospective registry was initiated in May 2004 by 20 pediatric centers in 11 European countries and Israel as a method to audit the diagnostic workup of pediatric IBD patients in the years following publication of the Porto criteria[7] and secondly, to accurately describe disease phenotype in newly diagnosed pediatric IBD patients. During the first 5 years, the registry has extended to allow inclusion of patients from 44 centers in 18 countries: Belgium, Croatia, Czech Republic, Denmark, France, Germany, Greece, Hungary, Israel, Italy, Latvia, the Netherlands, Norway, Poland, Portugal, Slovenia, Sweden and the United Kingdom.

The great majority of participating hospitals provide tertiary care, with six centers providing both secondary and tertiary care. Several centers from Norway provide secondary care only. Five centers report that they treat only the most severe pediatric IBD cases.

Participating centers prospectively record data on every newly diagnosed child or adolescent (aged 0 – 18 years) with IBD. The main data are collected at diagnosis, and are age at first symptoms and final diagnosis, gender, ethnicity, family history of IBD, type of IBD, presenting symptoms, and height and weight at diagnosis. All diagnostic procedures performed at and within 3 months of diagnosis are recorded, as well as disease extent and localization (endoscopic, histologic, and radiologic aspect of each segment of the GI tract). All patient data for this study (inception cohort May 2004 – April 2009) were accessed from the online registry on 24 February 2010. Exclusion criteria for this study were: age at diagnosis > 18 years, type of IBD missing, data recorded retrospectively, IBD diagnosis date after April 2009, or incorrect IBD diagnosis date (i.e. diagnosis date more than one month after registration date).

Ethics committee permission was obtained in the United Kingdom, Sweden and Poland. In the other countries, a Statement of No Objection was released by the local ethics committees, because data are anonymously collected.

Definitions

According to the Porto criteria, the workup in patients diagnosed with CD and IBD-U was considered complete, when EGD (with biopsies), colonoscopy with ileal intubation (with biopsies), and adequate imaging of the small bowel were performed.[7] A colonoscopy was defined as a procedure reaching proximal to the splenic flexure. Imaging of the small bowel was considered adequate when one of the following modalities was used: conventional radiology (small bowel follow-through (SBFT), enteroclysis), magnetic resonance imaging (MRI, MR-enteroclysis or MR-enterography), computed tomography (CT) scan, capsule endoscopy, and/or enteroscopy. In patients diagnosed with UC, a complete workup was defined as performance of EGD and ileocolonoscopy (both with biopsies).

Center size was determined by the number of newly diagnosed pediatric IBD patients/ year. A 'small center' was empirically defined as a hospital recruiting less than 15 newly diagnosed pediatric IBD patients/year, a 'medium center' as a hospital recruiting 15 – 30 newly diagnosed pediatric IBD patients/year, and a 'large center' as a hospital recruiting more than 30 newly diagnosed pediatric IBD patients/year.

We defined the diagnostic yield of EGD and ileal intubation during colonoscopy as the percentage of patients in whom this procedure contributed to a definitive diagnosis of CD. The diagnostic yield of EGD in the evaluation of children suspected of having IBD was determined by the detection of granuloma(s) isolated to the upper GI tract in patients without perianal disease or clear ileocolonoscopic evidence of CD. Perianal disease was defined as the presence of perianal abscess(es) and/or fistula(s), while clear ileocolonoscopic

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evidence of CD consisted of isolated terminal ileitis or ileocecal disease. As information on granuloma(s) was not available in the first year of the registry, we determined the diagnostic yield of EGD in patients diagnosed from year 2 onwards, and only in cases who had biopsies from all segments of the GI tract. In patients diagnosed with CD, we used both the isolated detection of granuloma(s) in the upper GI tract and the presence of macroscopic abnormalities in the upper GI tract for determining the diagnostic yield of EGD. Macroscopic abnormalities in the upper GI tract that were considered significant for the diagnosis of CD consisted of ulceration, cobblestoning, or stenosis.

The diagnostic yield of ileal intubation during colonoscopy was evaluated in all children registered in years 2 to 5 who had biopsies from the terminal ileum and all segments of the colon. Both the presence of isolated terminal ileitis (without perianal disease or granuloma(s) in the colon) and isolated granuloma(s) in the terminal ileum (without perianal disease or ileocolonoscopic evidence of CD) were used for determining the diagnostic yield. Alternatively, we also determined the disconcordance between the endoscopic and radiologic aspect of the terminal ileum in patients who underwent both ileocolonoscopy and adequate imaging of the small bowel.

The additional value of adequate imaging of the small bowel was evaluated using two different definitions: 1) abnormal aspect of the terminal ileum on small bowel imaging in pediatric IBD patients who had colonoscopy without ileal intubation; 2) normal aspect of the terminal ileum on endoscopy, but an abnormal aspect of jejunum and/or proximal ileum on small bowel imaging in patients who had both ileocolonoscopy and adequate imaging of the small bowel.

Statistical analysis

Data were analyzed in SPSS (version 15.0, SPSS, Inc., Chicago, IL, USA). Descriptive statistics were calculated as percentages. For comparisons of proportions we used the χ^2-test. All reported P-values are two-sided. P-values < 0.05 were considered significant.

RESULTS

As of 24 February 2010, 2606 newly diagnosed pediatric IBD patients were registered. After exclusion of 519 patients, a study cohort of 2087 patients remained, of whom 59% were diagnosed with CD, 9% with IBD-U, and 32% with UC (Figure 1). The mean age at diagnosis was 12.1 years (range 0.6 – 17.9 years), with 56% being male. Figure 2 shows the age distribution of the study cohort according to type of IBD.

A total of 424 patients (20%) were reported from 'small centers' (n=25), 1124 patients (54%) from 'medium centers' (n=16), and 539 patients (26%) from 'large centers' (n=3). The distribution of participating centers and patients throughout Europe and Israel is displayed in Table 1.
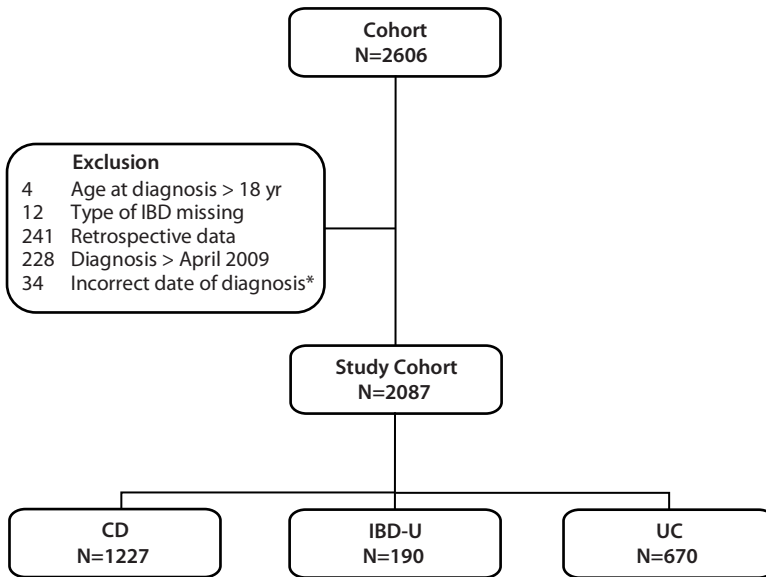
Figure 1 | Flowchart of the study population in the EUROKIDS registry.
* Date of diagnosis more than one month after date of registration. IBD: inflammatory bowel disease. CD: Crohn's disease. IBD-U: IBD-unclassified. UC: ulcerative colitis.

Endoscopy

EGD was performed in 87% (1811/2087) of all pediatric IBD patients, colonoscopy in 96% (1995/2087), and ileocolonoscopy in 72% (1495/2087). Biopsies were taken in 95% (1711/1811) of EGD, 98% (1964/1995) of colonoscopies, and 93% (1392/1495) of ileocolonoscopies. Three patients were diagnosed with CD by surgery. Medical reasons for not inspecting the terminal ileum (i.e. risk of perforation, presence of a stenosis, perforation, abnormal cecum with a pseudodiverticulum) were registered in 102 patients (5%). Other reasons were: 'technical problem' (n=149, 7%), insufficient bowel preparation (n=50, 2%), lack of time (n=34, 2%), judged unnecessary by the endoscopist (n=21, 1%), colonoscopy done elsewhere (n=9, 0.4%), insufficient sedation (n=4, 0.2%), and biopsies taken in error at the cecum (n=1, 0.05%). In the remaining patients (n=219, 11%), it was not clear why the terminal ileum was not visualized by endoscopy.

Figure 3 shows the proportion of newly diagnosed pediatric IBD patients who underwent EGD, colonoscopy, and ileocolonoscopy during the first 5 years of the registry. Between years 1 and 5, performance of EGDs (p=0.003), colonoscopies (p=0.013), and ileocolonoscopies (p<0.001) increased significantly. A combination of EGD and ileocolonoscopy was performed in 64% of all pediatric IBD patients, and increased significantly by 19% between years 1 and 5 (p<0.001).

Table 1 | Participants in the EUROKIDS registry.

Country	No. of participating centers	No. of patients
Belgium	2	17
Croatia	1	73
Czech Republic	2	108
Denmark	1	121
France	2	67
Germany	4	195
Greece	1	50
Hungary	1	40
Israel	2	90
Italy	4	181
Latvia	1	4
Netherlands	1	103
Norway	11	41
Poland	3	266
Portugal	1	39
Slovenia	1	33
Sweden	2	155
United Kingdom	4	504

EGD was performed significantly more often in patients diagnosed with CD than in patients diagnosed with IBD-U and UC (Table 2). Patients diagnosed with CD also underwent colonoscopy and ileocolonoscopy significantly more often than patients diagnosed with UC. There were no significant differences in performance of endoscopic procedures between patients diagnosed with UC and IBD-U.

Cases from 'large centers' were more likely to have had EGD (96%) than those from 'small centers' (85%, p<0.001) or 'medium centers' (83%, p<0.001), but were less likely to have had ileocolonoscopy (58% vs. 77% and 76%, both p<0.001).

Table 2 | Endoscopic procedures in pediatric IBD patients according to type of IBD.

	All (n=2087)	CD (n=1227)	IBD-U (n=190)	UC (n=670)
EGD	1811 (87%)	1115 (91%)*	161 (85%)	535 (80%)
Colonoscopy	1995 (96%)	1184 (97%)**	181 (95%)	630 (94%)
Ileocolonoscopy	1495 (72%)	905 (74%)**	129 (68%)	461 (69%)
EGD + ileocolonoscopy	1333 (64%)	831 (68%)*	112 (59%)	390 (58%)

* Significant difference compared with UC (p<0.001) and IBD-U (p<0.03).
** Significant difference compared with UC (p<0.03).
IBD: inflammatory bowel disease. CD: Crohn's disease. IBD-U: IBD-unclassified. UC: ulcerative colitis. EGD: esophagogastroduodenoscopy.
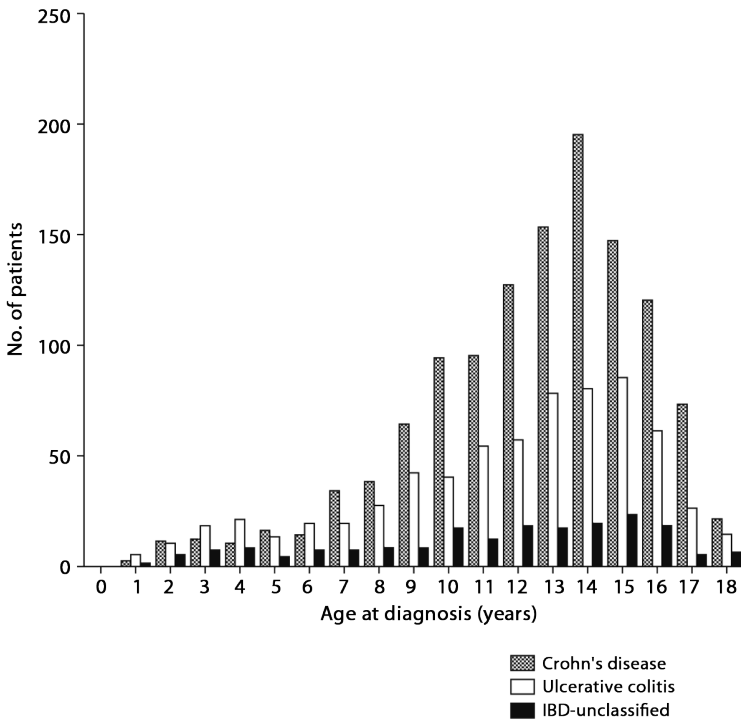
Figure 2 | Age distribution of newly diagnosed pediatric inflammatory bowel disease patients in the EUROKIDS registry.
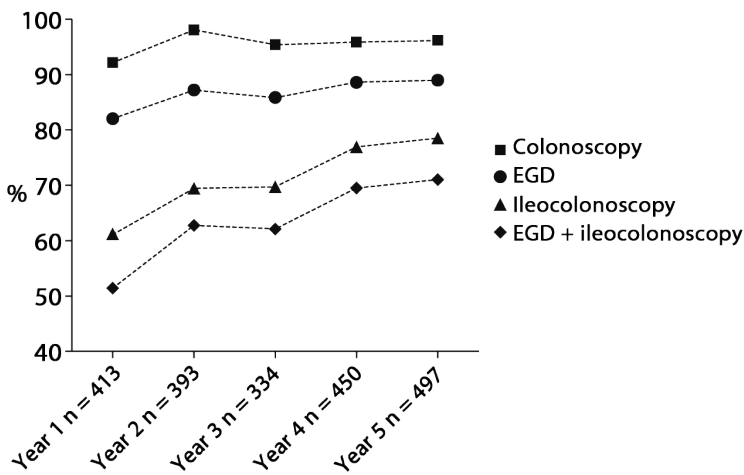

Figure 3 | Endoscopic procedures in pediatric inflammatory bowel disease patients during the first 5 years of the EUROKIDS registry. EGD: esophagogastroduodenoscopy.

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Imaging of the small bowel in pediatric patients newly diagnosed with CD and IBD-U

Information on imaging of the small bowel was available in 99% (1404/1417) of patients diagnosed with CD and IBD-U. Adequate imaging of the small bowel was performed in 87% (1061/1216) of pediatric patients at or within 3 months of CD diagnosis: SBFT in 58% (n=707), MRI in 29% (n=355), CT abdomen in 7% (n=80), capsule endoscopy in 4% (n=52), and enteroscopy in 0.4% of patients (n=5). The small bowel was visualized by more than one imaging technique in 10% (125/1216) of patients diagnosed with CD. In patients diagnosed with IBD-U, adequate radiology was performed in 73% (138/188), which was significantly lower than in patients diagnosed with CD (p<0.001). Fifty-six percent of patients diagnosed with IBD-U underwent SBFT (n=106), 18% MRI (n=33), 2% CT abdomen (n=3), and 3% capsule endoscopy (n=5). In 4% (7/188) of patients diagnosed with IBD-U, more than one imaging technique was used to visualize the small bowel. Radiologic examination by abdominal ultrasound alone was performed in 6% of patients diagnosed with CD (n=69), and 11% of patients diagnosed with IBD-U (n=21, p=0.009).

Variation in small bowel imaging of patients diagnosed with CD and IBD-U during the years is displayed in Figure 4. Use of small bowel imaging increased significantly from 84% in year 1 to 92% in year 3 (p=0.004), but decreased significantly to 81% in year 4 (p<0.001) and returned to 84% again in year 5. Between years 1 and 5, use of SBFT decreased significantly by 44% (p<0.001), whereas use of MRI and CT abdomen increased significantly by 42% and 7% (both p<0.001). Use of capsule endoscopy increased significantly during the first 4 years (year 1: 1 %; year 4: 8%; p<0.001), but decreased significantly in the last year (3%; p=0.003). When examined by center size, significant variations in use of small bowel imaging were observed. Patients diagnosed with CD and IBD-U in 'large centers' were more likely to have had SBFT (82%) than those in 'small centers' (43%, p<0.001) or 'medium centers' (51%, p<0.001), but were less likely to have had MRI (10% vs. 35% and 34%, p<0.001), CT abdomen (3% vs. 10% and 6%, p<0.001), or capsule endoscopy (1% vs. 5% and 6%, p=0.001).

Complete diagnostic workup according to the Porto criteria

In total, 57% (1191/2083) of pediatric IBD patients had a diagnostic workup according to the full Porto criteria. A combination of EGD, ileocolonoscopy, and adequate imaging of the small bowel was performed in 59% (715/1223) of patients diagnosed with CD and 45% (86/190) of patients diagnosed with IBD-U (p=0.001). In the patients with a complete diagnostic workup, biopsies from the upper GI tract and also from the colon and terminal ileum were taken in 89% (634/715) of patients diagnosed with CD and 88% (76/86) of patients diagnosed with IBD-U. If less strict criteria were used (EGD, colonoscopy, and either ileocolonoscopy or adequate imaging of the small bowel), 87% (1061/1223) of patients diagnosed with CD, and 75% (143/190) of patients diagnosed with IBD-U had this combination of diagnostic procedures. In patients diagnosed with UC, 58% (390/670)

underwent a combination of EGD and ileocolonoscopy. In the patients with a complete workup, biopsies of all segments were taken in 87% (338/390).

Adherence to the full Porto criteria increased significantly from 45% in year 1 to 64% in year 5 (p<0.001). When examined by type of IBD, there was a significant time trend in adherence to the full Porto criteria for patients diagnosed with CD (year 1: 49%; year 5: 64%, p<0.001) and patients diagnosed with UC (year 1: 41%; year 5: 68%, p<0.001), but not for patients diagnosed with IBD-U 1: 33%; year 5: 44%, p=0.35).

IBD patients from 'large centers' were less likely to have had a complete diagnostic workup (51%) than patients from 'small centers' (59%, p=0.013) or 'medium centers' (60%, p=0.001).
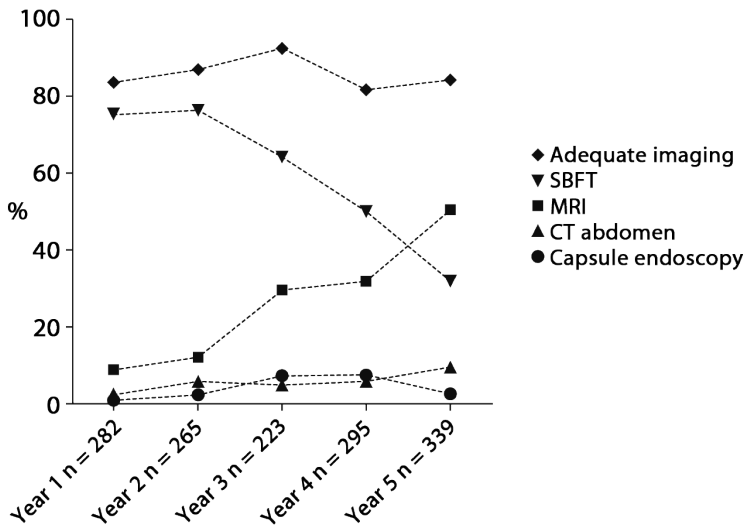
Figure 4 | Small bowel imaging in pediatric patients diagnosed with Crohn's disease and IBD-unclassified during the first 5 years of the EUROKIDS registry. SBFT: small bowel follow-through. MRI: magnetic resonance imaging. CT: computed tomography.

Diagnostic yield of EGD, ileal intubation, and additional value of small bowel imaging

In years 2 to 5 of EUROKIDS, there were 740 pediatric IBD patients with biopsies from all segments of the GI tract. EGD with biopsies led to the isolated detection of granuloma(s) in the upper GI tract (without detection of granuloma(s) in ileocolonic biopsies) in 2.4% (18/740) of pediatric IBD patients. Five of these patients also had perianal disease or clear ileocolonoscopic evidence of CD (isolated terminal ileitis, ileocecal disease), which decreased the diagnostic yield slightly to 1.8% (13/740). During colonoscopy, 6 of these 13 patients

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were also found to have inflammation in the colon, while 5 patients had inflammation of both the colon and terminal ileum. The remaining 2 patients had small bowel involvement and upper GI involvement, respectively. In CD, 428 patients had biopsies from all segments of the GI tract in years 2 to 5. The frequency of patients diagnosed with CD whose diagnosis relied on isolated detection of granuloma(s) at EGD, was 3.0% (13/428). In addition, there were 19 patients diagnosed with CD who had ulcerations in the upper GI tract (without perianal disease, ileocolonoscopic evidence of CD, or detection of granuloma(s) in the GI tract). Cobblestoning or stenosis without the other characteristics of CD did not occur. In 10 patients, the type of macroscopic abnormality was missing. When including only the patients with isolated granuloma(s) or ulcerations in the upper GI tract, the total diagnostic yield of EGD was 7.5% (13+19/428).

The diagnostic yield of ileal intubation could be determined in 962 IBD patients in years 2 to 5 who had biopsies from all segments of the colon and the terminal ileum. Fifty-six patients (5.8%) had isolated terminal ileitis without perianal disease or granuloma(s) in the colon. In addition, 19 patients (2.0%) had isolated granuloma(s) in the terminal ileum without the other characteristics of CD (i.e. perianal disease or ileocolonoscopic evidence of CD), resulting in a diagnostic yield of 7.8% (75/962). In CD, 559 patients in years 2 to 5 had biopsies from all segments of the colon and the terminal ileum. The frequency of patients diagnosed with CD whose diagnosis relied on ileocolonoscopy (i.e. isolated detection of granuloma(s) in the terminal ileum or isolated terminal ileitis), was 13% (75/559). Information on both the endoscopic and radiologic aspect of the terminal ileum was available in 875 pediatric IBD patients. In 152 (17%) patients, the terminal ileum was considered abnormal on endoscopy, but normal on adequate small bowel imaging. The opposite combination, a normal endoscopic appearance of the terminal ileum in combination with an abnormal terminal ileum on adequate small bowel imaging, occurred in 58 (7%) patients.

There were 418 pediatric IBD patients who underwent colonoscopy without ileal intubation but with adequate imaging of the small bowel. The terminal ileum was abnormal in 170 patients (41%), normal in 194 patients (46%), and data were missing in 54 patients (13%). In 829 pediatric IBD patients, information was available on the aspect of the terminal ileum by ileocolonoscopy, as well as on the aspect of jejunum and proximal ileum by adequate small bowel imaging. Fifty-one patients (6.2%) had a normal terminal ileum on endoscopy, and an abnormal jejunum and/or proximal ileum on small bowel imaging.

DISCUSSION

The Porto criteria recommend a uniform diagnostic workup in children and adolescents suspected of having IBD in order to reliably classify disease type, extent, and localization.[7] From this workup, disease can be classified according to the Montreal classification[8] or even the more recently published Paris classification.[9] In the present study, the IBD Working Group

of ESPGHAN has performed an audit in order to evaluate diagnostic performance in children suspected of having IBD, and to analyze the usefulness of a consensus-based guideline over a 5-year period. For this purpose, a web-based prospective registry, EUROKIDS, was initiated in 2004. While it is generally known that the incidence of IBD increases with age, the peak incidence occurred around 14 – 15 years of age in our European cohort. This reflects daily practice, where adolescents are often diagnosed by 'adult' gastroenterologists. One of the most interesting results of our study was the clear increase in quality of diagnostic workup during the first 5 years of EUROKIDS.

The acceptance in Europe of performing an EGD during the first diagnostic workup of a pediatric IBD patient was high, starting with 82% in year 1 and reaching almost 90% in year 5. In UC and IBD-U, the number of EGDs was significantly lower than in CD, but still between 80% and 90%. The routine use of EGD at diagnosis is not recommended in all guidelines on pediatric IBD. According to The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN), EGD with biopsies should be 'considered' in children suspected of having IBD, but more research on the diagnostic value of EGD is mandatory.[10] In our study, we evaluated the diagnostic yield of EGD, based on both endoscopic and histologic criteria, while also taking into account the endoscopic and histologic findings from ileocolonoscopy. Mild, nonspecific mucosal changes (such as erythema, erosions, and aphthae) in the upper GI tract are very common in both CD and UC. As ulcerations, cobblestoning and stenosis are rarely seen in UC[9], we used only these specific abnormalities for determining the diagnostic yield of EGD. This yield was 7.5%, indicating that EGD contributed to a diagnosis of CD in one out of 13 pediatric patients diagnosed with CD. Previous studies on the diagnostic role of EGD have focused primarily on the isolated detection of granulomas in the upper GI tract. In a recent review, the results of these studies were summarized: the frequency of pediatric patients diagnosed with CD whose diagnosis relied on isolated detection of granulomas at EGD seemed to range between 2% and 21%.[11] This large range of granuloma detection may well vary with number and site of biopsies, as well as the quality of histologic workup in the pathology laboratory. We have no data concerning the number of biopsies taken in our patients, other than the guideline advice to take 2 or more biopsies from each segment. Using another definition for diagnostic yield of EGD, Lemberg et al. reported that endoscopic and histologic assessment of the upper GI tract established a diagnosis of CD in 13 of 38 patients (34%) with otherwise non-specific pancolitis.[12] Taken together, all these results indicate that EGD contributed to a diagnosis of CD in a substantial number of patients, justifying its use in the initial assessment of children suspected of having IBD. Besides the diagnostic implications of EGD, knowledge about involvement of the esophagus, stomach, and duodenum may have therapeutic consequences. For example, it has been shown recently that in pediatric patients with esophageal CD, disease course has a high probability for early need of azathioprine.[13]

In addition to the rising numbers of EGDs, the success rate of ileal intubation increased steadily from 61% in year 1 to 79% in year 5. This significant increase may well be due to the process of continued registration within the EUROKIDS study group. An even more dramatic improvement in success rate of ileal intubation was reported in a study from 2002.[14] Batres et al. analyzed pediatric colonoscopies from 1994 through 2000 and found an increase of ileal intubation from 22% between 1994 and 1996, to 66% in 2000. Possible explanations for this improvement were the technical developments of endoscopes, video images and screens in the 90ies, as well as growing experience and skills of pediatric endoscopists.

The terminal ileum was not visualized by endoscopy in 28% of all IBD patients. Medical reasons (such as risk of perforation or presence of a stenosis) were responsible for examinations terminated outside the terminal ileum in at least 5% of all procedures. Adult IBD literature has reported ileal intubation rates of 95% of all colonoscopies[15], which also underlines that in about 95% of all patients the terminal ileum should be possible to reach. Technical problems should be overcome by teaching and training, while lack of time, insufficient colon preparation, and insufficient sedation can be avoided by optimizing protocols for bowel preparation, as well as the timing of procedures.

Ileal intubation with ileal biopsies has been shown to increase the diagnostic yield of CD in adult patients presenting with symptoms of IBD.[16] In our dataset, the diagnostic yield of ileal intubation in patients diagnosed with CD was 13%. Ileal intubation can also contribute to a diagnosis of CD in patients with non-specific pancolitis who have distinct macroscopic lesions in the terminal ileum, such as cobblestoning and linear ulcerations. This information was not registered in our database. The role of ileal intubation was also highlighted by de Matos et al. who found isolated granulomas in the terminal ileum in 26 of 112 (23%) untreated pediatric patients diagnosed with CD.[17]

A combination of EGD and ileocolonoscopy was performed in 64% of all IBD patients, and in even less patients diagnosed with IBD-U (59%). This low performance rate is primarily due to lack of ileal intubation (in 28% of the patients). Eighty-four percent of all pediatric IBD patients underwent both EGD and colonoscopy, thus reflecting a high grade of endoscopic examination of the upper and lower GI tract. Differences in numbers of EGDs and ileocolonoscopies between patients diagnosed with CD and UC are probably inherent to the differences in disease distribution. Although not in accordance with guidelines, pediatric endoscopists might decide to refrain from ileoscopy and EGD to save time when the macroscopic aspect of the colon is typical for UC. 'Small' and 'medium centers' perform less EGDs, but have a higher success rate of ileal intubation than 'large centers'. The reasons for these differences are not clear, but the results could have been biased as there were only three 'large centers' in two countries (United Kingdom and Poland). Other reasons might be differences in technical experience, limited time for the diagnostic program, and different in-house-strategies, although not in accordance with guidelines and not based on any evidence.

Radiologic examination of the small bowel by SBFT, as proposed in the Porto criteria, was highest in the first 2 years of EUROKIDS, when 76% of patients diagnosed with CD and IBD-U underwent SBFT. As stated in the Porto criteria, SBFT with barium contrast gives information on the extent and possible complications of small bowel involvement in CD including stenosis, stricture or internal fistulae.[7] In the following years, use of SBFT decreased significantly and was replaced by use of MRI. This technique has no radiation exposure, while SBFT is responsible for 16 – 36% of all radiation exposure in children with IBD, as was demonstrated in recent studies.[18-19] In addition, adult and pediatric data have shown that MRI was even more sensitive than fluoroscopy in detecting ileitis and inflammatory changes of the bowel wall.[20-23] In a recent ESPGHAN-endorsed ECCO-guideline on pediatric CD, MRI is therefore recommended as primary investigation for small bowel imaging in children with IBD[24], but local expertise should also be taken into account when choosing a small bowel imaging technique. For instance, evaluation of MRIs requires experienced radiologists, as interpretation and scoring of MRI findings can sometimes be difficult.[23]

Use of CT also increased significantly during the years, with 9% of patients diagnosed with CD and IBD-U having a CT in year 5. CT has been shown to be superior over SBFT in both sensitivity and specificity.[25] Although comparative data on MRI and CT are limited, evidence from small adult studies suggests that both imaging techniques have a similar accuracy in detecting active inflammation in the small intestine of CD patients.[25-26] Despite its obvious advantages, CT also causes significant radiation exposure (25 – 43% of all radiation exposure in pediatric IBD).[18-19]

A diagnosis of IBD-U is usually used for IBD patients who have features that make the clinician uncertain as to whether the diagnosis is CD or UC. According to the Porto criteria, a diagnosis of IBD-U is therefore only acceptable when a complete diagnostic workup has been performed. In our study cohort, 9% of pediatric IBD patients were diagnosed with IBD-U, which is quite similar to the prevalence reported in other large pediatric IBD cohort studies.[6, 27] However, it may have been the result of an incomplete diagnostic workup (in 55%) that patients were labeled as IBD-U. It might very well be that this diagnosis could have been changed to CD or UC when a full workup had been performed. Establishing a definitive diagnosis of CD or UC is essential, especially in the context of choosing therapeutic options and discussing long-term prognosis with a patient.

Previous studies on adherence to adult gastroenterologic guidelines (e.g. evaluation and management of osteoporosis in IBD patients, surveillance colonoscopy in UC, colon polyp surveillance) have demonstrated that adherence is frequently suboptimal amongst clinicians.[28-31] This was also shown in our study, with overall adherence rates to the full Porto criteria varying between 45% and 59%, depending on the type of IBD. However, there was a positive and significant time trend, showing the positive impact of the guideline audit on clinical practice. The even higher rate of 87% of patients diagnosed with CD and 75% of patients diagnosed with IBD-U who underwent at least EGD and colonoscopy plus

either ileal intubation or small bowel imaging, documents the high level of acceptance of the criteria and suggests that other factors play a role for implementation. For example, center size had an influence on performance rates, indicating that the results mirror daily practice in diagnosing IBD more than keeping to a study protocol with additional checks and routines.

In summary, this first analysis of the EUROKIDS registry shows that the performance of EGD and ileocolonoscopy has been constantly rising since the publication of the Porto criteria. Taking serial biopsies for histology is an accepted standard. Small bowel imaging by MRI has increased during the years, and has superseded the use of SBFT. In some cases, CT and capsule endoscopy contribute to the diagnosis. The diagnostic workup can be further improved by increasing the success rate of ileal intubation in all IBD patients, and by stimulating the use of small bowel imaging, especially in patients diagnosed with IBD-U. The diagnostic yield of EGD (7.5%) and ileocolonoscopy (13%), combined with the additional value of small bowel imaging, underlines the importance of a full diagnostic workup in children and adolescents with a suspicion of IBD. In the near future, data from this 5-year EUROKIDS cohort will provide accurate and reliable information on the unique phenotype of pediatric-onset IBD.

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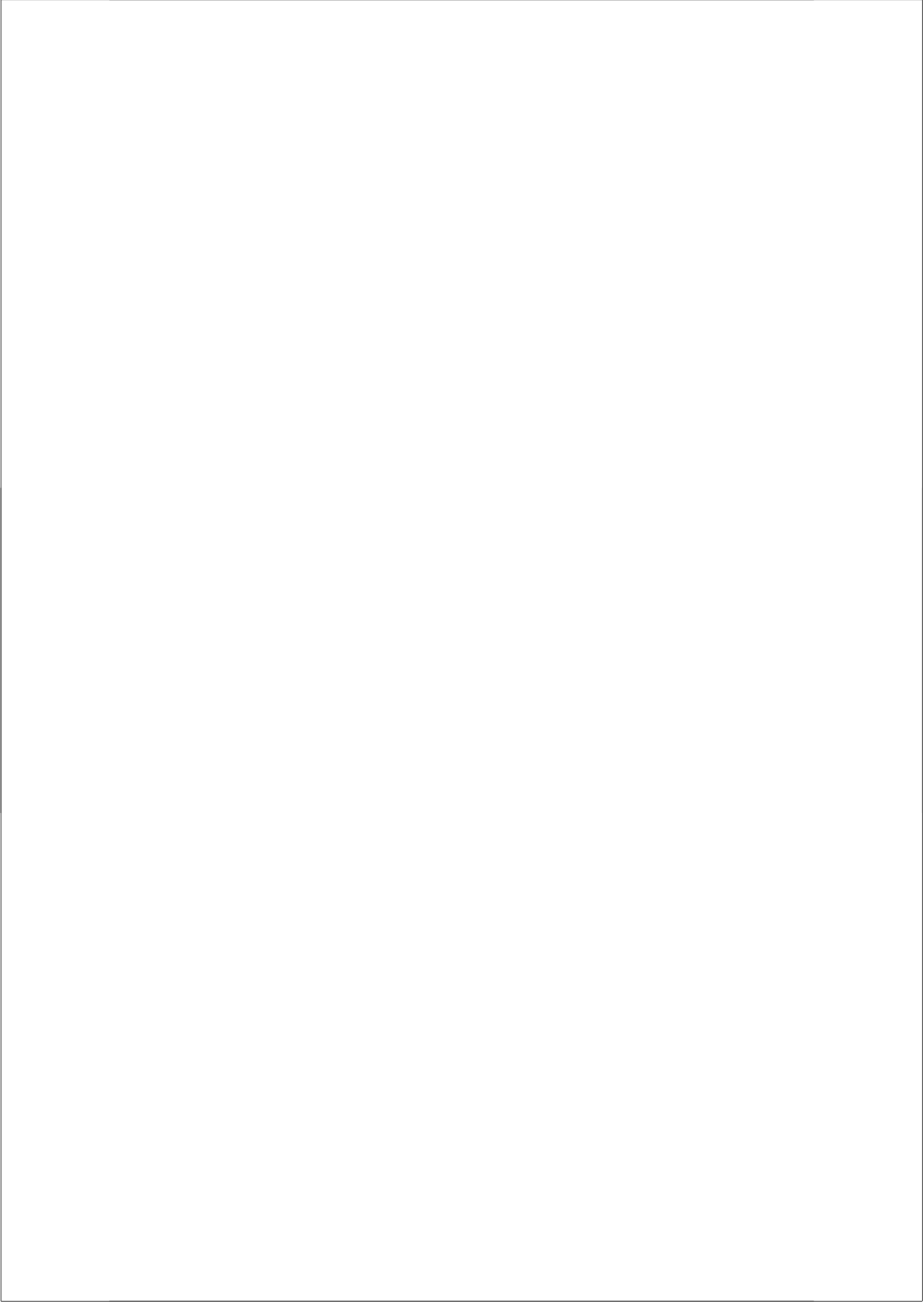3. Orel R, Kamhi T, Vidmar G, et al. Epidemiology of pediatric chronic inflammatory bowel disease in central and western Slovenia, 1994-2005. *J Pediatr Gastroenterol Nutr*. 2009;48:579-586.

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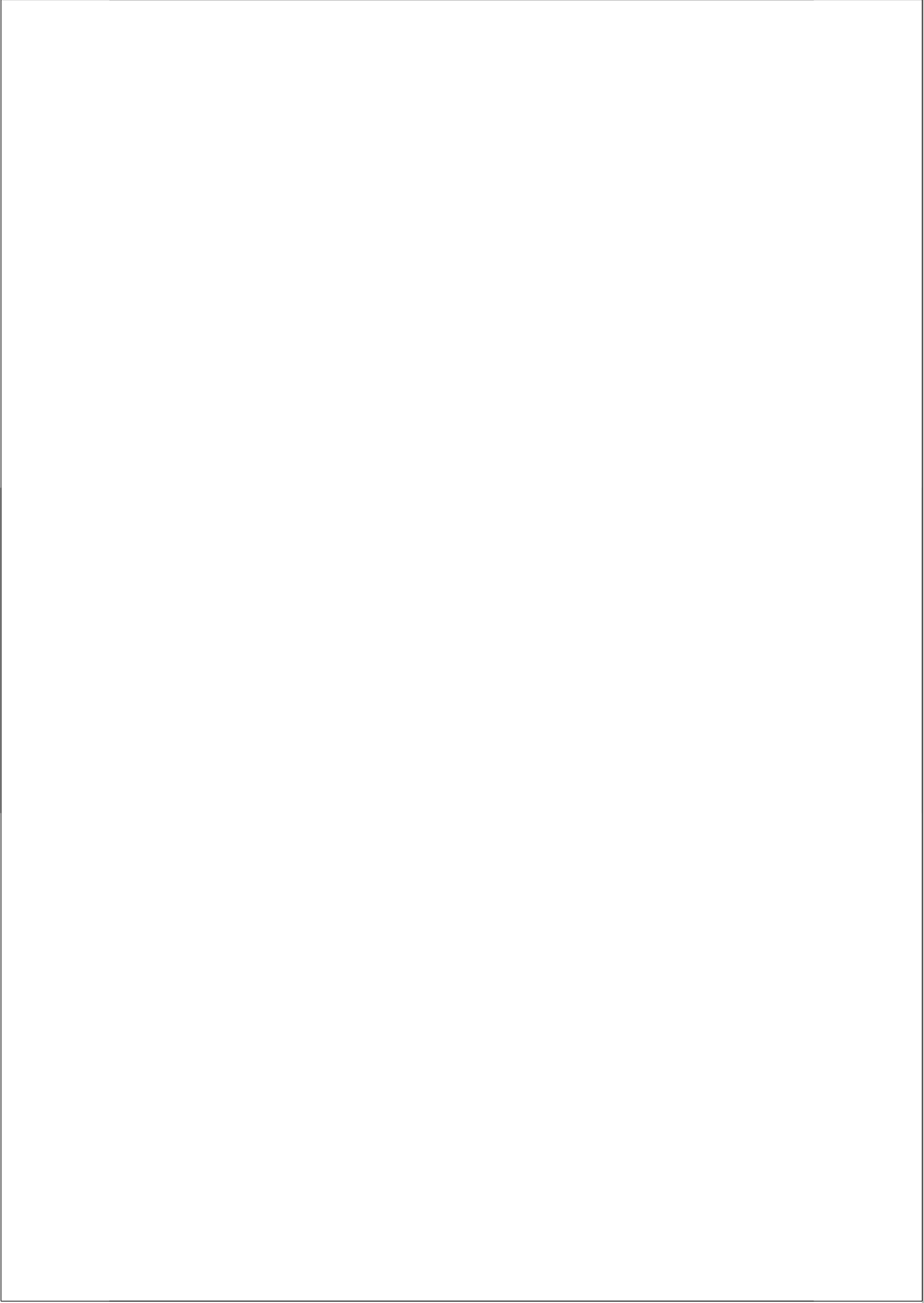
Part II

Disease phenotype of newly diagnosed pediatric IBD patients in Europe

Chapter

3

Disease phenotype at diagnosis in pediatric Crohn's disease: 5-year analyses of the EUROKIDS registry

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ABSTRACT

Backhaground

It has been speculated that pediatric Crohn's disease (CD) is a distinct disease entity, with probably different disease subtypes. We therefore aimed to accurately phenotype newly diagnosed pediatric CD by using the pediatric modification of the Montreal classification, the Paris classification.

Methods

Information was collected from the EUROKIDS registry, a prospective, web-based registry of new-onset pediatric IBD patients in 17 European countries and Israel. When a complete diagnostic workup was performed (ileocolonoscopy, upper gastrointestinal (GI) endoscopy, small bowel imaging), CD patients were evaluated for ileocolonic disease extent, eso-phagogastroduodenal involvement, and jejunal/proximal ileal involvement. Disease behavior and the occurrence of granulomas were also analyzed.

Results

582 pediatric CD patients could be classified according to the Paris classification. Isolated terminal ileal disease (±limited cecal disease) was seen at presentation in 16%, isolated colonic disease in 27%, ileocolonic disease in 53%, and isolated upper GI disease in 4% of patients. In total, 30% had esophagogastroduodenal involvement, and 24% jejunal/proximal ileal disease. Patients with L2 disease were less likely to have esophagogastroduodenal involvement or stricturing disease than patients with L1 or L3 disease. Terminal ileal disease and stricturing disease behavior were more common in children diagnosed after 10 years of age than in younger patients. Granulomas were identified in 43% of patients.

Conclusions

Accurate phenotyping is essential in pediatric CD, as this affects the management of individual patients. Disease phenotypes differ according to age at disease-onset. The Paris classification is a useful tool to capture the variety of phenotypic characteristics of pediatric CD.

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INTRODUCTION

Inflammatory bowel diseases (IBD), such as Crohn's disease (CD) and ulcerative colitis (UC), are an increasing health concern and medical burden for the Western, and particularly European and North American countries, affecting up to 1 in 250 individuals in the general population.[1] Every fourth patient with IBD is diagnosed already during childhood and adolescence. After a continuous rise in the incidence of adult CD over the last five decades, several recent studies have shown that the rates reached a stable plateau.[2-5] In contrast to adults, incidence rates for children continue to rise[5-12], especially in children < 10 years of age.[13]

There is a striking variety of pediatric-onset IBD regarding age, disease distribution and severity at onset, endoscopic appearance, histology, genetic background, serologic markers, co-morbidities, complications during follow-up, and response to different treatment options. Up till now, no single diagnostic procedure or even a combination of diagnostic tests allows the definite diagnosis of CD. It has been speculated that pediatric CD is a distinct disease entity, with probably different disease subtypes.[14] The recent pediatric modification of the Montreal classification for IBD could facilitate future studies and help to further explore this hypothesis, as it enables a more precise phenotypic classification of disease location.[15] The European multicenter 5-years recruitment of children with newly developed IBD (EUROKIDS registry) provides a unique opportunity to test this hypothesis, as the majority of included patients have undergone a complete diagnostic workup suggested by the so-called Porto criteria.[16]

The aim of this paper is to accurately phenotype newly diagnosed CD in pediatric patients prospectively recruited within the EUROKIDS registry in respect to: disease location, disease behavior, and presence of granulomas. Associations between phenotype and age at disease-onset, gender, family history of IBD, ethnicity, geographical region, and extraintestinal involvement will also be investigated.

MATERIALS AND METHODS
EUROKIDS registry

The EUROKIDS registry is a prospective, web-based registry of newly diagnosed pediatric IBD patients in Europe and Israel, established by the IBD Working Group of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). The enrolment of patients into the registry began in May 2004. During the first 5 years, the registry has extended to allow inclusion of patients (aged 0 – 18 years) from 44 centers in 18 countries. Details on the establishment of the registry and data collection have been previously reported.[17]

Participating centers were all committed to perform a diagnostic workup of their patients (who were suspected of having IBD) according to the Porto criteria.[16] This implies that

ileocolonoscopy and upper gastrointestinal (GI) endoscopy were expected to be performed in all patients, as well as imaging of the small bowel (except in patients with a definitive diagnosis of UC). Also according to the agreed Porto criteria, participating centers were expected to take at least two biopsies from each segment of the GI tract (esophagus, stomach, duodenum, terminal ileum, and all segments of the colon), and to register the endoscopic and histologic findings from each segment separately. Each segment visualized by ileocolonoscopy could be registered as macroscopically "normal" or "abnormal" (i.e. abnormalities consistent with IBD, such as (aphthous) ulcerations, erosions, cobblestoning, strictures). Histology was classified as "normal" or "abnormal" in the first year of the registry (May 2004 – April 2005), while the presence or absence of granulomas could be registered from May 2005 onwards (2nd year of the registry). The number of biopsies taken from each segment was not registered in the database. Results from upper GI endoscopy were reported in a similar fashion. Macroscopic esophagogastroduodenal findings were classified as "normal" or "abnormal" in the first 3 years of the registry (i.e. May 2004 – April 2007), whereas additional information on the type of macroscopic abnormality was registered in years 4 and 5 only (i.e. May 2007 – April 2009). To have more specific information on the "abnormal" esophagogastroduodenal findings in pediatric CD patients, participating centers were asked to review the medical charts of these patients for additional information on the type of macroscopic abnormality in the upper GI tract. Results from small bowel imaging ("normal" or "abnormal") were also registered per segment of the GI tract.

Ethics committee permission was obtained in the United Kingdom, Sweden and Poland. In all other countries, a Statement of No Objection was released by the local ethics committees, because data were anonymously collected.

Eligibility

As previously described[17], 2087 newly diagnosed pediatric IBD patients who were diagnosed between May 2004 and April 2009, were correctly registered in the database. For this study, we identified all patients who were classified as having CD. Exclusion criteria were: a diagnosis of UC or IBD-unclassified, missing information on ileocolonoscopy and ileocolonic histology, and a diagnostic workup without endoscopic, histologic, and radiologic abnormalities.

Definitions

A diagnosis of CD was made according to the discretion of the investigator/treating physician, and was based on clinical presentation, physical examination, endoscopic appearance, histologic findings, and small bowel imaging studies.

Participating countries were divided into two *geographical regions*: Northern Europe (Belgium, Czech Republic, Denmark, France, Germany, Latvia, the Netherlands, Norway,

Poland, Sweden, United Kingdom) and Southern Europe and Israel (Croatia, Greece, Hungary, Italy, Portugal, Slovenia).

Family history of IBD was defined as the presence of IBD in first-degree relatives.

Extraintestinal manifestations (including dermatologic, ophthalmologic, musculoskeletal, and/or hepatobiliary manifestations) were registered as being present or absent. Registration of the type of manifestation was optional.

To optimally classify *disease location*, we decided to select the pediatric CD patients who had a complete diagnostic workup according to the Porto criteria.[16] This workup had to consist of upper GI endoscopy, ileocolonoscopy, and adequate imaging of the small bowel by small bowel follow-through (SBFT), magnetic resonance imaging (MRI), computed tomography (CT), capsule endoscopy, and/or enteroscopy. Disease location was determined by the endoscopic appearance of the mucosa and radiologic involvement of the small bowel, not by microscopic findings. Endoscopic information on the terminal ileum was considered more accurate than radiologic findings, in case of disagreement. Disease location was categorized according to the Paris classification[15]: (L1) involvement of the terminal ileum only, with limited or no cecal disease; (L2) colonic involvement only; (L3) involvement of both the terminal ileum and colon; (L4) isolated upper GI disease, defined as macroscopic and/or radiologic abnormalities proximal to the terminal ileum. Isolated upper GI disease (L4) was further separated into esophagogastroduodenal disease (L4A), jejunal/proximal ileal disease (L4B), or both L4A and L4B. Upper GI disease (i.e. L4A, L4B, L4AB) can also coexist with L1, L2, or L3. We defined esophagogastroduodenal disease (L4A) as the presence of ulcerations, erosions/aphthae, cobblestones and/or stenosis. The presence of mucosal erythema, edema, granularity, and/or nodularity was not sufficient to be considered evidence of involvement.

Disease behavior was registered as the presence of strictures, intra-abdominal fistulas, and/or intra-abdominal abscesses. We categorized disease behavior according to the Paris classification[15]: (B1) nonstricturing, nonpenetrating disease; (B2) stricturing disease; (B3) penetrating disease (excluding isolated perianal or rectovaginal fistulas); (B2B3) the presence of both B2 and B3 phenotypes in the same patient.

Perianal disease was defined as the presence of a perianal abscess and/or fistula, and did not include the isolated presence of skin tags, fissures, or hemorrhoids.

Histology was registered as "normal", "abnormal" or "granulomas" from May 2005 onwards (i.e. the 2nd year of the registry). As details on the histologic abnormalities (i.e. other than granulomas) were not available, we only used data on the presence of granulomas. For these analyses, we selected the patients diagnosed from May 2005 onwards who had biopsies from at least 10 segments of the GI tract, including the esophagus, stomach, duodenum, terminal ileum, cecum, ascending colon, transverse colon, descending colon, sigmoid, and rectum. Information on the number of granulomas found was not available.

Statistical analysis

Data were analyzed in SPSS (version 17.0, SPSS, Inc., Chicago, IL, USA). Descriptive statistics were calculated as percentages for discrete data. Continuous variables were presented as means and standard deviations (SD). Age at diagnosis was dichotomized into two categories (< 10 years, ≥ 10 years), in accordance with the age cut-offs recommended in the Paris classification.[15] To test for differences between more than two categories of disease location or disease behavior, we used Pearson χ^2 tests. Two-sample t-tests were used to compare two continuous variables, while Fisher's exact tests were used to compare two proportions. Multivariable logistic regression was performed to examine the possible independent determinants of the occurrence of granulomas, after adjusting for gender, age (< 10 years, ≥ 10 years), family history of IBD, ethnicity, and geographical region. Statistical significance was defined as a two-tailed P-value < 0.05.

RESULTS

Patient characteristics

Between May 2004 and April 2009, 1227 of 2087 (59%) newly diagnosed pediatric IBD patients were classified as having CD. Six patients (0.5%) were excluded, because of missing information on ileocolonoscopy and histology (n=4), and a diagnostic workup without endoscopic, histologic, and radiologic abnormalities (n=2).

In the remaining 1221 patients, mean age at diagnosis was 12.5 years (±3.3; range 0.8 – 17.9; 20% younger than 10 years), with 59% (n=723) being male. The majority of patients (77%, n=936) were from Northern Europe. Information on ethnicity was available in 1210 (99%) patients. Most patients were Caucasian (87%, n=1049), 4% (n=50) were Asian, 4% (n=43) of Arab origin, 1% (n=18) of Africa-Caribbean origin, and 4% (n=50) had another ethnicity. Eleven percent (129/1193) of patients had a first-degree relative with IBD. When analyzed by age category (< 10 years, ≥ 10 years), there was no significant difference in the prevalence of a positive family history in first-degree relatives (p=0.82). Extraintestinal manifestations were present in 20% (231/1178) of patients at diagnosis.

Disease location according to the Paris classification

A total of 582 CD patients (48%) were eligible for determination of disease location according to the Paris classification (Figure 1). Isolated terminal ileal disease (±limited cecal disease, L1) was seen at presentation in 16% (n=95), isolated colonic disease (L2) in 27% (n=159), ileocolonic disease (L3) in 53% (n=307), and isolated upper GI disease (L4) in 4% (n=21) of pediatric CD patients (Figure 2).
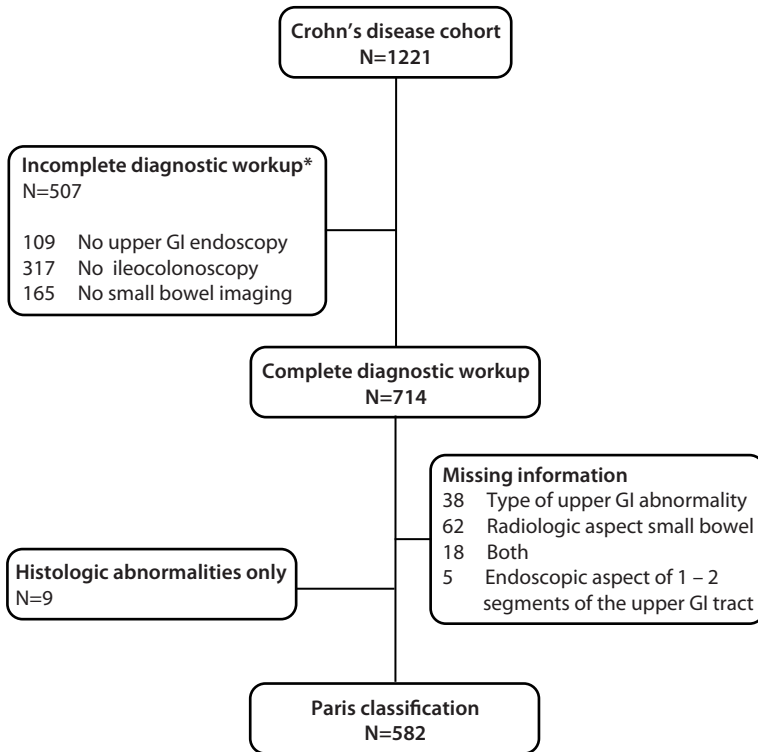
Figure 1 | Flowchart of Crohn's disease patients selected for the analyses on disease location according to the Paris classification.

*Multiple diagnostic tests can be absent in one patient simultaneously. GI: gastrointestinal.

Differences in disease location according to age at diagnosis are shown in Figure 3. Isolated colonic disease was recorded in 41% (47/114) of children diagnosed before 10 years of age compared with 24% (111/467) of older children (p<0.001). Consequently, the proportion of patients diagnosed with L1 disease (9% vs. 18%, p=0.016) and, to a lesser extent, L3 disease (47% vs. 54%, p=0.14) were lower in the younger age category. There was no difference in the occurrence of L4 disease between the two age categories (both 4%). Gender, family history of IBD, or presence of extraintestinal manifestations did not differ significantly between the four disease locations. L4 disease was more often diagnosed in Southern Europe and Israel than in Northern Europe (7.3% vs. 2.2%, p=0.005), whereas the occurrence of the other three disease locations did not differ according to geographical region. Ethnicity differed significantly between the four disease locations, as L3 disease occurred more often in Caucasian patients (55% vs. 38%, p=0.016). Consequently, L1 disease (25% vs. 15%, p=0.048) and L4 disease (13% vs. 3%, p=0.001) were more often present in non-Caucasian patients.
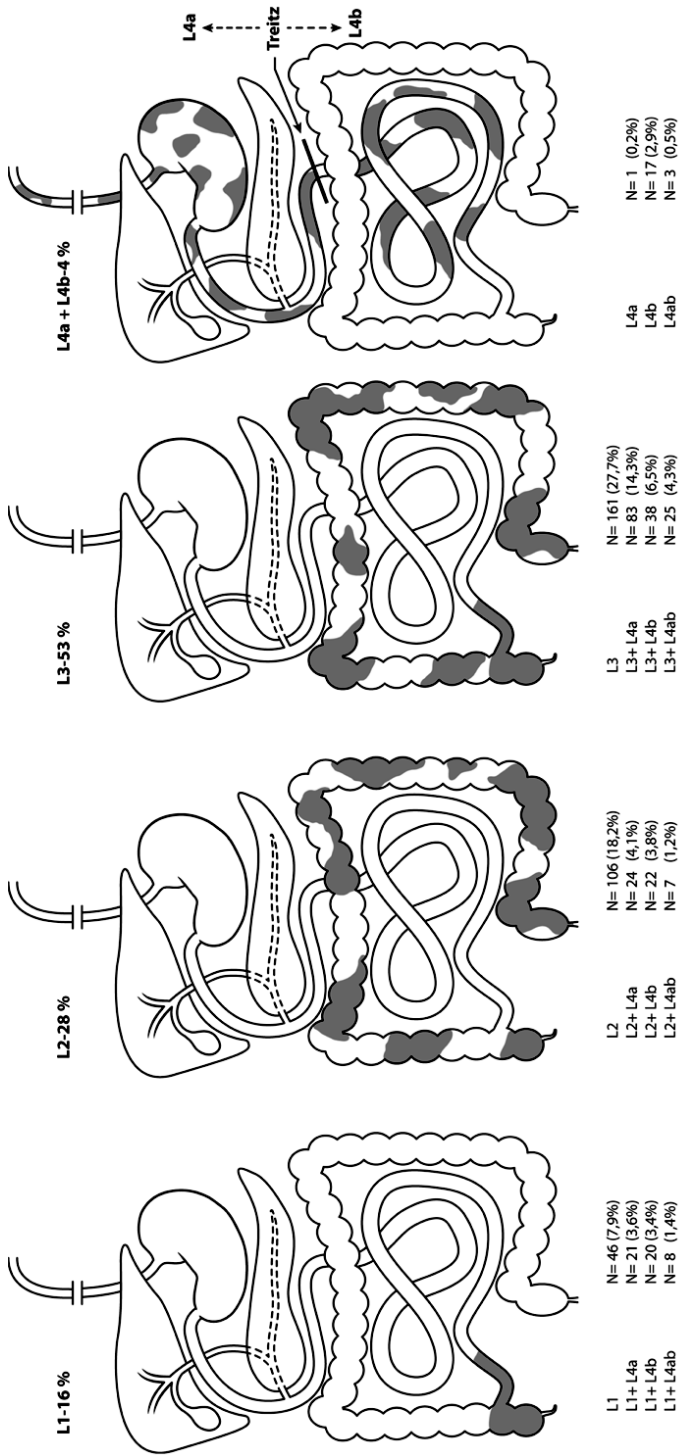
Figure 2 | Disease location according to the Paris classification in 582 newly diagnosed pediatric Crohn's disease patients who underwent a complete diagnostic workup according to the Porto criteria.[16]

L1: terminal ileal disease (±limited cecal disease). L2: colonic disease. L3: ileocolonic disease. L4: isolated upper gastrointestinal tract disease. L4A: esophagogastroduodenal disease. L4B: jejunal/proximal ileal disease.

L4a
Treitz
L4b

L4a + L4b-4 %

L4a   N= 1   (0,2%)
L4b   N= 17 (2,9%)
L4ab   N= 3   (0,5%)

L3-53 %

L3   N= 161 (27,7%)
L3+ L4a N= 83 (14,3%)
L3+ L4b N= 38 (6,5%)
L3+ L4ab N= 25 (4,3%)

L2-28 %

L2   N= 106 (18,2%)
L2+ L4a N= 24 (4,1%)
L2+ L4b N= 22 (3,8%)
L2+ L4ab N= 7   (1,2%)

L1-16 %

L1   N=46 (7,9%)
L1+ L4a N= 21 (3,6%)
L1+ L4b N= 20 (3,4%)
L1+ L4ab N= 8 (1,4%)

Figure 3 | Disease location in newly diagnosed pediatric Crohn's disease patients according to age at diagnosis.

L1: terminal ileal disease (±limited cecal disease). L2: colonic disease. L3: ileocolonic disease. L4: isolated upper gastrointestinal tract disease.

Table 1 | Macroscopic findings in the upper gastrointestinal tract of 582 pediatric Crohn's disease patients who underwent a complete diagnostic workup according to the Porto criteria.[16]

Esophageal involvement	34 (6%)
Ulcerations	12
Erosions/aphthae	23
Gastric involvement	102 (18%)
Ulcerations	36
Erosions/aphthae	71
Cobblestones	1
Duodenal involvement	100 (17%)
Ulcerations	31
Erosions/aphthae	72
Cobblestones	2
Stenosis	2

Multiple abnormalities may be present in one segment simultaneously.

Esophagogastroduodenal disease (L4A) was present in 30% (n=172) of pediatric CD patients at disease-onset. The distribution of the macroscopic findings in the upper GI tract is displayed in Table 1. In the majority of patients with L4A disease (68%, 117/172), the mucosal abnormalities were limited to one upper GI segment, preferentially the stomach (n=54) or duodenum (n=49). L4A disease occurred more often in patients with L1 or L3 disease than in those with L2 disease (31% vs. 35% vs. 20%, p=0.002, Table 2). There were no significant differences between patients with and without L4A disease according to age category, gender, family history of IBD, geographical region, ethnicity, presence of extraintestinal manifestations, or L4B disease.

Jejunal/proximal ileal disease (L4B) was present in 24% (n=140) of pediatric CD patients. L4B disease occurred more often in patients with L1 disease than in those with L2 or L3 disease (30% vs. 18% vs. 21%, p=0.092, Table 2). The presence of L4B disease was not related to age, gender, family history of IBD, geographical region, or presence of extraintestinal manifestations. Caucasian patients were less likely to have disease involvement of the jejunum and/or proximal ileum than Non-Caucasian patients (22% vs. 41%, p=0.002). L4B disease was present in 47% (9/19) of Asian patients, 22% (4/18) of patients of Arab origin, 75% (3/4) of patients of Africa-Caribbean origin, and 46% (10/22) of patients with another ethnicity.

Table 2 | Associations between ileocolonic disease location and upper gastrointestinal disease, disease behavior, and perianal disease in 582 pediatric Crohn's disease patients who underwent a complete diagnostic workup according to the Porto criteria.[16]

	Disease location according to the Paris classification				
	L1	L2	L3	L4	P[A]
L4A	29/95 (31%)[B]	31/159 (20%)	108/307 (35%)[B]	NA	0.002
L4B	28/95 (30%)[B]	29/159 (18%)	63/307 (21%)	NA	0.092
Stricturing disease behavior	20/95 (21%)[B]	9/155 (6%)	45/306 (15%)[B]	3/21 (14%)	0.005
Penetrating disease behavior	5/94 (5%)	6/153 (4%)	17/302 (6%)	0/21 (0%)	0.62
Perianal disease	2/95 (2%)[C]	13/156 (8%)	32/305 (11%)	1/21 (5%)	0.070

[A]L1 vs. L2 vs. L3 (vs. L4), Pearson χ^2
[B]p<0.05 vs. L2
[C]p<0.05 vs. L3
L1: terminal ileal disease (±limited cecal disease). L2: colonic disease. L3: ileocolonic disease. L4: upper gastrointestinal tract disease. L4A: esophagogastroduodenal disease. L4B: jejunal/proximal ileal disease. NA: not applicable.
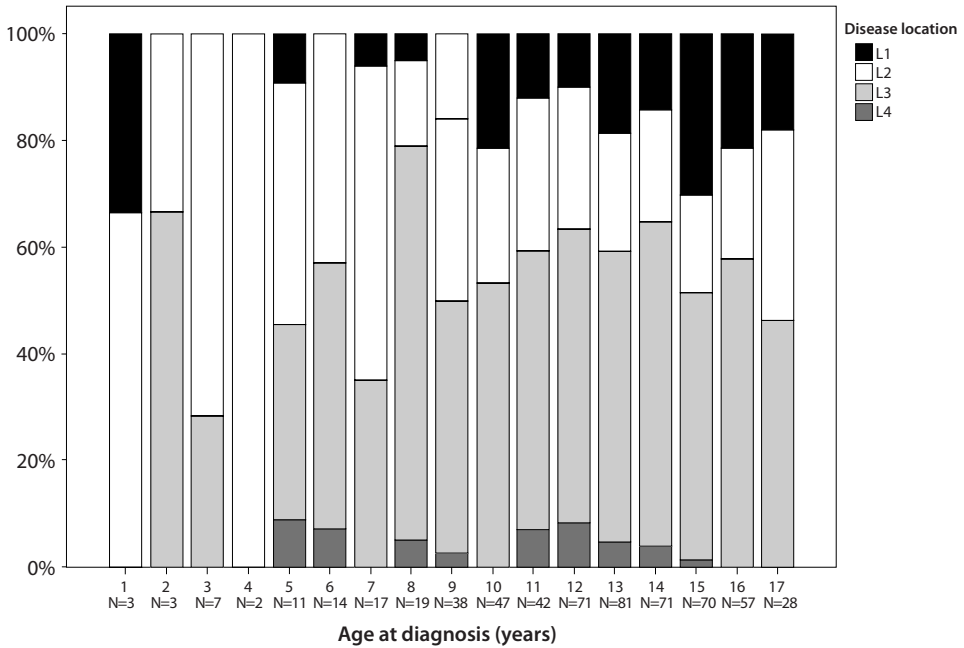
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Disease behavior

Information on disease behavior was available in 1177 (96%) patients. The majority of pediatric CD patients (82%, n=959) presented with nonstricturing, nonpenetrating disease (B1), while stricturing disease (B2) was seen in 12% (n=144), penetrating disease (B3) in 5% (n=55), and both stricturing and penetrating disease (B2B3) in 2% (n=19) of patients at initial diagnosis. Patients diagnosed before 10 years of age were more likely to present with B1 disease compared with older children (88% (208/236) vs. 80% (750/940), p=0.003). Consequently, the proportion of patients with B2 disease (7% (16/236) vs. 14% (128/940), p=0.004) and B2B3 disease (0.4% (1/236) vs. 2% (18/940), p=0.15) were lower in the younger age category. The occurrence of B3 disease did not differ between the two age categories (both 5%). Disease behavior was not related to gender, family history of IBD, geographical region, ethnicity, or presence of extraintestinal manifestations.

Perianal disease (i.e. presence of fistula(s) and/or abscess(es)) at diagnosis was seen in 9% (114/1207) of pediatric CD patients. Male patients were more likely to have perianal disease than female patients (12% vs. 6%, p=0.002). There was no significant association with age at diagnosis, family history of IBD, geographical region, ethnicity, or presence of extraintestinal manifestations. Presence of perianal disease differed significantly between the four disease behavior categories (p<0.001). Perianal disease occurred more often in patients with B3 disease than in patients with B1 disease (38% vs. 8%, p<0.001), B2 disease (38% vs. 7%, p<0.001), or B2B3 disease (38% vs. 17%, p=0.15).

Table 2 displays the associations between disease location and disease behavior in the 582 pediatric CD patients who could be classified according to the Paris classification. Patients with L2 disease were less likely to have stricturing disease complications compared with patients with L1 or L3 disease (6% vs. 21% vs. 15%, p=0.005). The occurrence of penetrating disease behavior did not differ significantly between the four disease locations, nor were there significant differences in disease behavior between patients with or without L4A/L4B disease.

Granulomas

In years 2 to 5, there were 427 pediatric CD patients with biopsies from at least 10 segments of the GI tract. Granulomas were identified in 43% (184/427) of these patients. The distribution of granulomas per segment of the GI tract is represented in Table 3. In 79 CD patients (19%), granulomas were found in one or more macroscopically normal-looking segments.

Granulomas confined solely to the upper GI tract were present in 4% (18/427), granulomas confined solely to the terminal ileum in 5% (21/427), and granulomas confined solely to the colon in 15% of CD patients (65/427). Eight percent of patients (32/427) had granulomas in the upper GI tract, as well as in the terminal ileum and colon.

There was no significant age difference between CD patients with and without granulomas (12.4 vs. 12.2 years, p=0.57). In addition, the presence of granulomas was not related to

gender, family history of IBD, geographical region, ethnicity, presence of extraintestinal manifestations, esophagogastroduodenal disease, jejunal/proximal ileal disease, perianal disease, stricturing disease behavior, or penetrating disease behavior. Subsequent multivariate analyses revealed no other significant determinants of granulomas

Table 3 | Distribution of granulomas in the gastrointestinal tract of 427 pediatric Crohn's disease patients at diagnosis who had biopsies of at least 10 segments of the gastrointestinal tract, including the esophagus, stomach, duodenum, terminal ileum, cecum, ascending colon, transverse colon, descending colon, sigmoid, and rectum.

Biopsy site	Presence of granulomas
Esophagus	20 (5%)
Normal macroscopic appearance	13
Stomach	49 (12%)
Normal macroscopic appearance	27
Duodenum	14 (3%)
Normal macroscopic appearance	5
Terminal ileum	86 (20%)
Normal macroscopic appearance	23
Colon	141 (33%)
Normal macroscopic appearance	31

Granulomas may be present in biopsies from multiple sites simultaneously.

DISCUSSION

This is one of the largest European studies so far describing disease phenotype at diagnosis in pediatric CD patients. Data from 17 European countries and Israel were included in the EUROKIDS registry in a prospective manner, based on clearly defined diagnostic criteria. Among 2087 children with IBD, 1227 (59%) were classified as having CD, which is in accordance with other pediatric publications that predominantly report CD to be more common than UC.[18] Extraintestinal manifestations occurring in 20% and perianal disease in 9% of patients are also in line with other recent pediatric reports.[14, 19-21]

We were able to stratify macroscopic disease location according to the Paris classification for pediatric IBD[15] in 582 patients with a complete workup according to the Porto criteria.[16] Little more than half of the patients presented with ileocolonic disease, which is in keeping with recent pediatric reports based upon the Montreal classification.[14, 19] Our data also confirm that disease location is clearly dependent on the age of disease-onset, with younger children having a tendency to isolated colonic disease and elder children having a more frequent involvement of the terminal ileum. Clinical observations have suggested that the sites of initial inflammation in ileal CD are the lymphoid follicles and Peyer's

patches.[22] The number of Peyer's patches increases during childhood and reaches a peak in late adolescence[23], which is highly correlated with the age-related occurrence of CD. French data have confirmed the importance of ileal maturation and thus function of Peyer's patches[24-25], which might be an explanation for the association between age and disease location.

The Paris classification enables a more detailed phenotypic description of upper GI disease than the Montreal classification[26], thereby adding new information about the phenotype of childhood IBD to the pediatric literature. Using a stringent definition for esophagogastroduodenal disease (L4A) based on macroscopic criteria, we found that 30% of patients presented with ulcerations, erosions/aphthae, cobblestones and/or stenosis in the upper GI tract. When we had defined L4A disease as the presence of ulcerations only, the prevalence would have been 11%. In previous pediatric cohort studies, esophagogastroduodenal disease has been variably defined by macroscopic and/or histologic definitions, resulting in a large range of reported frequencies varying from 11 to 52%.[14, 19, 27-29] Future studies should use clear definitions for esophagogastroduodenal disease in order to determine the effect of this phenotype on the disease course. Jejunal/proximal ileal disease (L4B) was present in 24% of patients, which is slightly higher compared with rates reported in other studies (19 and 17%, respectively).[29-30] Our increased detection rate of L4B involvement may be explained by the technologic advances in radiologic imaging techniques in recent years. In total, 64% (373/582) of pediatric CD patients underwent small bowel follow-through, 38% (218/582) MRI, 6% (37/582) CT abdomen, and 5% (29/582) capsule endoscopy. Previous studies have demonstrated that patients with the L4B phenotype were more likely to be stunted at diagnosis[29-30], and develop early complications, particularly of the stricturing type.[31-32] Early diagnosis of proximal small bowel disease is therefore important, as this may allow physicians to treat these patients more aggressively in order to improve linear growth and prevent complications.

Disease behavior was classified as inflammatory (nonstricturing, nonpenetrating; B1: 82%), stricturing (B2: 12%), penetrating (B3: 5%), or both stricturing and penetrating (B2B3: 2%). In comparison, two other recently published pediatric cohort studies from Europe found the B1, B2, and B3 phenotype at diagnosis in 92, 4 and 4%, and 71, 25 and 4%, respectively.[14, 19] The large differences in reported frequencies of the B2 phenotype may reflect difficulties in precise discrimination of fibrostenotic from inflammatory stenotic disease. Our study showed that disease behavior differed with respect to age at diagnosis, as older patients had a higher risk of stricturing disease. Previous studies have yielded conflicting results regarding the influence of age on disease behavior. Gupta et al. demonstrated that older children with CD had an increased risk of developing strictures, but also of developing abscesses or fistulas.[33] In contrast, Shaoul et al. did not find an association between age and disease behavior.[34] The association between age and disease behavior might be the effect of the influence of age on disease location, as older patients are more likely to have

ileal disease, which in turn has been demonstrated to be associated with stricturing disease complications.[14] We also found an association between the occurrence of perianal disease and intra-abdominal penetrating disease, similar to results from adult studies.[35-36] Although the two phenotypes are related to one another, perianal disease and intra-abdominal penetrating disease have different clinical associations with disease location and smoking behavior.[36-37] This suggests that the mechanisms for these types of penetrating disease are at least partly different.

We found granulomas in 43% of patients who were biopsied in at least 10 segments of the GI tract, with isolated localization in the terminal ileum in 5%, and in the upper GI tract in 4%. This differs considerably with the study of De Matos et al., who have published the hitherto most detailed study regarding location of granulomas in pediatric CD.[38] They found granulomas in 61% (112/184) of untreated patients, of which 23% had granulomas only in the terminal ileum and 13% only in the upper GI tract. This variation in occurrence of granulomas may reflect differences in patient populations (either due to geographical variation or selection bias) or methodology (number of biopsies taken, number of sections per paraffin block, number of high-power fields evaluated, and definition of granulomas). However, both studies underscore the potential usefulness of intubating the terminal ileum and performing upper GI endoscopy at the time of diagnosis of IBD. We recently estimated the diagnostic yield of ileoscopy and upper GI endoscopy in CD patients to be 13% and 7.5%, respectively (i.e. the presence of isolated granulomas, or the presence of macroscopic abnormalities in the terminal ileum/upper GI tract without other characteristics of CD).[17] Data from the literature regarding the usefulness of upper GI endoscopy in the diagnostic workup of pediatric IBD have recently been reviewed.[39] Diagnostic yields ranged between 7 and 24%. This topic has not been studied in adult IBD patients.

Our study has certain limitations. First of all, EUROKIDS is not a population-based registry, but a selection of centers and pediatric gastroenterologists with a special interest in IBD. This has probably resulted in some selection bias. However, ESPGHAN recommends that all children with a suspicion of IBD should be referred to a pediatric gastroenterologist for diagnostic workup.[16] Consequently, the majority of our participating centers diagnoses and treats all pediatric IBD patients in their region; only five centers have reported that they treat only the most severe IBD cases and four centers have a mixed population of "regular" IBD patients and severe IBD cases. Selection bias may also have been introduced due to our decision to include only CD patients with a complete workup according to the Porto criteria in the analyses on disease location according to the Paris classification, as patients with severe disease (risk of perforation; strictures) and younger patients (more difficult to reach the terminal ileum) are more prone not to have undergone a complete workup. However, age at diagnosis did not differ significantly between the included and excluded patients.

Another limitation is that the number of adolescents older than 14 years is underestimated in our study cohort. While it is generally known that the incidence of CD increases with
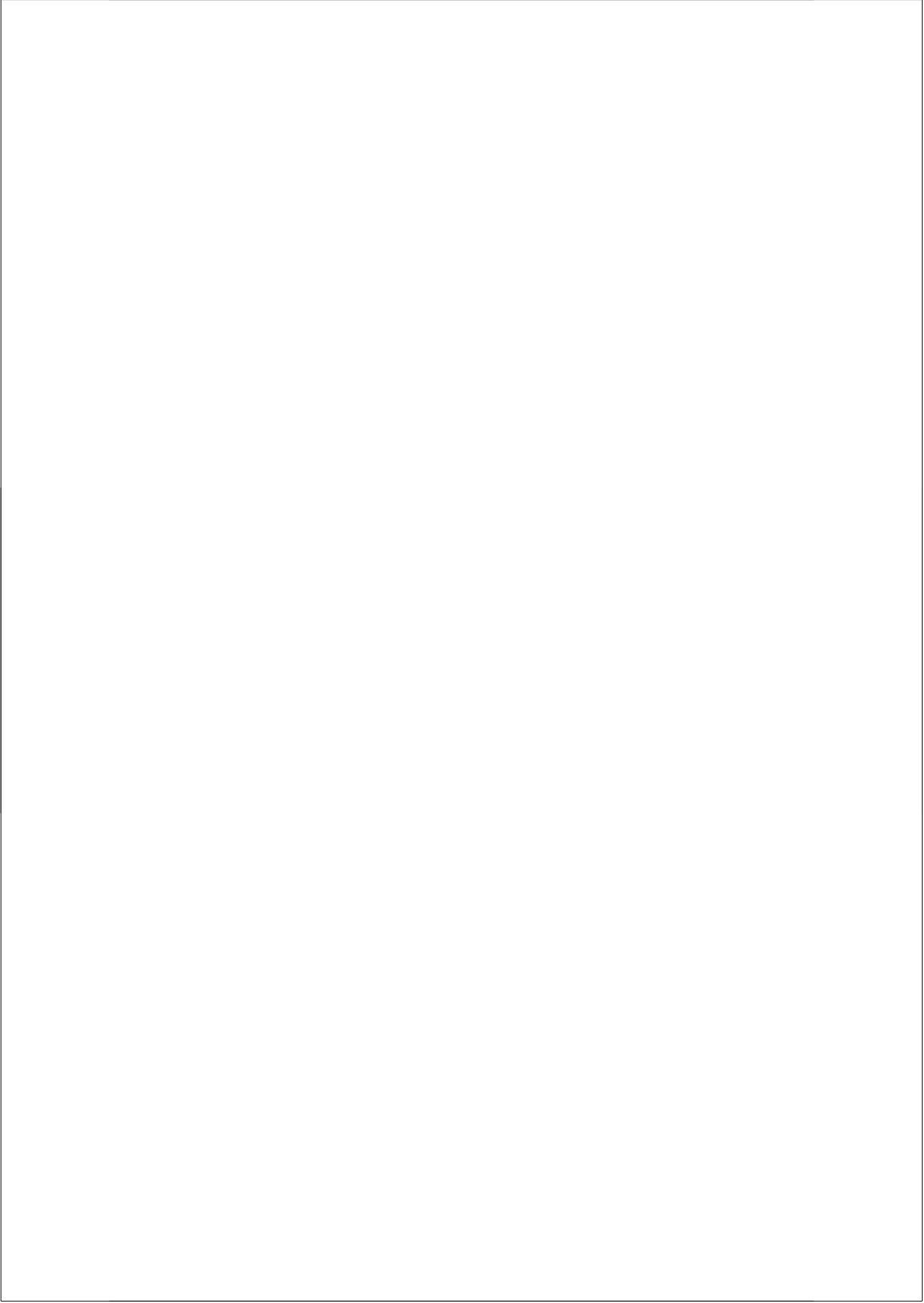
age, the peak incidence in our study occurred at 14 years of age. This is a reflection of daily practice, where adolescents are often diagnosed by adult gastroenterologists, and are thus not included in our EUROKIDS registry. Approximately one third of the participating centers reported that new patients older than 15 years are always referred to an adult gastroenterologist. Fourthly, a clear definition for the occurrence of extraintestinal manifestations was lacking, which makes the incidence rate less reliable. However, our incidence is similar to rates reported in other large cohorts of newly diagnosed pediatric CD patients.[19-20, 40] Other limitations are the risk of inter-observer variation regarding interpretation of endoscopic and histologic findings, variation in number of biopsies taken at specific locations, and lack of data on follow-up to evaluate the correctness of the initial diagnosis.

In conclusion, our study has applied the Paris classification in a large cohort of newly diagnosed pediatric CD patients, thereby providing detailed information on disease phenotype and confirming the results of previous studies on disease phenotype in newly diagnosed pediatric CD. During recent years pediatric IBD studies have improved in quality and quantity due to more extensive use of multicenter collaborations and large databases, such as the US Pediatric IBD Consortium Registry[33], the US/Canadian Pediatric IBD Collaborative Research Group Registry[20-21], the EPIMAD registry of Northern France[19], the Scottish cohort[14], the Italian pediatric IBD registry[28], the Danish Crohn Colitis Database[11], and the German pediatric IBD registry CEDATA.[40] Increasingly, future pediatric IBD studies are likely to be the result of large registry collaborations more than single center reports. Uniformity in disease classification will then be essential for assessing disease prognosis, choosing the most appropriate therapy, and investigating genotype-phenotype correlations.

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Chapter 4

Atypical disease phenotypes in pediatric ulcerative colitis: 5-year analyses of the EUROKIDS registry

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ABSTRACT

Background

Definitive diagnosis of pediatric ulcerative colitis (UC) may be particularly challenging since isolated colitis with overlapping features is common in pediatric Crohn's disease (CD), while atypical phenotypes of UC are not uncommon. The Paris classification allows more accurate phenotyping of atypical IBD patients. Our aim was to identify the prevalence of atypical disease patterns in new-onset pediatric UC using the Paris classification.

Methods

Information was collected from the EUROKIDS registry, an inception cohort of untreated pediatric IBD patients undergoing evaluation at diagnosis. Patients with IBD-unclassified were excluded. Patients with isolated Crohn's colitis served as a control group.

Results

Data from 898 pediatric patients (643 UC, 255 CD colitis) were included. Extensive or pancolitis was present in 77% of UC patients, and macroscopic rectal sparing in 5%. Rectal sparing was inversely associated with age (mean age with rectal sparing 9.9 years vs. 11.8 without; p=0.02). Upper gastrointestinal (UGI) involvement occurred in 4% of patients. Erosions in the stomach were present in 3.1% of children, but frank ulcerations in 0.4%; 0.8% of children had erosions or ulcerations limited to the esophagus or duodenum. The corresponding UGI involvement in Crohn's colitis was 22%. A cecal patch occurred in 2% of patients.

Conclusion

Extensive disease and rectal sparing are age-dependent phenotypes in pediatric UC. Rectal sparing, cecal patch, backwash ileitis, and gastric erosions are not uncommon at diagnosis, while gastric ulcerations and erosions in the duodenum or esophagus are. Recognition of atypical phenotypes in pediatric-onset UC is crucial to prevent misclassification of IBD.

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INTRODUCTION

Ulcerative colitis (UC), as defined by previous ECCO guidelines, is "a chronic inflammatory condition causing continuous mucosal inflammation of the colon without granulomas on biopsy, affecting the rectum and a variable extent of the colon in continuity, and characterized by a relapsing and remitting course".[1]

No single criteria can accurately diagnose UC, while there are multiple pitfalls in accurately diagnosing UC. Issues that may be particularly confusing and lead to misclassification or re-classification of UC include patchy disease, rectal sparing, and upper gastrointestinal (UGI) involvement. In addition, disease in children is more extensive.[2]

Macroscopic rectal sparing has been reported to vary between 0 – 30% particularly in children with early-onset UC, of whom many have "relative" rectal sparing (mild patchy disease) rather than "absolute" macroscopic rectal sparing.[3-7] Diagnosis of pediatric UC may therefore be particularly challenging since atypical disease patterns are not rare.

The recent Paris classification which examined this issue[8], recognized that rectal sparing may be consistent with the diagnosis of UC with the condition that rectal sparing was macroscopic but not microscopic. However, the true prevalence of this phenomenon and its impact on classification are hard to gauge, since data have relied on small case series and variable definitions of rectal sparing.

Histologic findings in young children at disease-onset, with a short duration of symptoms, may also lead to confusion. Early-onset disease may have more patchy disease, or have normal or minimally disturbed crypt architecture.[9] The relative paucity of architectural changes and chronicity demonstrated in pediatric UC is age-dependent, and occurs primarily in children ≤ 10 years of age.[6-7, 9]

A problem with corroborating these reports and implementing guidelines for classification of UC and IBD-unclassified (IBD-U) is that these reports have generally been based on very small cohorts with very different definitions of phenotypes. Rectal sparing has been defined by microscopic or macroscopic involvement, while UGI involvement has been defined variably by macroscopic or histologic definitions. In order to further clarify the issue of pediatric phenotypes of UC, and implement evidence-based guidelines for classification of colitis as UC, Crohn's disease (CD) or IBD-U based on the newer definitions of these phenotypes, we investigated several of these phenotypes in a large inception cohort of children with UC using the Paris classification.

MATERIALS AND METHODS
EUROKIDS registry

The EUROKIDS registry is a prospective, web-based registry of newly diagnosed pediatric IBD patients in Europe and Israel, established by the IBD Working Group of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). The enrolment

of patients into the registry began in May 2004. During the first 5 years, the registry has extended to allow inclusion of patients (aged 0 – 18 years) from 44 centers in 18 countries. Details on the establishment of the registry and data collection have been previously reported.[10] The number of pediatric IBD patients registered by the different centers varied considerably (range 4 – 206), which was caused by differences in center size, as well as differences in number of years that centers participated in the registry. Most centers (64%) participated less than 5 years in the EUROKIDS registry. Patient data were entered into the web-based registry by different members of the medical team, varying from (fellow) pediatric gastroenterologists, pediatricians, and/or research nurses. Before they were authorized to enter patient data into the system, several training sessions were given by the local investigator, who is a member of the Porto IBD Working Group of ESPGHAN. All data for this study were collected and analyzed by two researchers (CdB and JCE). To guarantee good quality of the data, there were training sessions for the persons who were responsible for data-entry. Additionally, as of 2004, there were two meetings of the EUROKIDS Porto IBD Working Group of ESPGHAN per year, in which issues on data-entry were discussed. Thirdly, regular individual feedback and queries on incorrect data were given by two researchers (JCE, CdB).

Participating centers were all committed to perform a diagnostic workup of their patients (who were suspected of having IBD) according to the Porto criteria.[11] This implies that in all patients, ileocolonoscopy and UGI endoscopy needed to be performed, as well as imaging of the small bowel (except in patients with a definitive diagnosis of typical UC). In clinical practice, 80% of UC patients underwent UGI endoscopy at diagnosis, 94% colonoscopy, and 69% ileocolonoscopy.[10] Small bowel imaging (small bowel follow-through, MRI, CT abdomen, and/or capsule endoscopy) was performed in 41% of UC patients.

Also according to the agreed Porto criteria, participating centers were expected to take at least two biopsies from each segment of the gastrointestinal tract (esophagus, stomach, duodenum, terminal ileum, and all six segments of the colon), and were required to register the endoscopic and histologic findings from each segment separately. Each segment visualized by ileocolonoscopy could be registered as macroscopically "normal" or "abnormal", and histologically "normal" or "abnormal" (see section on *Definitions*). Information on the presence or absence of granulomas was registered from year 2 onwards. The number of biopsies taken from each segment was not registered in the database. Results from UGI endoscopy were reported in a similar fashion. Macroscopic esophagogastroduodenal findings were classified as "normal" or "abnormal" in the first 3 years of the registry, whereas additional information on the type of macroscopic abnormality was registered in years 4 and 5 only (see section on *Definitions*).

Ethics committee permission was obtained in the United Kingdom, Sweden and Poland. In the other countries, a Statement of No Objection was released by the local ethics committees, because data were anonymously collected.

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Eligibility

As previously described[10], 2087 newly diagnosed pediatric IBD patients who were diagnosed between May 2004 and April 2009, were correctly registered in the database. For this study, we identified all patients who were classified as having UC. Exclusion criteria were: a diagnosis of CD or IBD-U, no information on sigmoidoscopy or colonoscopy, and disease characteristics precluding a diagnosis of UC as per the recent Paris classification (i.e. macroscopically normal appearing rectum with normal rectal biopsies, microscopically normal appearing skip lesions, macroscopic ileitis in the presence of a normally looking cecum, and presence of granulomas in biopsies, or multiple or serpiginous ulcers in the UGI tract).[8]

Definitions

A diagnosis of UC was made according to the discretion of the investigator/treating physician, and was based on clinical presentation, physical examination, endoscopic appearance, and histologic findings.

The period (in months) between the first onset of IBD symptoms and IBD diagnosis date was represented by the diagnostic delay.

Macroscopic disease extent was categorized according to the Paris classification[8] by two researchers (CdB and JCE): (E1) proctitis only; (E2) left-sided colitis, defined as inflammation distal to the splenic flexure; (E3) extensive colitis, defined as inflammation proximal to the splenic flexure but distal to the hepatic flexure; and (E4) pancolitis, defined as inflammation extending proximal to the hepatic flexure. Disease location was determined by endoscopic appearance only, which required evaluation of the colon beyond the transitional zone between normal and inflamed mucosa. Definitions for "normal" or "abnormal" ileocolonoscopy and histology have been extensively discussed in several meetings of the EUROKIDS Porto IBD Working Group of ESPGHAN. From these discussions, a preliminary consensus on endoscopic and histologic criteria for pediatric IBD was outlined that will be the basis for the revised Porto criteria (manuscript in preparation). In UC, abnormal macroscopic features that can be found during colonoscopy are erythema, granularity, friability, mucopus and ulcerations (usually superficial small ulcerations).

Rectal sparing was defined as a rectum with a normal appearance during endoscopy and with abnormal histology. Abnormal histology in UC may consist of chronic inflammation, cryptitis, crypt abscesses, architectural distortion, and basal lymphoplasmacytosis. The term backwash ileitis required the presence of pancolitis involving the cecum, and was used to describe an abnormal endoscopic appearance of the terminal ileum felt to be consistent with the diagnosis of UC (i.e. erythematous or granular appearance).

In accordance with the Paris classification[8], we defined involvement of the UGI tract as the presence of ulcerations, aphthous ulcerations, or erosions. The presence of an erosion (superficial mucosal break) or ulceration was defined by the endoscopist. Other findings

(such as mucosal erythema, edema, granularity, and/or nodularity) were considered as non-specific, and were not included in the analysis of UGI involvement.

Statistical analysis

Data were analyzed in SPSS (version 17.0, SPSS, Inc., Chicago, IL, USA).

Descriptive statistics were calculated as percentages for discrete data. Continuous variables were presented as means and standard deviations (SD) if normally distributed, otherwise as medians and interquartile ranges (IQR). The two-sample t-test, the Wilcoxon rank-sum test, and the Kruskal-Wallis test were used to compare continuous variables, as appropriate for the data normality and number of contrasting groups. For comparisons of proportions, we used the Pearson chi-square analysis or Fisher's exact test, as appropriate. A logistic regression model was constructed with the presence of rectal sparing as the dependent variable, and other clinical and demographic factors as the explanatory variables. The model was assessed using c-statistics. Results were expressed as odds ratios (ORs) and 95% confidence intervals (CIs). Statistical significance was defined as a two-tailed P-value < 0.05. To calculate positive predictive values (PPVs) of rectal sparing and UGI involvement in diagnosing UC, we included the pediatric CD patients in the EUROKIDS registry presenting with an UC-like phenotype. In this way, we were able to determine the likelihood of diagnosing UC when rectal sparing or UGI involvement is present in a new pediatric patient presenting with a chronic colitis characteristic of IBD. For determining the incidence of rectal sparing in the pediatric CD cohort, we selected consecutive patients who had information available on the endoscopic and histologic aspect of the rectum, and presented with colonic inflammation without endoscopic abnormalities in the terminal ileum and/or evidence of granulomas in colonic and terminal ileal biopsies. For the incidence of UGI involvement in the pediatric CD cohort, we used the following selection criteria: a diagnosis of CD in year 4 or 5 of the registry, performance of UGI endoscopy, information on the type of macroscopic abnormality in the UGI tract, and presence of colonic inflammation without endoscopic abnormalities in the terminal ileum and/or evidence of granulomas in biopsies of the gastrointestinal tract. The reference standard for diagnosing UC or CD was based on the diagnosis made by the treating physician, who relied on a combination of clinical presentation, physical examination, endoscopic appearance, and histologic findings. Results were expressed as sensitivities and PPVs with 95% CIs. Specificities and negative predictive values were not calculated, as we aimed to determine the diagnostic value of the presence of atypical disease patterns in diagnosing UC.

RESULTS

Patient characteristics

Between May 2004 and April 2009, 670 of 2087 (32%) newly diagnosed pediatric IBD patients were classified as having UC. Figure 1 displays a flowchart of the UC patients fulfilling the different eligibility criteria. In the cohort of 643 patients, mean age at diagnosis was 11.6 years (± 4.0; range 0.6 – 17.9), with 50% (n=319) being male. The diagnostic delay was median 3.0 months (IQR 1.9 – 7.9).

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Ulcerative colitis cohort
(n=670)

Concerns on the validity of the diagnosis
(n=23)

10   Macroscopic and microscopic
     rectal sparing
8   Microscopically normal
     appearing skip lesions
4   Ileitis and a normal cecum
1   Granulomas in colonic biopsies

Missing information on
colonoscopy (n=4)

Study Cohort (n=643)

No endoscopic evaluation beyond the
transitional zone between normal and
inflamed mucosa (n=59)

36   Inflammation until descending colon
23   Inflammation until transverse colon

Histologic abnormalities
only (n=6)

Paris classification (n=578)

Analyses rectal sparing
Data on endoscopy and
histology of rectum (n=553)

Analyses backwash ileitis
Data on ileoscopy in patients
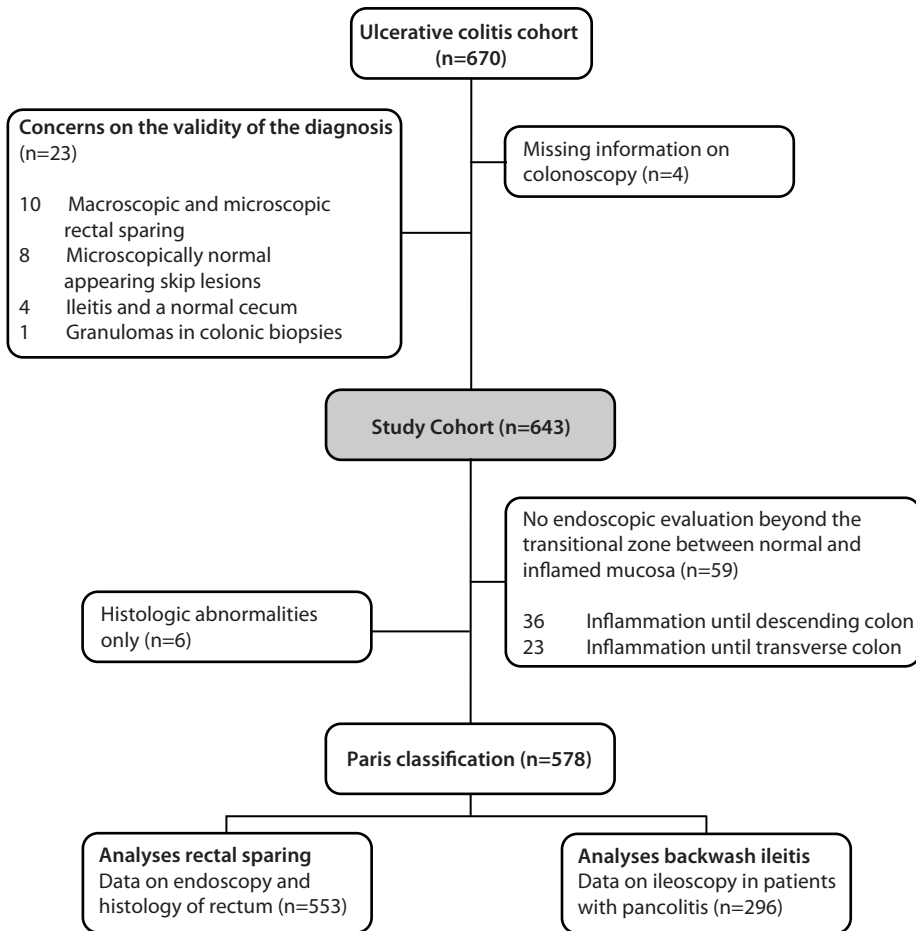with pancolitis (n=296)

Figure 1 | Flowchart of pediatric ulcerative colitis patients selected for the analyses on disease location, rectal sparing, and backwash ileitis.

Macroscopic and microscopic disease extent in the colon

Macroscopic disease extent according to the Paris classification could be determined in 578 (90%) patients (Figure 1). Proctitis (E1) was seen at presentation in 5% of patients (n=27), left-sided colitis (E2, distal to the splenic flexure) in 18% of patients (n=104), extensive colitis (E3, distal to the hepatic flexure) in 9% of patients (n=50), whereas pancolitis (E4, proximal to the hepatic flexure) occurred in the majority of patients (69%, n=397). Endoscopic involvement of the cecum, consistent with a cecal patch, was present in 11 patients (2%): two (7%) patients with proctitis, seven (7%) patients with left-sided colitis, and two (4%) patients with extensive colitis.

Figure 2 displays the disease distribution according to age at diagnosis. Patients with proctitis had a mean age at diagnosis of 13.4 years (±3.4, range 6.1 – 17.9), which was significantly older than patients with left-sided colitis (mean 11.8 years, p=0.04), extensive colitis (mean 11.0 years, p=0.01), and pancolitis (mean 11.5 years, p=0.02). There were no significant differences in age at diagnosis between the other disease locations.

The gender distribution between patients with extensive colitis and pancolitis was significantly different (p=0.004), with males being more likely to have pancolitis (73% vs. 65%) than extensive colitis (5% vs. 12%). This is probably a statistical finding of clinical insignificance due to the large sample size of the cohort.

There were no significant differences in diagnostic delay between the four disease locations (p=0.70). In all four groups, the median diagnostic delay was 3 months (IQR 2 – 8).

In 478 patients, information on biopsies of all six segments of the colon (cecum, ascending colon, transverse colon, descending colon, sigmoid, and rectum) was available. There were 69 patients (14%) in which microscopic disease extent was more extensive than macroscopic disease.

Rectal sparing

In 553 (96%) pediatric UC patients who could be classified according to the Paris classification, information on the endoscopic and histologic aspect of the rectum was available (Figure 1). Macroscopic rectal sparing was present in 28 (5%) of these patients.

Characteristics of pediatric UC patients with and without rectal sparing are shown in Table 1. Patients with rectal sparing were significantly younger at diagnosis than patients without rectal sparing (9.9 years±4.3 vs. 11.8 years±3.9, p=0.02). Patients with extensive colitis or pancolitis were more likely to have rectal sparing than patients with left-sided colitis (6% (27/428) vs. 1% (1/98), p=0.04). After controlling for gender (males: OR 1.7, 95% CI 0.77 to 3.7, p=0.20) and disease extent (E3 or E4: OR 6.2; 95% CI 0.82 to 46.0; p=0.08) in a logistic regression model, age at diagnosis continued to be a significant predictor of rectal sparing (OR 0.91; 95% CI 0.84 to 0.99; p=0.03; c-statistic = 0.68).
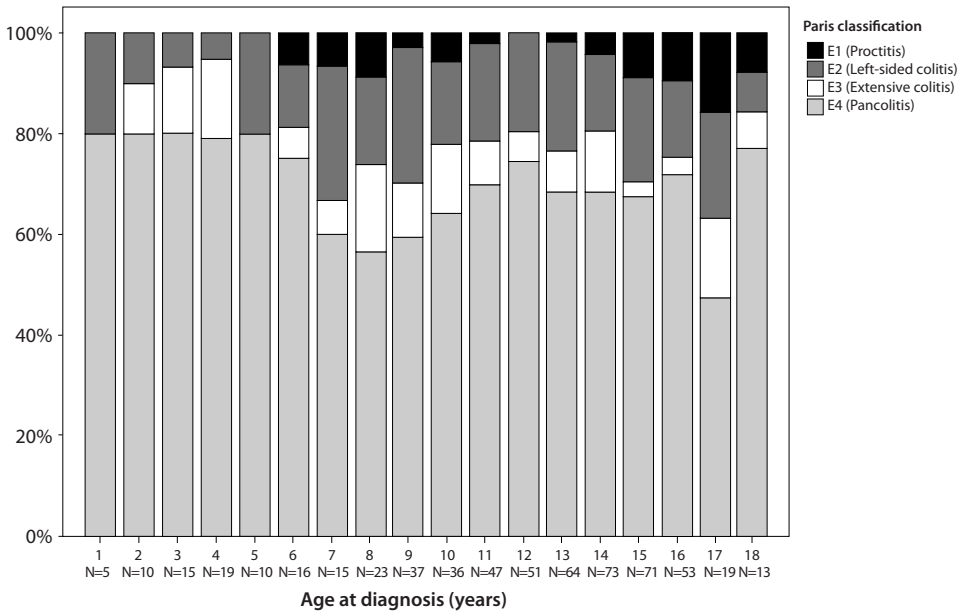
Figure 2 │ Disease location in newly diagnosed pediatric ulcerative colitis patients according to age at diagnosis.

Table 1 │ Characteristics of newly diagnosed pediatric ulcerative colitis patients with and without macroscopic rectal sparing.

	Rectal sparing (n=553)		
	Present (n=28)	Absent (n=525)	P-value
Gender (male)	17 (61%)	251 (48%)	0.24
Age at diagnosis (yr)	9.9 (4.3)	11.8 (3.9)	0.02
Diagnostic delay (months)	6.0 (2.2 – 10.8)	3.0 (1.9 – 7.1)	0.07
Disease location, no.			
Left-sided colitis (E2)	1 (4%)	97 (20%)	0.09[A]
Extensive colitis (E3)	4 (14%)	43 (9%)	
Pancolitis (E4)	23 (82%)	358 (72%)	

[A]P = 0.04, when combining E3 and E4.
Counts (%), means (standard deviation), or medians (interquartile range) are presented according to the distributional normality as appropriate.

Backwash ileitis

Among 397 UC patients with pancolitis, information regarding the endoscopic appearance of the terminal ileum was available in 75% (n=296). Thirty (10%) of these patients had macroscopic abnormalities in the terminal ileum. Backwash ileitis was more frequently seen in males than in females (14% (22/160) vs. 6% (8/136), p=0.03). No significant differences were found in age at diagnosis and diagnostic delay.

Involvement of the UGI tract

In total, 80% (535/670) of all patients initially classified as UC underwent UGI endoscopy. In years 4 and 5 (i.e. the years in which the type of inflammation was documented), this percentage was 86% (260/303). In total, 11 (4%) patients diagnosed in years 4 and 5 had UGI involvement (manifesting as ulcerations or erosions), of whom only 2 (0.8%) had ulcerations in the esophagus or duodenum (Table 2). Additionally, only one of the nine children with gastric involvement had ulcerations, whereas all others had erosions. The centers, in which the 11 UC patients with UGI involvement were diagnosed, were contacted for additional information on H. Pylori status and current type of IBD. All patients were H. Pylori negative, as assessed by histology. Additionally, there had been no changes in diagnosis from UC to CD during a minimum of two years of follow-up.

Table 2 | Involvement of the upper gastrointestinal tract (i.e. erosions or ulcerations) in pediatric patients presenting with an isolated colitis.

	Ulcerative colitis (n=260)	Crohn's disease (n=86)
UGI not involved	249 (96%)	67 (78%)
UGI involved	11 (4%)*	19 (22%)*
Esophagus	1	2
Stomach	8	4
Duodenum	1	6
Esophagus and stomach	0	3
Stomach and duodenum	1	3
All three segments	0	1

*P<0.001
UGI: upper gastrointestinal tract.

Positive Predictive Values (PPVs)

By including data on the incidence of rectal sparing and UGI involvement in pediatric CD patients presenting with an UC-like phenotype, we were able to calculate PPVs for these two primary atypical phenotypes. In children with Crohn's colitis who met all eligibility criteria, rectal sparing was seen in 20 of 255 (8%) children. The calculated PPV based on these figures

was 58% (28/48; 95% CI 44% to 72%), which means that given the presence of rectal sparing in a child with colitis, UC may still exist in 58% of cases.

UGI involvement (defined as presence of ulcerations, aphthous ulcerations, erosions, cobblestoning, and/or stenosis) was present in 22% (19/86, Table 2) of pediatric CD patients who met all eligibility criteria. The PPV of UGI involvement in diagnosing UC was 37% (11/30; 95% CI 19% to 54%), while the PPV of erosions and ulcerations limited to the esophagus/duodenum only was 25% (2/8; 95% CI 0 to 55%).

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DISCUSSION

Accurate phenotyping and classification is essential in IBD, as this affects both medical and surgical management of the individual patient. Conversely, misclassification may have significant repercussions and lead to poor outcomes. We have tried to provide more clarity regarding the prevalence of macroscopic phenotypes by applying the Paris classification to the raw data in a large cohort at diagnosis, using well defined criteria, even though any large registry dataset has its limitations.

Age of onset has also been shown to affect phenotypes in both pediatric CD and UC, requiring larger focused datasets to provide the evidence for classification, which is a prerequisite for investigating the natural history of pediatric-onset IBD.[2, 8] Use of general anesthesia and UGI endoscopy has become a standard of care in the evaluation of pediatric IBD. This has lead to increasing rates of ileal intubation and successful UGI endoscopy in pediatric patients, as recommended by the Porto criteria.[11] In the EUROKIDS cohort, 87% of CD and IBD-U patients had adequate imaging of the small bowel, while the use of MRE increased from 9% in 2004/2005, through 30% in 2006/2007, to 50% in 2008/2009.[10] Reflecting these trends, the gold standard for IBD classification has also changed from the Vienna statement[12], through the Montreal classification[13], to the recent pediatric Paris classification.[8]

The increasing diagnostic accuracy has placed a challenge on the classic definition of UC (i.e. continuous inflammation from the anus confined to the colon). Increasing numbers of publications suggest that macroscopic rectal sparing, macroscopic skip lesions in the colon, mild cecal inflammation (i.e. cecal patch), mild limited ileitis in the presence of pancolitis (backwash ileitis), and limited UGI inflammation, do not necessarily preclude the diagnosis of UC at disease-onset.[11, 14-15] However, previous publications did not provide standardization, sensitivity, specificity and predictive values which are essential in determining the value of a variable in diagnosing a disease state. Moreover, most previous studies are small, retrospective, suffer from referral bias, and report ambiguous definitions of macroscopic or microscopic involvement, mainly due to the retrospective nature of the studies (e.g. some report only ulcerations, some non-specific inflammation, and some only histologic abnormalities).

The current manuscript is unique in several ways. This is the largest pediatric UC cohort to evaluate atypical phenotypic variables in UC and it is based on prospectively collected predefined data representing a wide spectrum of centers and countries. The rectal and UGI involvement has been robustly defined, and UGI involvement has been classified so that non-specific inflammation without erosions or ulcerations has been excluded. Moreover, the UGI tract has been separated into segments, to allow separate evaluation of the esophagus and duodenum which are much less frequently involved in UC.

Our data confirm the high proportion of children with extensive disease (78%) which was inversely correlated with age, and the rarity of proctitis (5%) at diagnosis, in accordance with the published literature.[2, 8]

Some findings in the UGI tract are clearly incompatible with the diagnosis of UC, including extensive ulcerations, serpentine deep ulcers, and the presence of granulomas. As found here, erosions and ulcerations may be present in 4% of pediatric UC cases at diagnosis anywhere in the UGI tract, and only in 0.8% in the esophagus or duodenum. Nevertheless, the presence of frank ulcerations, especially in the esophagus and duodenum, while insufficient to preclude the diagnosis of UC, should lead to careful evaluation of other atypical manifestations that may assist in reaching the correct diagnosis.

Similarly, macroscopic rectal sparing was demonstrated in 5% of our UC cases, and importantly, was inversely correlated with age. In previous publications, macroscopic rectal sparing was common, reaching 10 – 30%.[3-5, 16-18] These high rates may have been reflected by inclusion of younger patients, partially treated disease, or selection bias of colectomy series, since rectal sparing has been reported to be more refractory to medical therapy.[16] The lower rate of 5% found here may be explained by the fact that all our children were evaluated before therapy was initiated, and patients with microscopic rectal sparing were reclassified as IBD-U. It must be emphasized that per definition of the Paris classification, *microscopic* rectal sparing precludes the diagnosis of UC and prompts the diagnosis of IBD-U or CD.

Irrespective if one uses a clinical or statistical approach with PPV (the PPV for diagnosing UC versus Crohn's colitis using rectal sparing without granulomas as the sole criteria is as high as 58%), it is clear that if rectal sparing is present in 5% of children with UC at diagnosis, rectal sparing as an isolated atypical finding should not automatically preclude the diagnosis of UC.

Backwash ileitis has been reported in 6 – 20% of UC patients with pancolitis[17, 19-22], and 10% in our study. The severity of ileal inflammation correlates with the degree of inflammation in the colon.[20-21] In children, 16 of 76 those with pancolitis (22%) had backwash ileitis over a 5-year follow-up period.[23] However, this cohort represents the severe end of the spectrum and thus selection bias may have overestimated the prevalence of backwash ileitis. Indeed, in another pediatric study, only 4/30 (13%) children had backwash ileitis[16], similar to our findings.

Our data, while bringing clarity into recognition of atypical phenotypes, do not provide data about the natural history of rectal sparing in UC. Rectal sparing in UC has been associated in small studies with refractory disease and primary sclerosing cholangitis (PSC).[16, 24-25] This may be due to a different pathogenesis (association with an autoimmune phenomenon such as PSC), an age-related phenomenon that precludes rectal involvement, or lack of efficacy with topical therapy if rectal involvement is absent. In adults, PSC-associated IBD is clearly associated with rectal sparing. In the study by Loftus et al., rectal sparing was present in 52% vs. 6% with typical UC.[24] In children, this topic has not been studied sufficiently. The study by Rajwal et al., which described a high prevalence of autoimmune phenomena and intractability in rectal sparing, involved only 7 children with rectal sparing.[16] By increasing awareness and recognition of this previously described phenotype, we hope that patients will not be reclassified based solely on this finding, while allowing researchers to accurately document and further investigate the clinical significance of rectal sparing.

Our study has certain limitations. First of all, EUROKIDS is not a population-based registry, but a selection of centers and pediatric gastroenterologists with a special interest in IBD. This has probably resulted in some selection bias. However, ESPGHAN recommends that all children with a suspicion of IBD should be referred to a pediatric gastroenterologist for diagnostic workup.[11] Consequently, the majority of the participating centers diagnoses and treats all pediatric IBD patients in their region; only five centers have reported that they treat only the most severe IBD cases (12% in this study) and four centers have a mixed population of "regular" IBD patients and severe IBD cases (8% in this study).
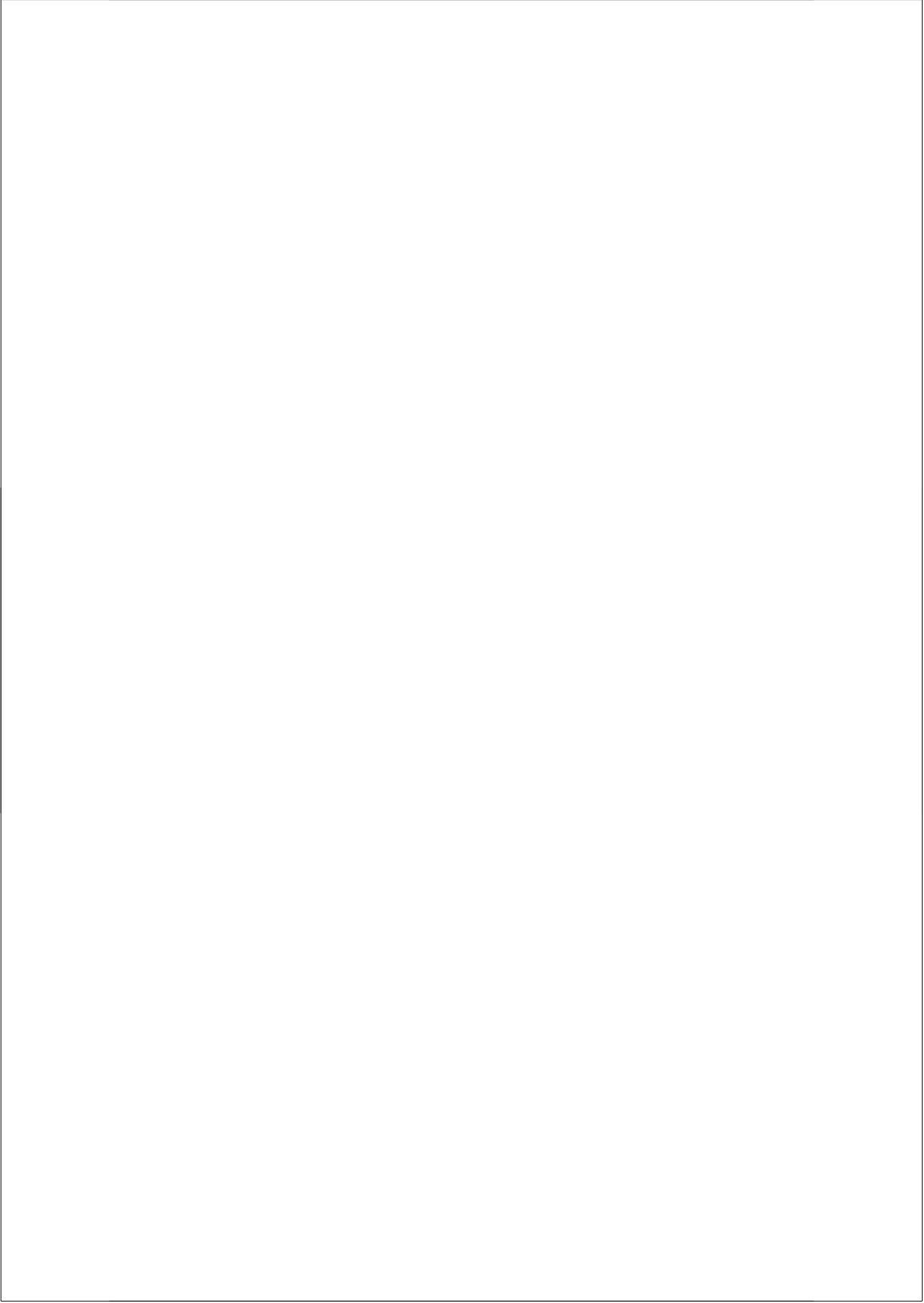
Other possible limitations of this study are the lack of follow-up, lack of registered details regarding histology, and risk of inter-observer variation regarding interpretation of endoscopic and histologic findings, which are limitations in all large cohort multicenter registries. There may have been bias to exclude patients who could not be defined as UC or CD, this type of selection bias will always be true at diagnosis since IBD-U is most prevalent at diagnosis. We do not have natural history data for UC in the Paris classification era, which would greatly enhance our ability to categorically define IBD phenotypes. However, we believe that this is compensated for by predetermined standardization and definitions in a very large well defined cohort using the recent Paris classification. Our goal was confined to definition of these phenotypes only at disease-onset, and to define the role of age of onset on these phenotypes, as accurate initial classification is important for treatment decisions. Growing evidence suggests that pediatric UC and CD are challenging to treat, as has been recently highlighted in a cohort of new-onset pediatric UC patients.[26]

Epidemiological data about the frequency of atypical phenotypic characteristics in early-onset UC (e.g. extent of inflammation) are essential for providing evidence-based classification schemes. The findings of this large multicenter prospective study, which demonstrate the effect of age of onset on phenotype, and the prevalence of atypical phenotypes along, will serve as a basis for the diagnosis and subsequent treatment of pediatric-onset UC.

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4

C h a p t e r

5

Assessment of height and BMI in newly diagnosed European pediatric IBD patients using World Health Organization and national growth references

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ABSTRACT

Objectives
Growth abnormalities and malnutrition are important elements of disease phenotype in pediatric inflammatory bowel disease (IBD). We aimed to assess height and BMI in a European cohort of new-onset pediatric IBD patients by using different growth references. Additionally, we determined associations between disease location and height and BMI.

Methods
Information was collected from the EUROKIDS registry, a prospective registry of new-onset pediatric IBD patients in 18 countries. Height and BMI were analyzed in Crohn's disease (CD) patients who underwent a complete diagnostic workup, and in ulcerative colitis (UC) patients who underwent colonoscopy. The WHO growth reference and national growth references were used to determine standard deviation scores (SDS).

Results
459 CD (age 12.8±3.1 years) and 475 UC patients (age 11.9±3.6 years) met eligibility criteria. In CD, mean height-for-age SDS was -0.11 (95% CI -0.21 to -0.001) according to the WHO growth reference, and -0.39 (95% CI -0.49 to -0.28) according to national growth references. BMI-for-age SDS were -0.76 (95% CI -0.90 to -0.62) and -0.82 (95% CI -0.96 to -0.68), respectively. CD patients had lower mean height and BMI-for-age SDS than UC patients (-0.12 and -0.40 SDS respectively; both *P*<0.001). In UC, the presence of pancolitis was negatively associated with height (*P*=0.02) and BMI (*P*=0.001), while there was no significant effect of disease location in CD.

Conclusion
The use of different growth references has an important effect on the anthropometric assessment of a European cohort of pediatric IBD patients. Disease location only affects height and BMI in UC, not in CD patients.

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INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) may present during childhood or adolescence in up to 10 – 20% of all patients with inflammatory bowel disease (IBD).[1-2] Unique to pediatric-onset IBD is linear growth impairment, which has been attributed to a complex interaction between nutritional status, inflammation, disease severity, and genotype.[3-5]

Impaired growth may be the first sign of pediatric IBD and may start several years before the onset of gastrointestinal symptoms.[6-7] Growth failure at diagnosis has been reported in 10 – 40% of pediatric CD patients[8-13], and to a much lesser extent in UC patients.[7,9,11,14] Malnutrition is seen in 14 – 32% of newly diagnosed pediatric CD patients[7,11-13,15], and 5 – 9% of children with UC.[7,11,15] Variation in the reported prevalence of growth failure and malnutrition could partly be attributed to differences in definitions, age of included patients, and/or study population.[16]

Previous studies on pediatric CD have identified potential clinical factors that affect height, such as the interval from onset of symptoms until time of diagnosis (diagnostic delay)[10-11], disease severity[8-9,12], and disease location. Involvement of the terminal ileum has been associated with a higher risk of growth retardation in some studies[12,17], but this association was not found in other studies.[8,11,13] Additionally, pediatric CD patients with jejunal disease activity were demonstrated to have a significantly reduced stature, but this effect disappeared in multivariable analysis.[11] Other studies did not find an effect of upper gastrointestinal disease on growth.[12-13]

Growth charts are essential for evaluating growth in children. Numerous growth reference charts are available worldwide[18], but assessing height and nutritional status in multicenter European studies remains a challenge.[19] National growth reference charts are available for several European countries[20-31], but the methods used to construct these charts vary considerably. Alternatively, international growth standards and references based on global samples of children have been developed by the World Health Organization (WHO).[32-33] By using data from a large cohort of newly diagnosed pediatric IBD patients recruited from an European registry (EUROKIDS registry), we therefore aimed to: 1) assess height and body mass index (BMI) in newly diagnosed pediatric CD and UC patients, by using the WHO growth reference as well as national growth references; 2) determine the association between height and BMI and disease location in a cohort of newly diagnosed pediatric CD and UC patients who could be classified according to the Paris classification.[34] This recent pediatric modification of the Montreal classification enables a more precise phenotypic classification of disease location.

METHODS

EUROKIDS registry

The EUROKIDS registry is a prospective, web-based registry of newly diagnosed pediatric IBD patients in Europe and Israel, established by the Porto IBD Working Group of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). The enrolment of patients into the registry began in May 2004. During the first 5 years, the registry has extended to allow inclusion of patients (aged 0 – 18 years) from 44 centers in 18 countries. Details on the establishment of the registry and data collection have been previously reported.[35-37]

Ethics committee permission was obtained in the United Kingdom, Sweden and Poland. In all other countries, a Statement of No Objection was released by the local ethics committees, because data were anonymously collected.

Eligibility

As previously described[35], 2087 newly diagnosed pediatric IBD patients who were diagnosed between May 2004 and April 2009, were registered in the database. For this study, we selected the CD patients who had a complete workup according to the Porto criteria[38], and in whom disease location could be assessed according to the Paris classification.[34] Characteristics of this selected patient cohort have been previously reported.[36] In the UC cohort, we selected the patients who underwent endoscopic evaluation beyond the transitional zone between normal and inflamed mucosa, which enabled categorization according to the Paris classification.[37] In both the CD and UC cohorts, patients from Croatia, Hungary, Israel, Latvia, Portugal, and Slovenia were excluded from the analyses, as national growth reference data were not available or could not easily be converted to standard deviation scores (SDS).

Height and BMI

In all participating centers, height was measured on a wall-mounted stadiometer by a trained nurse or clinician. Height and BMI were converted to SDS using two different methods:

1) *WHO Anthro* (version 3.0.1) and *WHO AnthroPlus* (version 1.0.2) software was used to calculate height-for-age and BMI-for-age SDS of all eligible pediatric CD and UC patients. This software was developed to facilitate the application of the WHO Child Growth Standards (0 – 5 years) and Growth Reference for school-aged children and adolescents (5 – 19 years), respectively. The Growth Standards are a result of the Multicenter Growth Reference Study (MGRS), conducted by the WHO. The MGRS harbors growth data from approximately 8,500 children (aged 0 – 5 years) from six countries with various ethnic backgrounds and cultural settings (Brazil, Ghana, India, Norway, Oman and the USA).[32] The Growth Reference is a reconstruction of the 1977 National Center for Health Statistics (NCHS)/WHO reference which was based on three data sets from the USA (n=22,917).[33]

2) *National growth references* were used to calculate height-for-age SDS and, when available, BMI-for-age SDS of children from Belgium[20], the Czech Republic[21], Denmark[22], France[23], Germany[24], Greece[25], Italy[26], the Netherlands[27], Norway[28], Poland[29], Sweden[30], and the United Kingdom.[31] Polish growth reference data were not available for children < 7 years of age, and the same applied for Italian patients < 2 years of age. Additionally, we did not have access to BMI reference data for children from Denmark, France, Greece, Norway and Sweden. Height and BMI-for-age SDS were calculated by Growth Analyzer software (version 3.0 and 4.0, Dutch Growth Foundation). These national growth references were constructed with data from large cross-sectional and longitudinal studies carried out between 1953 and 2010.

Growth retardation was defined as height-for-age ≤ -1.96 SDS, and malnutrition as BMI-for-age ≤ -1.96 SDS. Using these definitions, 2.5% of the general population was expected to be growth retarded or malnourished.

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Definitions disease location

Disease location was determined by the endoscopic appearance of the gastrointestinal mucosa and radiologic involvement of the small bowel, not by microscopic findings. In CD, we divided disease location into four dichotomous variables: involvement of the colon, involvement of the terminal ileum, involvement of the jejunum/proximal ileum, and involvement of the esophagus/stomach/duodenum. This latter variable was defined as the presence of ulcerations, erosions/aphthae, cobblestones and/or stenosis. The presence of mucosal erythema, edema, granularity, and/or nodularity was not sufficient to be considered evidence of upper gastrointestinal involvement. Additionally, we categorized disease location according to the Paris classification[34]: (L1) involvement of the terminal ileum only, with limited or no cecal disease; (L2) colonic involvement only; (L3) involvement of both the terminal ileum and colon; and (L4) isolated upper gastrointestinal disease, defined as macroscopic and/or radiologic abnormalities proximal to the terminal ileum.

In UC, disease location was dichotomized into the presence or absence of pancolitis. Pancolitis was defined as inflammation extending proximal to the hepatic flexure.

Statistical analysis

Data were analyzed in SPSS (version 17.0, SPSS, Inc., Chicago, IL, USA).

Descriptive statistics were calculated as percentages for discrete data. Continuous variables were presented as means and standard deviations (SD) if normally distributed, and as medians and interquartile ranges (IQR) if not normally distributed.

For both methods used to calculate height/BMI-for-age SDS, mean values, 95% confidence intervals (CI), and the proportion of CD and UC patients with height/BMI-for-age ≤ -1.96 SDS, ≤ -0.99 SDS, or ≤ 0 SDS were determined. Binomial tests were used to examine whether height and BMI percentile distributions of pediatric IBD patients differed from

the distribution in the general population. Differences in mean SDS and rates of growth retardation and malnutrition between CD and UC patients were assessed by two-sample t-tests, and Fisher's exact tests, respectively. Multivariable linear regression models were constructed with height/BMI-for-age SDS as the dependent variable to investigate associations with disease location, after adjustment for age, gender, diagnostic delay, and country. P-values < 0.05 were considered statistically significant.

RESULTS
CD cohort
A flowchart of the eligible CD population is presented in Figure 1, and their baseline characteristics are displayed in Table 1.
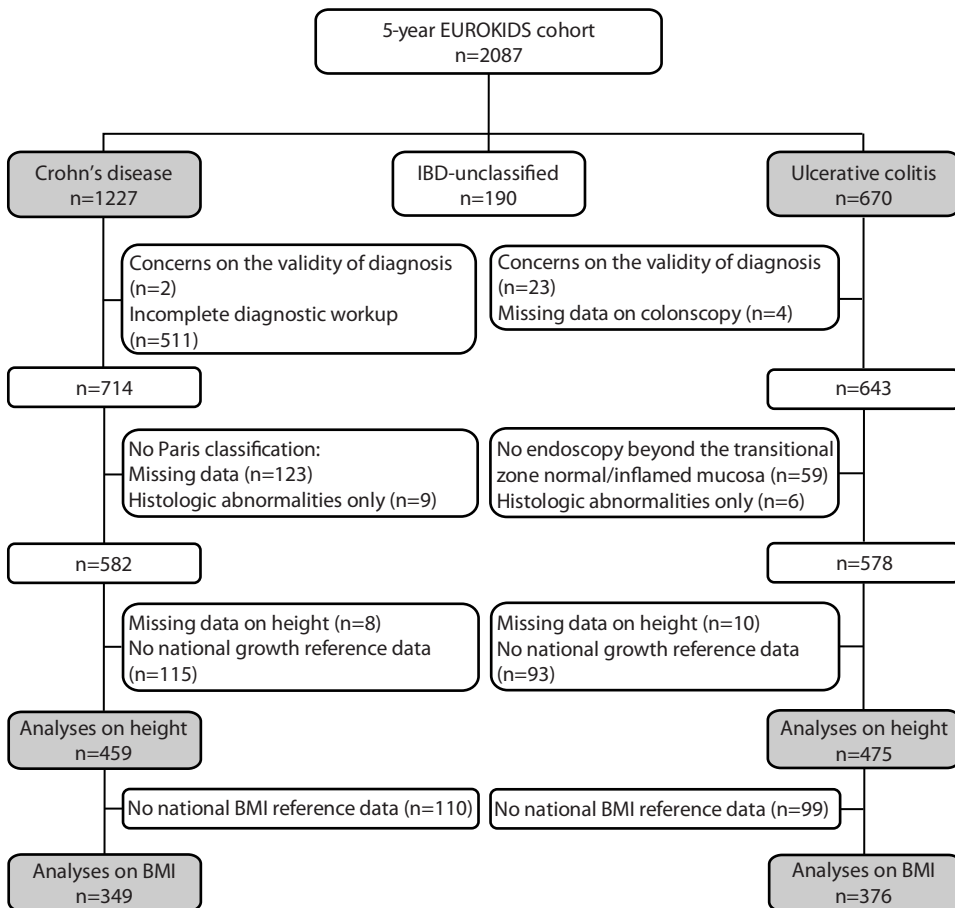

Figure 1 | Flowchart of the pediatric Crohn's disease and ulcerative colitis patients selected for the analyses on height and BMI.

Table 1 | Baseline characteristics of newly diagnosed pediatric Crohn's disease and ulcerative colitis patients.

	Crohn's disease N=459	Ulcerative colitis N=475
Age at diagnosis (yr), mean (SD)	12.8 (3.1)	11.9 (3.6)
Delay in diagnosis (mo), median (IQR)	5 (3 – 10)	4 (2 – 8)
Gender (male)	278/459 (61%)	233/475 (49%)
Ethnicity (White European)	408/458 (89%)	422/471 (90%)
Family history of IBD in 1st degree relatives	36/450 (8%)	39/460 (9%)
Extraintestinal manifestations	102/443 (23%)	51/467 (11%)
Disease location		
L1 (terminal ileal disease, ±cecal disease)	75/459 (16%)	
L2 (colonic disease)	129/459 (28%)	
L3 (ileocolonic disease)	243/459 (53%)	
L4 (isolated upper GI disease)	12/459 (3%)	
L4A (esophagogastroduodenal disease)	130/459 (28%)	
L4B (jejunal/proximal ileal disease)	114/459 (25%)	
E1 (proctitis)		18/475 (4%)
E2 (left-sided colitis)		85/475 (18%)
E3 (extensive colitis)		41/475 (9%)
E4 (pancolitis)		331/475 (70%)
Perianal disease	42/455 (9%)	NA

IQR: interquartile range. IBD: inflammatory bowel disease. GI: gastrointestinal. NA: not applicable.

At diagnosis, mean height-for-age SDS was -0.11 (95% CI -0.21 to -0.001) according to the WHO growth reference, and -0.39 (95% CI -0.49 to -0.28) according to national growth references (Figure 2). Differences in mean SDS per country, according to the reference method used, are displayed in Figure 3. In most European countries, mean height-for-age SDS based on national growth references were lower than those based on the WHO growth reference, except for children from France, Denmark, and the United Kingdom. Consequently, the proportion of pediatric CD patients presenting with growth retardation (height ≤ -1.96 SDS) was higher using national growth references (9%) than the WHO growth reference (5%). Additionally, the proportions of children whose height-for-age were ≤ -0.99 SDS (31%) or ≤ 0 SDS (62%), were highest when national growth references were used (Table 2).

BMI-for-age SDS could be determined in 349 pediatric CD patients (Figure 1). Mean BMI-for-age SDS was -0.76 (95% CI -0.90 to -0.62) according to the WHO growth reference, and -0.82 (95% CI -0.96 to -0.68) according to national growth references (Figure 2). When analyzed per country, differences between the growth references were relatively small, except for Italy and the Netherlands (Figure 3). The malnutrition rate (BMI ≤ -1.96 SDS) was 17% according to the WHO growth reference, and 18% according to national growth references (Table 2).
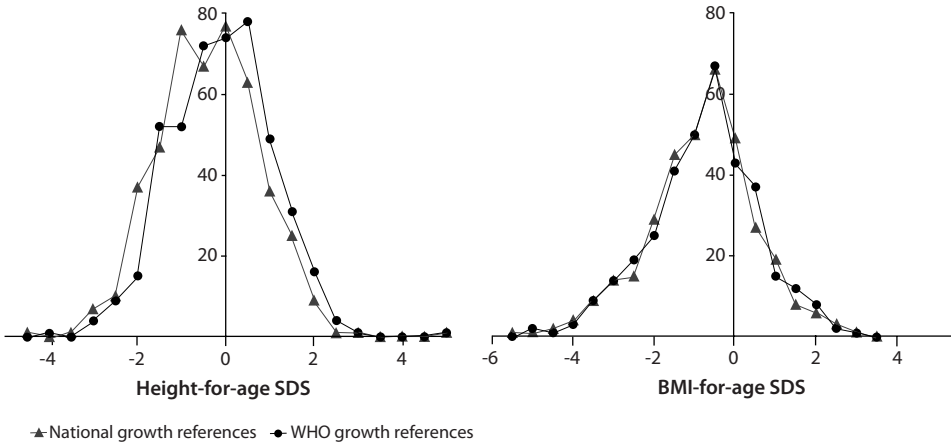
Figure 2 | Mean height-for-age SDS distribution (n=459) and BMI-for-age SDS (n=349) distribution in newly diagnosed pediatric Crohn's disease patients according to the WHO growth reference and national growth references of 11 and 6 European countries, respectively.
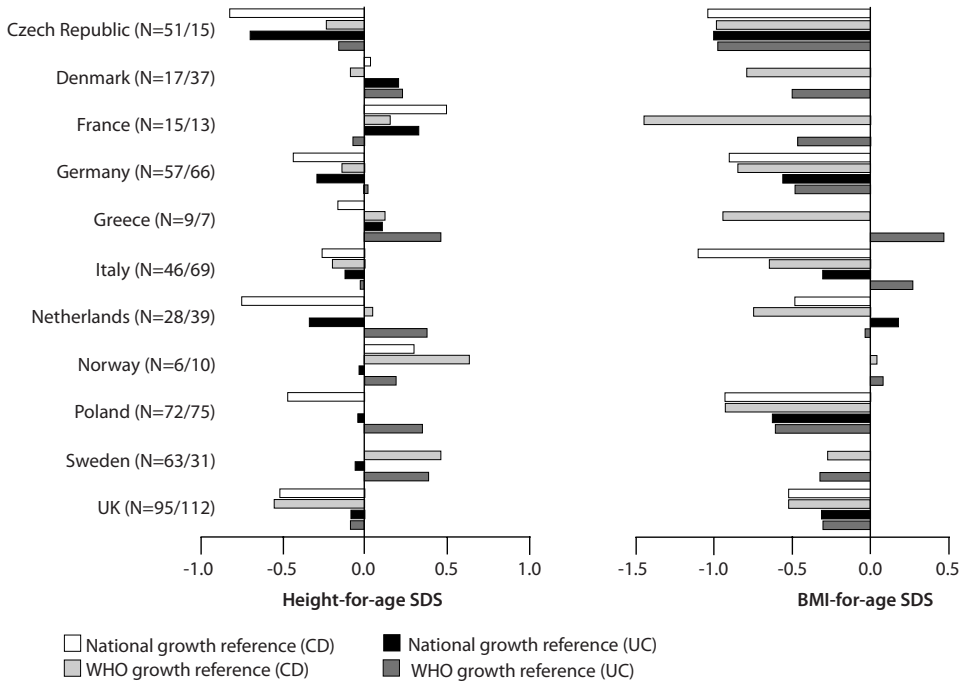SDS: standard deviation score.

Figure 3 | Differences per country in mean standard deviation scores (SDS) between the WHO growth reference and national growth references, as assessed in a cohort of newly diagnosed pediatric Crohn's disease (CD) and ulcerative colitis (UC) patients. Data from one Belgian ulcerative colitis patient are not displayed in the figure. N = CD/UC.

Table 2 | Height and BMI-for-age SDS of newly diagnosed pediatric Crohn's disease and ulcerative colitis patients assessed by the WHO growth reference and national growth references.

	WHO Growth Reference		National Growth References	
	Crohn's disease	Ulcerative colitis	Crohn's disease	Ulcerative colitis
Height				
N	459	475	459	475
Mean SDS (95% CI)	-0.11 (-0.21 to -0.001)	0.10 (-0.002 to 0.21)	-0.39 (-0.49 to -0.28)	-0.12 (-0.23 to -0.02)
≤ -1.96 SDS (< 2.5th centile)	22 (5%)[A]	22 (5%)[A]	41 (9%)[B]	28 (6%)[B]
≤ -0.99 SDS (< 16th centile)	111 (24%)[B]	71 (15%)	141 (31%)[B]	93 (20%)[A]
≤ 0 SDS (< 50th centile)	243 (53%)	221 (47%)	284 (62%)[B]	261 (55%)[A]
BMI				
N	349	376	349	376
Mean SDS (95% CI)	-0.76 (-0.90 to -0.62)	-0.29 (-0.43 to -0.16)	-0.82 (-0.96 to -0.68)	-0.40 (-0.53 to -0.27)
≤ -1.96 SDS (< 2.5th centile)	58 (17%)[B]	38 (10%)[B]	61 (18%)[B]	41 (11%)[B]
≤ -0.99 SDS (< 16th centile)	140 (40%)[B]	105 (28%)[B]	144 (41%)[B]	114 (30%)[B]
≤ 0 SDS (< 50th centile)	254 (73%)[B]	227 (60%)[B]	263 (75%)[B]	233 (62%)[B]

[A] p<0.05, compared with general population
[B] p<0.001, compared with general population
SDS: standard deviation score. CI: confidence interval.

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To determine the effect of disease location on height and BMI, we used the data from national growth references. A multivariable model consisting of the four gastrointestinal segments (adjusted for age, gender, diagnostic delay and country) demonstrated that involvement of the terminal ileum, colon, jejunum/proximal ileum, or esophagus/stomach/duodenum had no significant effect on height and BMI-for-age SDS (Table 3). Diagnostic delay and country were weak, but significant determinants of height-for-age SDS at diagnosis. When disease location was categorized according to the Paris classification (L1 to L4), there was again no significant effect of disease location on height-for-age SDS (P=0.56) or BMI-for-age SDS (P=0.49).

Table 3 | Effect of disease location (adjusted for gender, age, diagnostic delay, and country) on height and BMI-for-age SDS in pediatric Crohn's disease and ulcerative colitis patients.

	Height-for-age SDS		BMI-for-age SDS	
	β	P	β	P
Crohn's disease (n=451/344)				
Diagnostic delay	-0.011	0.02	0.001	0.92
Involvement esophagus/stomach/duodenum	0.085	0.49	0.20	0.22
Involvement jejunum/proximal ileum	-0.17	0.20	-0.077	0.66
Involvement terminal ileum	-0.10	0.42	-0.20	0.28
Involvement colon	0.037	0.80	-0.19	0.33
Ulcerative colitis (n=472/373)				
Diagnostic delay	-0.016	0.003	-0.002	0.73
Pancolitis	-0.27	0.02	-0.48	0.001

SDS: standard deviation score based on national growth references.

UC cohort

A flowchart of the eligible UC population is presented in Figure 1, and their baseline characteristics are displayed in Table 1.

Newly diagnosed pediatric UC patients had a mean height-for-age SDS of +0.10 (95% CI -0.002 to +0.21) according to the WHO growth reference, and -0.12 (95% CI -0.23 to -0.02) according to national growth references (Table 2).

BMI-for-age SDS could be determined in 376 patients (Figure 1). Table 2 displays the mean BMI-for-age SDS values and percentile distributions of the pediatric UC patients. Growth retardation occurred in 5 or 6% of patients (depending on the growth reference used), and malnutrition was present in 10 or 11%.

In comparison with CD, pediatric UC patients had significantly higher mean height-for-age SDS (P=0.001, based on national growth reference) and BMI-for-age SDS (P<0.001). Growth

retardation rates did not significantly differ between pediatric CD and UC patients (*P*=0.08, based on national growth references), but there was a significant difference in malnutrition rates, with higher rates in CD patients (*P*=0.01).

National growth reference data were used to determine the effect of disease location on height and BMI at diagnosis. Multivariable models consisting of disease location adjusted for age, gender, diagnostic delay, and country demonstrated that patients with pancolitis had significantly lower height and BMI-for-age SDS than patients with less extensive disease (Table 3).

DISCUSSION

Our study has demonstrated marked differences in height, and to a lesser extent, nutritional status of pediatric CD and UC patients, as assessed by different growth references. In general, use of national reference data yielded lower mean height and BMI-for-age SDS compared with WHO growth reference data. We therefore consider national growth reference data as more appropriate than WHO growth reference data when analyzing a European cohort of children and adolescents. An independent effect of disease location on height and BMI was demonstrated for pediatric UC patients, but not for pediatric CD patients.

There was only a minimal left-shift in the distribution of height-for-age SDS of pediatric CD patients according to the WHO growth reference, which is in clear contrast with previous studies who have reported mean height-for-age SDS of -1.11 to -0.38.[7-8, 11-14, 39-40] This suggests that height of our European cohort of pediatric IBD patients was inappropriately represented by the WHO growth reference. Previous European studies have also demonstrated significant differences between national growth references and the WHO growth reference.[19, 41-42] These differences may have various explanations. The great majority of children in our study (95%) was assessed by the WHO growth reference for school-aged children and adolescents, which is based on cross-sectional samples from three separate samples of children and adolescents surveyed in the USA between 1963 and 1974.[33] Most national growth references are based on more recent growth data, and it is likely that changes in growth have occurred over time. Ethnic differences could also have played a role in the observed differences. A review of 53 studies demonstrated that pre-pubertal children of most populations grew similarly, but significant differences in height were observed during and after puberty[43], the period in which the majority of pediatric IBD patients is diagnosed. Heights of Northern European populations exceeded the NCHS/WHO reference from 1977 by approximately 5 cm. Taken together, the WHO growth reference does not seem to be applicable to most European populations. Use of national growth references should therefore be preferred in European studies on height. However, national growth references are not available in every country, and this method is not suitable for comparisons of height between different countries due to the large heterogeneity in methods used to construct

these references (i.e. differences in data quality, sample size, age categories). This problem might be solved by harmonizing growth references, which has been shown to be a novel and cost-effective approach for converting national growth references charts into a unified interchangeable parametric format.[19]

Differences in nutritional status between the WHO and national growth references tended to be smaller than those on height. In CD, we found a mean BMI-for-age of -0.82 SDS, which was higher compared with two previous studies (means of -1.37 and -1.15 SDS).[13-14] This difference might be explained by the growing global obesity epidemic, which has also been observed in pediatric IBD patients.[15] In contrast, our data on malnutrition in pediatric UC patients were comparable with values reported in previous literature.[14-15]

There may be several explanations for the observed inter-population differences in mean height and BMI-for-age SDS of our pediatric IBD patients. First of all, these differences can be caused by the heterogeneity in methods used to construct the growth references, as explained earlier. Additionally, differences in genetics, environment, socioeconomic conditions, diet, and lifestyle within Europe are likely to contribute to the observed differences in height and BMI. Thirdly, IBD-related factors (such as disease severity, diagnostic delay, and disease location in UC) could differ between the European countries. Disease severity was not assessed in our study. In UC, there were no significant differences in diagnostic delay and disease location between the countries (data not shown). In CD, median diagnostic delay significantly varied between 2 and 7 months. However, both 'countries' and 'diagnostic delay' were significant factors in the multivariable linear regression model on height-for-age SDS, suggesting that differences in diagnostic delay do not contribute to the observed inter-population differences.

In pediatric UC patients, the presence of pancolitis was negatively associated with both height and BMI at diagnosis. In general, these patients have more severe disease at diagnosis than those with less extensive disease. Disease severity has already been shown to be a predictor of growth retardation and malnutrition in CD.[8-9, 12] In our cohort of accurately phenotyped CD patients, there was no effect of disease location or extent on height and BMI at diagnosis. In contrast, small bowel disease has previously been shown to disrupt normal nutrient absorption, and to cause stricturing disease and poor weight gain.[11-12, 17, 44] These different outcomes could be explained by differences in diagnostic workup and definitions of disease location. Nevertheless, disease location at diagnosis may have an effect on final adult height, as Sawczenko et al. demonstrated that the presence of jejunal disease was negatively related to final adult height in CD patients.[40]

The negative effect of length of diagnostic delay on height in newly diagnosed pediatric IBD patients was already described in 2001.[10] This pediatric study from the United Kingdom reported a median length of diagnostic delay of 11 months in CD, and 5 months in UC. Although the median diagnostic delays were 5 and 4 months in our study, it continued to be a modest, but independent risk factor for impaired height at diagnosis. To diagnose pediatric

IBD earlier, it remains essential to educate primary care doctors and general pediatricians about the existence and clinical presentation of IBD in children and adolescents.
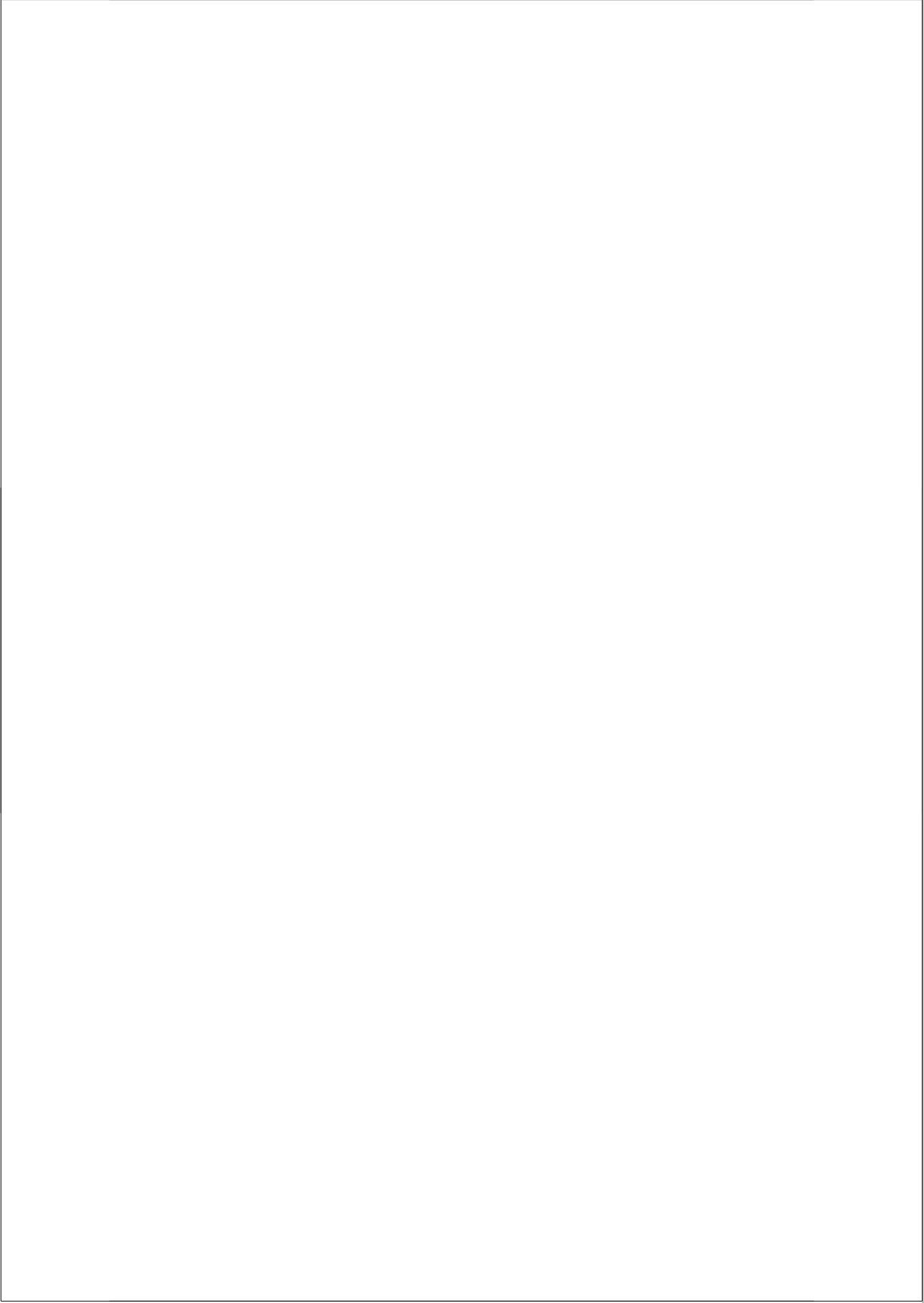
Our study has certain limitations. First of all, EUROKIDS is not a population-based registry, but a selection of centers and pediatric gastroenterologists with a special interest in IBD. This has probably resulted in some selection bias. However, ESPGHAN recommends that all children with a suspicion of IBD should be referred to a pediatric gastroenterologist for diagnostic workup.[38] Consequently, the majority of our participating centers diagnoses and treats all pediatric IBD patients in their region; only five centers have reported that they treat only the most severe IBD cases and four centers have a mixed population of 'regular' IBD patients and severe IBD cases. Besides, even in this setting, the incidence of growth failure was not higher than previously reported. Selection bias may also have been introduced due to our decision to only include CD and UC patients who could be fully and reliably classified according to the Paris classification, as patients with severe disease (risk of perforation; strictures), younger patients (more difficult to reach the terminal ileum), but also patients with mild disease may have had an incomplete workup. Another limitation of our study is that bone age or pubertal staging were not registered in the assessment of growth in our patients. It is possible that low height-for-age SDS could be attributed, to some extent, to delayed bone age, commonly reported in CD[45], and final expected height could be achieved eventually.

In conclusion, growth failure and malnutrition remain significant problems for many pediatric IBD patients at diagnosis, especially for children with CD. It is important to realize that the use of the WHO growth reference or national growth references has an important effect on the results on height and, to a lesser extent, on BMI in a European cohort of pediatric IBD patients. Future studies should further investigate the possibility of harmonizing growth references for assessing growth in older children and adolescents in multicenter European studies.
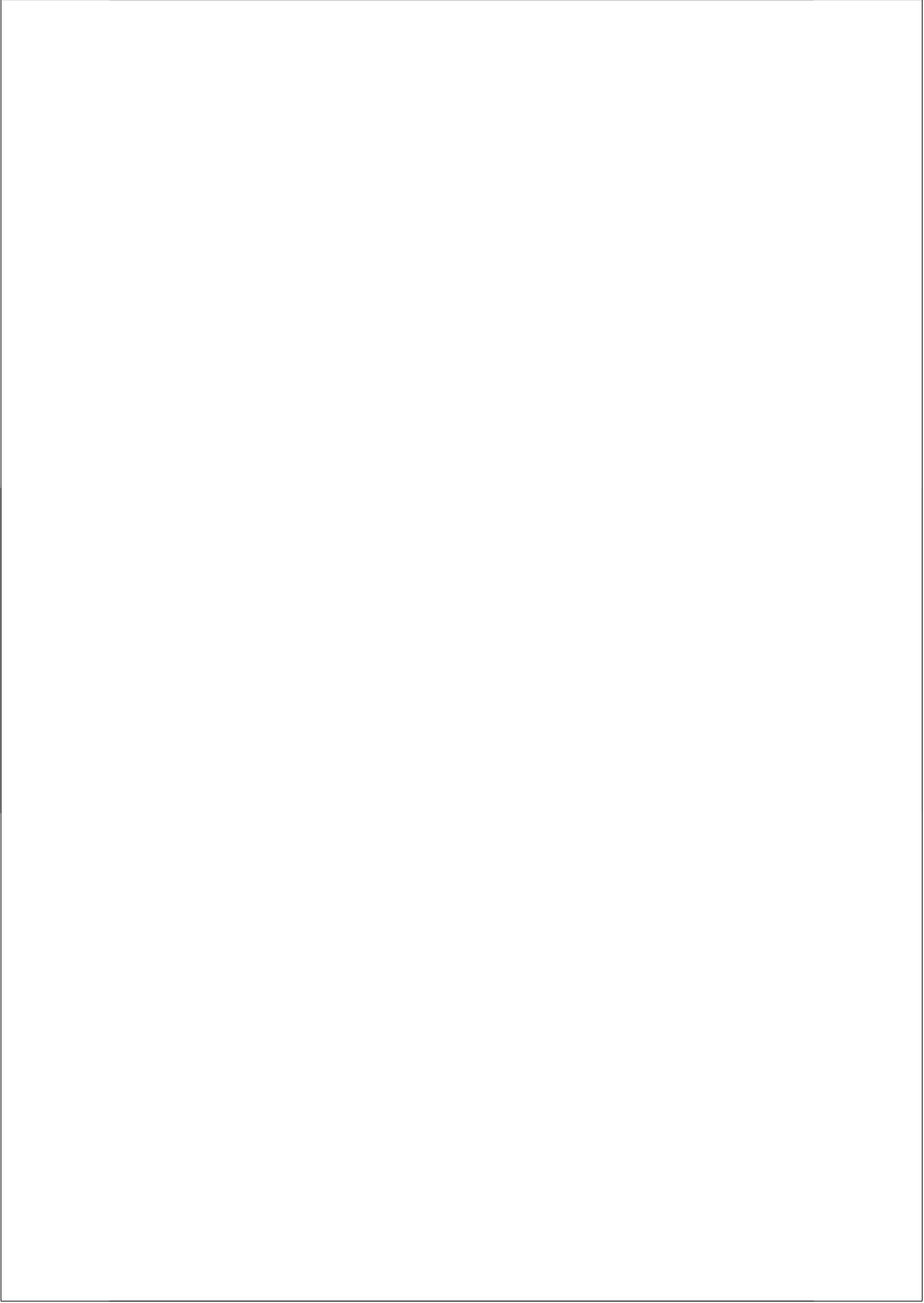
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Part III

Treatment of pediatric IBD

C h a p t e r

6

Use of exclusive enteral nutrition in pediatric Crohn's disease in the Netherlands

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ABSTRACT

Background and aims
A six-week course of exclusive enteral nutrition (EEN) is recommended as first treatment in active pediatric Crohn's disease (CD). We aimed to assess short-term and long-term outcome of EEN, and to identify predictive factors of treatment success.

Methods
The medical records of newly diagnosed pediatric CD patients initiating EEN as remission induction therapy between January 2008 and October 2011 were retrospectively studied. Treatment outcome was assessed using a previously described pattern recognition model.

Results
77 CD patients (median age 13.9 years, 57% male) initiated a six-week course of EEN, combined with azathioprine maintenance treatment in 92%. Patients received EEN as either hyperosmolar sip feeds or polymeric formula by nasogastric tube. In patients completing a six-week course of EEN (n=58), complete remission was achieved in 71%, partial remission in 26%, and no response in 3%. Complete remission rates were higher in children presenting with isolated ileal/ileocecal disease and malnutrition. Nineteen patients discontinued EEN before the intended treatment period due to worsening of symptoms (n=9) or adherence issues (n=10). Non-adherence occurred more often in older children, females, children from non-Dutch parents, and patients taking hyperosmolar sip feeds compared with polymeric formula by nasogastric tube. The likelihood of relapsing disease within the first year after EEN treatment was 59%.

Conclusion
A six-week course of EEN is effective in newly diagnosed pediatric CD, with response rates that seem to be influenced by disease location and nutritional status, but not by type of formula. Non-adherence occurs frequently and limits the success of this treatment in everyday clinical practice.

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INTRODUCTION

Induction of remission in pediatric patients with active Crohn's disease (CD) can be achieved by exclusive enteral nutrition (EEN) or corticosteroids. EEN has been shown to be as effective as corticosteroid therapy in inducing remission in pediatric CD.[1-2] However, EEN is more effective than corticosteroids in inducing mucosal healing[3-4], and improving nutritional status and linear growth recovery.[4-6] Additionally, EEN is not associated with any side-effects, and leads to improved quality of life.[7]

EEN usually involves a six to eight weeks course of liquid formula that replaces normal diet (no other food and drinks are allowed, except water), followed by the reintroduction of a normal diet over a period of one to two weeks.[8] In the Netherlands, a consensus-based guideline on treatment of pediatric IBD has become available since 2008.[9] EEN for a period of six weeks is recommended as first treatment for active newly diagnosed CD, which is similar to the recommendations of other European guidelines on the treatment of pediatric CD.[10-11] Polymeric formula (PF) is advised, but there are no clear guidelines on the exact composition and how to administer EEN. This retrospective study aimed to describe the experience of treating pediatric CD patients with EEN in two tertiary referral centers in the Netherlands after the publication of a national consensus-based guideline. Secondly, we aimed to determine the short-term and long-term treatment outcome of EEN, and to identify predictive factors of treatment success.

MATERIALS AND METHODS

Newly diagnosed pediatric CD patients were selected from the databases of two tertiary referral centers in the Netherlands (Erasmus MC – Sophia Children's Hospital, Rotterdam; Academic Medical Center – Emma Children's Hospital, Amsterdam). In both centers, a six-week course of EEN was offered to all newly diagnosed children with active luminal CD, but a minority of patients (11%) refused this treatment and was treated with corticosteroids instead. For this study, we included the newly diagnosed pediatric CD patients who initiated a primary induction course of EEN between January 2008 and October 2011. All patients were commenced on EEN aiming to complete six weeks of liquid diet therapy. Patients who were treated for relapse of disease or received prior corticosteroid treatment before initiation of EEN, were excluded from this study. The diagnosis of CD was based on endoscopic, histologic, and/or radiologic findings, according to the Porto criteria.[12]

The medical records were retrospectively reviewed by a single investigator (CdB). Baseline characteristics included age, gender, family history of IBD in first degree relatives, height and weight, laboratory parameters, disease location, and the presence or absence of perianal disease. Information on the type of formula, route of administration, duration of the liquid diet, and adherence to EEN treatment was also recorded (when available), as well as the initiation of immunomodulatory maintenance therapy.

Definitions

Disease location was categorized by a recent pediatric modification of the Montreal classification, the Paris classification[13]: (L1) involvement of the terminal ileum only, with limited or no cecal disease; (L2) colonic involvement only; and (L3) involvement of both the terminal ileum and colon. Involvement of the terminal ileum was based on the results of ileocolonoscopy and/or small bowel imaging by MRI. Upper gastrointestinal disease (L4 disease) was separated into esophagogastroduodenal disease (L4A disease) and jejunal/proximal ileal disease (L4B disease). L4A disease was defined as the presence of ulcerations, erosions/aphthae, cobblestones, and/or stenosis. The presence of mucosal erythema, edema, granularity, and/or nodularity was not sufficient to be considered evidence of involvement. Perianal disease was defined as the presence of a perianal abscess and/or fistula, and did not include the isolated presence of skin tags, fissures, or hemorrhoids.

EEN treatment outcome was retrospectively evaluated by a pattern recognition model, previously described and published by Nielsen et al.[14] This model has also been demonstrated to be useful for the assessment of other treatments for CD.[15-17] At the end or shortly after cessation of EEN treatment, patients were classified according to their clinical response as complete remission, partial remission, or no response. Complete remission was defined as ≤ 2 stools/day without blood, pus, or mucus, no abdominal pain, and no weight loss. Partial remission was defined as ≤ 4 stools/day, less than daily loss of blood, pus, or mucus with the stools, less than daily abdominal pain, or weight loss. When there was no regression of clinical symptoms, patients were classified as having no response. At the end of follow-up (minimal 3 months after cessation of EEN), the patients obtaining complete and partial remission were evaluated for relapse of disease, defined as symptoms requiring another induction course of treatment.

Statistical analysis

Data were collected and analyzed in SPSS (version 17.0, SPSS, Inc., Chicago, IL). Descriptive statistics were calculated as percentages for discrete data. Continuous variables were presented as medians and interquartile ranges (IQR). Data on height, weight, and body mass index (BMI) were converted to standard deviation scores (SDS) using the 2010 Dutch standards (Growth Analyzer RCT, version 4.0, Dutch Growth Foundation). For comparisons of proportions, we used Pearson chi-square analyses or Fisher's exact tests, as appropriate. Quantitative data were compared using Mann-Whitney U tests, or Wilcoxon signed rank tests for paired data. To test for independent predictive factors of EEN treatment outcome, a logistic regression model was constructed with treatment outcome (complete remission vs. partial remission/no response) as the dependent variable. Kaplan-Meier analysis was used to estimate the cumulative probability of maintaining remission over time. Time to event was analyzed from the date of EEN initiation until the date of relapse, or last known follow-up. Statistical significance was defined as a two-tailed P-value < 0.05.

RESULTS

Patient characteristics

During the study period, 77 newly diagnosed pediatric CD patients with active disease (median age 13.9 years, IQR 11.1 – 15.7 years; 57% male) initiated a six-week induction course of EEN. Most children (70%) were of Dutch origin. At start of treatment, the median height for age SDS was -0.79 (IQR -1.5 to -0.06), and the median weight for height SDS was -0.86 (IQR -1.7 to 0.11). Twenty percent of patients had a first-degree relative with IBD. Disease location could be determined in all patients but one, as there was no endoscopic or radiologic examination of the terminal ileum. Isolated terminal ileal disease (±limited cecal disease, L1) was seen at presentation in 25% (19/76), isolated colonic disease (L2) in 24% (18/76), and ileocolonic disease (L3) in 51% (39/76) of pediatric CD patients. In total, 38% (29/77) of patients had esophagogastroduodenal disease (L4A), and 29% (18/63) jejunal/ proximal ileal disease (L4B). Perianal disease occurred in 10% (8/77) of patients.

All patients were untreated at the time EEN was initiated. Most patients (n=71, 92%) were started on azathioprine maintenance treatment during or shortly after the course of EEN.

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EEN treatment

Most patients received either hyperosmolar sip feeds (HSF; n=41, 53%), or polymeric formula (PF) by nasogastric (NG) tube (n=30, 39%). Additionally, one patient was treated with semi-elemental formula by NG tube, three patients received PF by mouth, and two patients used a combination of PF by NG tube and HSF.

Children who initiated EEN treatment administered by NG tube were always admitted to the hospital for 2 – 4 days, whereas most patients on HSF initiated treatment at home. The volume and caloric density of the enteral feeds were determined by the dietician on the basis of the patient's daily nutritional requirements, in general 110 – 120% of the recommended dietary allowance of total energy and protein. No other foods and drinks (except water) were allowed during a course of EEN. By the end of the course, the dietician discussed a two-week scheduled return to a normal diet with the child and his/her parents. Various brands of polymeric and semi-elemental formulas were used, depending on the local preference of the treating physician and/or dietician. Information on their composition is summarized in Table 1. When receiving HSF, the patients were allowed to make a choice of the kind and combination of drinks from a test kit, taking into account the recommendations of the dietician concerning daily nutritional requirements (in general 6 – 10 HSF/day). Almost all patients taking HSF used a combination of flavored drinks, depending on their own preferences in taste, which made it impossible to determine the number of patients receiving a certain brand of sip feeds. HSF were milk-based, yoghurt-based, or juice-based (*Nutridrink, Nutridrink Yoghurt Style, Nutridrink Juice Style* by Nutricia, Zoetermeer, the Netherlands; *Ensure Plus, Ensure Plus Fresh* by Abbott Nutrition, Hoofddorp, the Netherlands; *Resource Energy,*

Table 1 | Composition of formulas used for exclusive enteral nutrition therapy in newly diagnosed pediatric Crohn's disease.

	Nutrison Standard[A]	Nutrison Energy[A]	Nutrini Max[A]	Nutrini Max Energy[A]	Osmolite HiCal[B]	Isosource Energy[C]	Peptisorb[A]
Number of patients	4	14	2	12	1	1	1
Type of formula	polymeric	polymeric	polymeric	polymeric	polymeric	polymeric	semi-elemental
Energy density (Kcal/100 ml)	100	150	100	150	151	160	100
Osmolarity (mOsmol/l)	265	385	225	330	392	298	455
Total protein (g/100 ml)	4	6	3.3	4.9	6.3	5.7	4
Total fat (g/100 ml)	3.9	5.8	4.2	6.3	4.9	6.2	1.7
Polyunsaturated (PUFA) (g)	1.2	1.8	1.3	1.9	0.7	2.2	0.5
Monounsaturated (MUFA) (g)	2.3	3.5	2.4	3.7	2.9	2.3	0.2
Total saturated fatty acids (g)	0.4	0.6	0.5	0.8	1.2	1.7	1
Total carbohydrate (g/100 ml)	12.3	18.5	12.3	18.5	20.4	20	17.6

All but three patients received the formulas by nasogastric tube. Two patients received both Nutrison Standard and Nutrison Energy. In one patient, the type of polymeric formula was missing.
[A]Nutricia Nederland BV, Zoetermeer, the Netherlands.
[B]Abbott Nutrition, Hoofddorp, the Netherlands.
[C]Nestlé Health Science, Oosterhout, the Netherlands.

Resource Fruit by Nestlé Health Science, Oosterhout, the Netherlands; *Fresubin Energy Drink, Fresubin Jucy Drink* by Fresenius Kabi Nederland BV, Zeist, the Netherlands). The energy density of these HSF varied from 125 – 150 Kcal/100 ml, and the osmolarity varied from 455 – 750 mOsmol/l. Juice-based HSF contained no fat, while other HSF had a total amount of fat of 4.9 – 5.8 g/100 ml.

Efficacy of EEN induction therapy

Treatment outcome of EEN is displayed in Figure 1. A six-week course of EEN was completed in 58 patients (75%), of which 41 (71%) achieved complete remission, and 15 (26%) partial remission. Two patients (3%) had no response after six weeks of EEN treatment, and were subsequently treated with corticosteroids. Withdrawal from EEN before the intended treatment period due to worsening of symptoms was necessary in nine patients (12%), who were all switched to corticosteroids. When treatment outcome was based on all initiated courses of EEN, complete remission was achieved in 53% (41/77) of patients, partial remission in 20% (15/77), and no response was seen in 14% (11/77). The remaining ten patients (13%) were not able to consume the prescribed volume of tube feeding (n=2) or HSF (n=8), and were subsequently treated with corticosteroids.
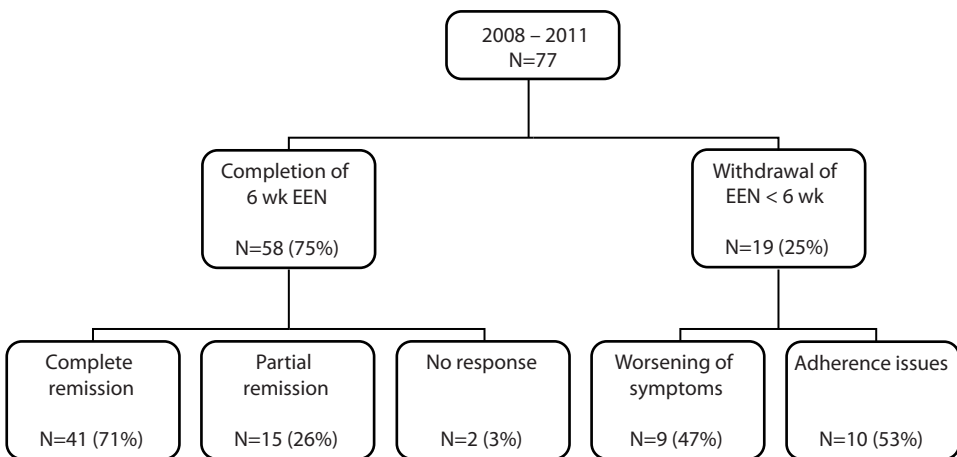
Figure 1 | Treatment outcome of a six-week course of exclusive enteral nutrition in 77 newly diagnosed pediatric Crohn's disease patients using a previously described pattern recognition model.[14]
EEN: exclusive enteral nutrition.

In patients achieving complete remission (n=41), both median weight for height SDS (-1.4 vs. -0.68) and BMI for age SDS (-1.6 vs. -0.69) improved significantly between the start and end of treatment with EEN (both *P*<0.001). When available, laboratory parameters before

and after EEN treatment were compared in patients achieving complete remission. During treatment, there was a significant improvement in ESR (n=25, median -19 mm/h, $P<0.001$), CRP (n=27, median -42 mg/L, $P<0.001$), albumin (n=25, median +8 g/l, $P<0.001$), and platelet levels (n=34, median -108 x10^9/l, $P<0.001$). Hemoglobin levels did not significantly change during EEN treatment.

Baseline characteristics of the patients achieving complete remission (n=41) were compared with those of the partial responders and non-responders (n=26, Table 2). Patients who did not complete a six-week course of EEN due to intolerance of or non-adherence to EEN were excluded from these analyses. Complete remission rates were not affected by age, gender, or type of formula (PF by NG tube versus HSF). Complete remission rates were higher in children from Dutch parents (69% vs. 42%), but this difference did not reach statistical significance ($P=0.06$). Patients with L1 disease had higher complete remission rates (88%) than patients with L2 disease (53%) or L3 disease (51%, $P=0.04$). Baseline weight for height SDS and BMI for age SDS also differed significantly between the two patient groups: patients who achieved complete remission had significantly lower median weight for height SDS (-1.4 vs. -0.06, $P<0.001$) and BMI for age SDS (-1.6 vs. -0.24, $P<0.001$) at start of EEN treatment compared with the other patient group. In a logistic regression model consisting of age, gender, nationality, disease location and weight for height SDS (or BMI for age SDS) as explanatory variables, both disease location and nutritional status remained significantly associated with treatment outcome.

Relapse rates were first determined in 37 CD patients who achieved complete remission by the end of EEN treatment and had a follow-up of at least 3 months after cessation of EEN. After a median follow-up of 1.5 years (IQR 0.7 – 2.5 years), 62% (n=23) of these patients had relapse of disease. Three patients did not receive immunomodulatory maintenance therapy when relapse of disease occurred. The median time to relapse of disease was 20.6 weeks (IQR 10 – 39 weeks, range 2 – 169 weeks). Kaplan-Meier analysis showed that the cumulative probability of relapsing disease within the first year after EEN treatment was 59% (Figure 2). In the partial remission group, 12 of 15 children had a follow-up of at least 3 months after cessation of EEN treatment. All these patients had initiated azathioprine maintenance therapy within the first weeks of EEN treatment. Nine patients had relapse of disease within 4 months, while one patient relapsed after 2 years. In the remaining two patients, partial remission was followed by a prolonged response with a follow-up of 2.2 and 1.4 years, respectively. Following relapse of disease, treatment consisted of a second course of EEN (n=4), corticosteroids (n=18), ileocecal resection (n=2), anti-TNF treatment (n=6), optimization of the azathioprine dosage (n=2), and switch of azathioprine to methotrexate (n=1).

Table 2| Characteristics of 67 newly diagnosed pediatric Crohn's disease patients according to exclusive enteral nutrition treatment outcome.

	Treatment outcome		
	Complete remission (n=41)	Partial remission/ No response (n=26)	P-value
Age at diagnosis (yr)	14.1 (11.3 to 15.8)	12.1 (10.8 to 15.0)	0.18
Gender (male)	26/41 (63%)	16/26 (62%)	1.0
Nationality (Dutch)	33/41 (81%)	15/26 (58%)	0.06
Height for age SD score	-0.96 (-1.6 to -0.23)	-0.51 (-1.2 to 0.41)	0.13
Weight for height SD score	-1.4 (-2.1 to -0.49)	-0.06 (-0.95 to 0.76)	<0.001
BMI for age SD score	-1.6 (-2.2 to -0.75)	-0.24 (-1.4 to 0.69)	<0.001
Positive family history	8/41 (20%)	4/26 (15%)	0.75
Disease location			
L1	14/40 (35%)	2/26 (8%)	0.04
L2	8/40 (20%)	7/26 (27%)	
L3	18/40 (45%)	17/26 (65%)	
L4A disease	16/41 (39%)	12/26 (46%)	0.62
L4B disease	11/34 (32%)	4/20 (20%)	0.37
Perianal disease	3/41 (7%)	5/26 (19%)	0.25
Type of formula[A]			
Polymeric formula by nasogastric tube	16/38 (42%)	12/24 (50%)	0.61
Hyperosmolar sip feeds	22/38 (59%)	12/24 (50%)	

[A]Patients who were treated with polymeric formula by mouth (n=2), semi-elemental formula (n=1), or a combination of polymeric formula and hyperosmolar sip feeds (n=2) were excluded from this analysis.
Continuous variables are presented as medians and interquartile ranges.
L1: isolated terminal ileal disease (± limited cecal disease). L2: isolated colonic disease. L3: ileocolonic disease. L4A: esophagogastroduodenal disease. L4B: jejunal/proximal ileal disease.

6

Adherence to EEN treatment

As was mentioned earlier, ten children discontinued EEN treatment due to non-adherence to the prescribed volume of EEN. In one of these patients, there was an unsuccessful attempt to switch from HSF to tube feeding.

In the 58 patients completing a six-week course of EEN, at least five patients (9%) experienced difficulties with adherence to EEN treatment. Two patients (one complete remission; one partial remission) did not comply with the exclusivity principle, as they admitted to have eaten other foods besides the treatment with HSF or tube feeding. In two patients (both partial remission), there were temporary difficulties with drinking the prescribed volume of HSF at the initiation of treatment. The fifth patient (non-responder) initially tolerated the volume of HSF well, but failed to drink the adequate volume after 5 weeks of EEN treatment due to nausea and continuing IBD symptoms.
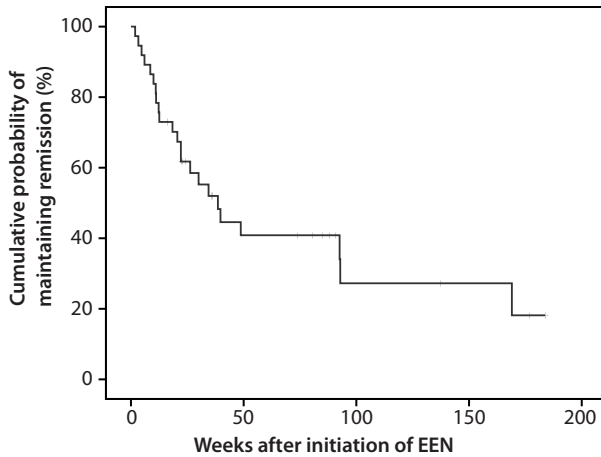
Figure 2 | Kaplan-Meier analysis of duration of remission in newly diagnosed pediatric Crohn's disease patients who achieved complete remission after a six-weeks induction course of exclusive enteral nutrition and had at least 3 months of follow-up after cessation of exclusive enteral nutrition (n=37). In most of these patients (n=34), azathioprine maintenance treatment was initiated during or shortly after the course of exclusive enteral nutrition.

Characteristics of children with established non-adherence were compared with those of the other patients. Children with established non-adherence were significantly older than the other patients (15.5 years vs. 13.4 years, P=0.04). Additionally, non-adherence was more often reported in females (36% vs. 7%, P=0.003), in patients from non-Dutch parents (35% vs. 13%, P=0.06), and in patients receiving oral treatment, i.e. HSF or PF by mouth (27% vs. 10%, P=0.08).

DISCUSSION

Our study has demonstrated that a six-week course of EEN was effective for induction of remission in newly diagnosed children with CD, but non-adherence occurred frequently and limited the success of this treatment in everyday clinical practice. Different types of formula were used as EEN treatment, but there was no significant difference between HSF and PF on treatment outcome. We found a significant variation in treatment response based on disease location and nutritional status at start of EEN treatment.

The complete remission rate of 71% in children completing a six-week course of EEN was similar to the rate reported in the Danish study that used the same definitions for EEN treatment outcome (i.e. 67%).[14] However, these remission rates are based on completed courses of EEN only. When all courses of EEN would have been included in the analyses, the

complete remission rate had been 53% (41/77) in our study and 54% (25/46) in the Danish study. This rate is relatively low in comparison with other studies on the efficacy of EEN[8], which could be explained by the frequently observed difficulties to fully comply with EEN in our study. At least 15 of 77 (20%) patients could not adhere to the prescribed volume of EEN or the exclusivity principle, resulting in early discontinuation of EEN treatment in ten patients. Other studies on EEN treatment have reported non-adherence rates of 5 – 20%[18-21], which negatively affects the clinical response to EEN.[19-20]

Adherence to treatment is a complex process, where a multitude of interacting variables (patient, family, treatment, and health-professional related factors) seems to play a role.[22] In our study, a significant patient-related factor affecting adherence was age, which is in accordance with previous data suggesting that non-adherence is more common among adolescent patients than in younger patients.[23] Additionally, we found that female CD patients experienced more difficulties with EEN treatment than male patients. Previous adult IBD literature has reported contradictory results on the association between gender and adherence.[24] Treatment-related factors that could affect adherence to EEN are the type of formula and/or route of administration. We found a trend toward higher non-adherence rates in children receiving oral EEN treatment (mostly HSF), which is in contrast with the study of Rubio et al. who reported similar adherence rates between children receiving PF by NG tube and orally.[20] It is also possible that the formula composition has affected the compliance rate in our study. HSF have a relatively high osmolarity, which can cause fullness and nausea, thereby negatively affecting adherence. Finally, health-professional related factors affecting adherence might be the intensity of monitoring a patient during EEN treatment. In general, our patients had one or two clinic visits with the pediatric gastroenterologist and two visits with the dietician during a course of EEN (at initiation, and at the end of a six-week course of EEN). This monitoring frequency is modest when compared with other studies, in which a weekly home visit of a clinical nutritionist was provided during the course of EEN[20], or patients were regularly phoned by the dietician and IBD nurse specialist during the first weeks of treatment.[25] Taken together, there are multiple factors possibly affecting adherence, which requires further investigation.

Length of EEN treatment and composition of the formulas might also have had an effect on the treatment outcome in our study, but data on the importance of these aspects are still limited. In most clinical studies on EEN treatment in pediatric CD, EEN is administered during a period of six to eight weeks.[8] Several patients in our study achieved partial remission at the end of their six-week treatment period, but experienced further improvement of their symptoms in the weeks following cessation of EEN, suggesting a potential benefit from a longer treatment course. Previous research on the importance of formula composition on EEN treatment outcome has shown that the nitrogen source of the diet (elemental, semi-elemental, polymeric) does not affect remission rates in pediatric CD.[4, 26-27] However, the importance of fat content and composition, the potential advantage of using TGF-beta

(an anti-inflammatory cytokine) enriched formulas, and the effect of using commercially available flavored drinks on treatment outcome are yet to be determined. Although our results should be interpreted with caution due to heterogeneity of the HSF used, we did not find a difference between HSF and PF by NG tube on treatment outcome.

Despite the increasing data on the positive effects of EEN in pediatric CD, there are still limited data on the way in which EEN reduces intestinal inflammation. Traditionally, reduction of antigenic pressure ('bowel rest') was considered an important working mechanism of EEN. However, this hypothesis is probably not the primary factor, as formulas with different protein sources achieve similar remission rates.[28] Recent data suggest that EEN modulates bacterial flora within the gut lumen, thereby reducing intestinal inflammation.[8, 29-30] A third explanation may be that EEN has direct anti-inflammatory effects on intestinal epithelial cells by down-regulation of mucosal pro-inflammatory cytokines.[3, 31] Finally, improvement of the nutritional status by repletion of nutritional deficiencies is likely to contribute to the benefits seen with EEN.[28] This latter hypothesis is strengthened by our observation that nutritional status at start of treatment was associated with treatment outcome: complete remission rates were higher in malnourished children. Further studies are required to determine the relative importance of the other hypotheses. Hopefully, this knowledge will enable us to optimize EEN treatment regimens.

Another unresolved question regarding EEN treatment is the effect of disease location on treatment outcome. The prevailing opinion of pediatric gastroenterologists is often that EEN is not as effective for isolated colonic disease as it is for ileal or ileocolonic disease.[32-33] Previous pediatric studies however have yielded conflicting results. Afzal et al.[34] demonstrated that pediatric CD patients with isolated colonic disease had significantly lower remission rates after an eight-week course of EEN (50%, 7/14) than patients with isolated ileal disease (92%, 11/12) or ileocolonic disease (82%, 32/39). Similarly, Wilschanski et al.[35] reported that fewer patients with isolated colonic CD achieved clinical remission compared with other anatomic sites. In contrast, more recent studies did not find an effect of disease location on EEN treatment outcome.[20, 25] There is a large heterogeneity between these studies regarding the indication for EEN treatment (treatment at initial diagnosis, or relapse of disease), definition of disease involvement (macroscopic, microscopic, or both), classification of disease location, and definitions of treatment outcome. These differences make it very difficult to draw a definite conclusion about the importance of disease location on treatment outcome. In our study, we included newly diagnosed CD patients only and used a clear definition to classify disease location, thereby finding the highest response rates (88%) in children with isolated ileal/ileocecal disease versus response rates of approximately 50% in children with colonic involvement.

Despite the frequent use of azathioprine maintenance therapy, the likelihood of relapsing disease within the first year after EEN treatment was 59%, which is markedly higher when compared with the results of the pivotal placebo-controlled randomized trial of Markowitz et al.[36] In this study, 55 newly diagnosed children with CD were randomized to treatment

with corticosteroids and either 6-mercaptopurine (6-MP) or placebo. After discontinuation of corticosteroids, only 9% of patients on 6-MP relapsed compared with 47% of controls during a follow-up period of 18 months. However, subsequent observational pediatric studies have not been able to reproduce these low relapse rates, as rates of 40 to 60% were found[37-39], comparable with the relapse rate in our study. These differences might be caused by different clinical settings: an ideal clinical setting with monthly outpatient clinic visits, weekly telephone contacts, and verification of treatment adherence by pill count versus standard clinical practice with less frequent contacts and limited possibilities to verify treatment adherence. Another explanation could be differences in study population, with a more heterogeneous population of pediatric CD patients in the observational studies.
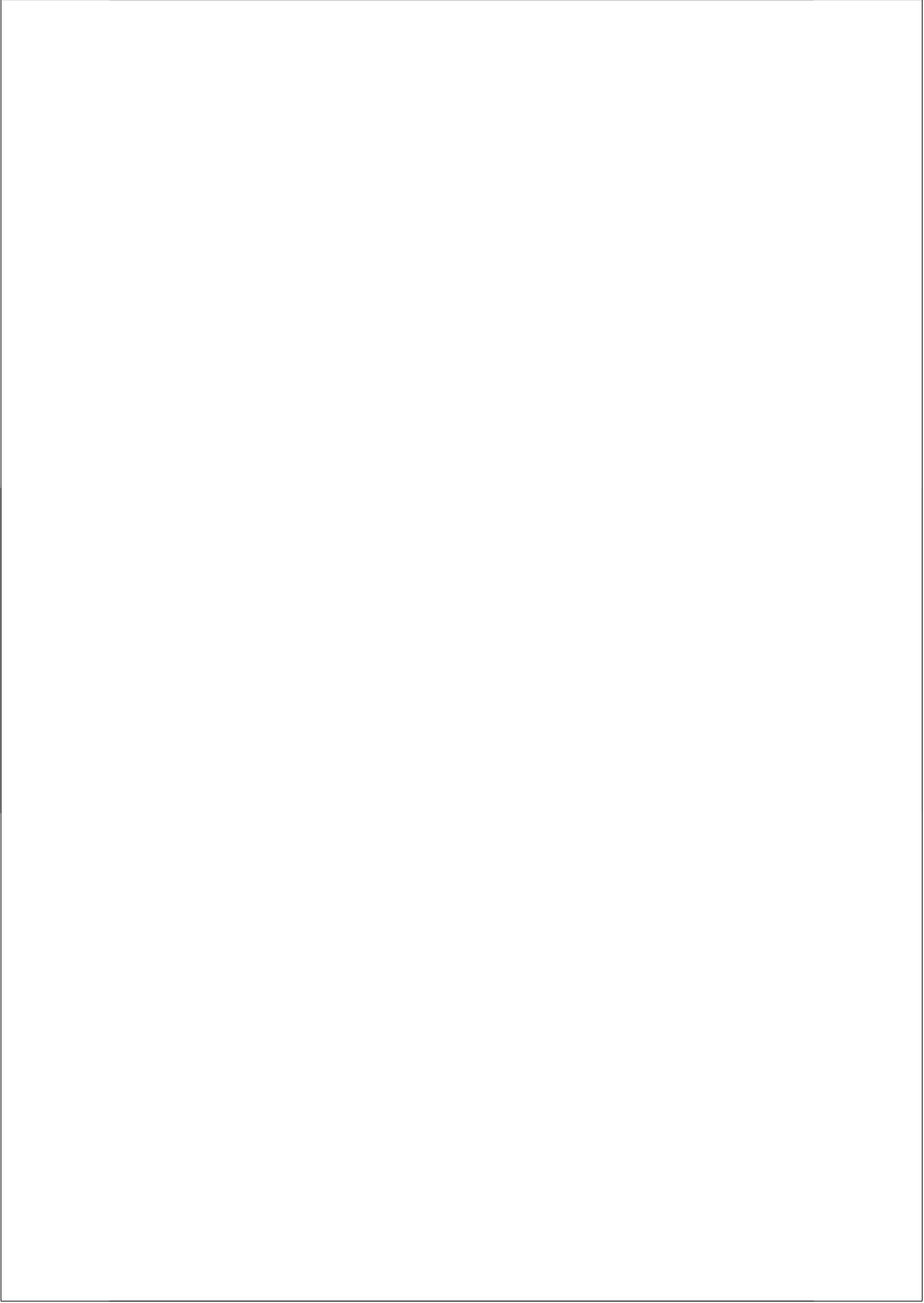
In our study, relapses were treated with corticosteroids in more than half of the cases (55%), which illustrates that the long-term avoidance of corticosteroid therapy in this patient group is still difficult. Supplementary enteral nutrition as additional maintenance treatment after the initial induction course has been demonstrated to have a positive effect on duration of remission.[35, 40] Our patients were advised to continue supplemental nutrition after a successful course of EEN (1 to 2 HSF daily). The volume of supplemental nutrition taken and adherence were however not carefully recorded, as this was not a prospective study. Consequently, we could not assess the effect of supplemental nutrition on our relapse rates. We acknowledge that our study also has other limitations due to its retrospective design. Retrospective studies are sensitive to bias, such as selection bias, as treatment was not allocated by randomization. Secondly, it was impossible to use the PCDAI (Pediatric Crohn's Disease Activity Index) for determination of treatment outcome, due to missing data in the medical records. Instead, we used a previously published pattern recognition model to evaluate EEN treatment response.[14] This model has also been demonstrated to be useful for the evaluation of treatment outcome of corticosteroids and infliximab in IBD patients.[15-17] Additionally, the results on non-adherence are based on self-report assessments documented in the medical record. It is likely that the occurrence of suboptimal adherence is even higher, as patients are often reluctant to tell their doctor about the difficulties they experience with their treatment.[41] The results on the factors that may have influenced adherence should therefore be interpreted with some caution.

In conclusion, this study has demonstrated the effectiveness of a six-week course of EEN, but also the problems that occur with EEN in everyday practice and that limit the success of this treatment. Type of formula does not seem to influence treatment outcome, but there is a trend towards more adherence issues when HSF are prescribed. Non-adherence also occurred more often in older children, females, and children from non-Dutch parents. Adherence issues should be actively addressed during a course of EEN, for example by a weekly (telephone) contact with the dietician and/or IBD nurse during a course of EEN. After cessation of EEN, relapse rates are high, despite frequent use of azathioprine maintenance treatment. Further research is urgently needed to determine the mechanism of action of this treatment, which will enable optimization of EEN treatment regimens.

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6

Chapter 7

The duration of effect of infliximab maintenance treatment in pediatric Crohn's disease is limited

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ABSTRACT

Background
Infliximab (IFX) is effective for induction and maintenance of remission in children with moderately to severely active Crohn's disease (CD).

Aim
To evaluate the long-term efficacy of IFX treatment in pediatric CD.

Methods
In this observational, multicenter study, all pediatric CD patients in the Netherlands treated with IFX from October 1992 to November 2009 and with minimal follow-up of 3 months since start of IFX, were studied.

Results
152 CD patients (81M; median age at start of IFX 15.0 years (IQR 13.1 – 16.4)) received a median number of 10.5 IFX infusions (IQR 6 – 21). Median follow-up after start of IFX was 25 months (IQR 13 – 40). Kaplan-Meier analysis showed that the cumulative probability of losing response to IFX in patients who initially required repeated infusions, was 13%, 40%, and 50% after 1, 3 and 5 years, respectively. Seventy-four patients (49%) needed dose adjustments, with a median time to any adjustment of 6 months.

Conclusions
Duration of effect of IFX is limited since 50% of patients on IFX maintenance treatment lose their therapeutic response after 5 years. Dose adjustments after start of IFX are frequently needed to regain therapeutic benefit. These findings emphasize the need for effective, long-term treatment strategies for pediatric CD.

INTRODUCTION

Infliximab (IFX; Remicade®) is a chimeric monoclonal antibody (75% human, 25% murine) that binds with high affinity and specificity to tumor necrosis factor-α (TNF-α)[1], a pro-inflammatory cytokine with increased expression in the inflamed intestinal mucosa of children with active Crohn's disease (CD).[2]

Since the first use of IFX for CD in 1992 in a thirteen-year old girl[3], several small non-randomized, non-placebo controlled studies[4-9] and a randomized multicenter open-label study[10] have demonstrated the efficacy of IFX to induce and maintain clinical remission in children with moderate to severe CD. This biological has greatly improved the therapeutic options for refractory pediatric CD. Although IFX has a good short-term safety profile[9-12], there are concerns about the long-term safety aspects, especially since post-marketing surveillance reported on the occurrence of 18 cases of hepatosplenic T cell lymphoma (HSTCL). (data on file, Centocor) This aggressive form of non-Hodgkin's lymphoma occurred in predominantly male adolescents and young adults with inflammatory bowel disease (IBD; mostly CD) who had been treated with anti-TNF-α and thiopurines.[13]

To date, data on long-term efficacy of IFX in pediatric CD are still limited. A recent study by Hyams et al.[14] showed that during the third year of IFX maintenance therapy, 33% of patients had sustained remission (defined as clinically inactive disease not requiring corticosteroids or surgery). In addition, our previous study[9] demonstrated that sustained clinical response after cessation of IFX treatment or on IFX maintenance therapy was seen in 70% of patients after a mean follow-up of 41 months.

To avoid exposure and toxicity in the patients who will not benefit from IFX therapy in the long-term, it is important to find predictors of prolonged response. Episodic treatment has been associated with higher relapse rates compared to scheduled maintenance treatment both in adults and children.[12, 15] Other clear risk factors for IFX failure have not been identified in children, except for the possible influence of disease duration before start of IFX treatment. Two pediatric studies have reported prolonged duration of response after IFX treatment when the drug was initiated early in the disease course[4, 7], but we were not able to confirm this difference in our previous study.[9]

The primary aim of this study was to evaluate the long-term efficacy of IFX treatment in a national cohort of pediatric CD patients treated with IFX. The secondary aim was to examine whether clinical factors, such as gender, age at diagnosis, disease location and disease duration before start of IFX, were associated with treatment outcome.

MATERIALS AND METHODS
Patients

All pediatric CD patients treated with IFX since 1992 by pediatric gastroenterologists in the Netherlands were reviewed. After the appearance of a national consensus guideline

on the indications and use of IFX in children with refractory CD, a database was initiated in 2002 with the purpose to audit IFX treatment given by pediatric gastroenterologists in the Netherlands. Patients who received IFX in the period 1992 – 2002, were retrospectively included in the database (n=22).

Patients were included in this study when IFX was started before the age of 19 years and follow-up was at least 3 months after initiation of IFX treatment. Patients who did not receive a three-dose induction scheme at 0, 2 and 6 weeks and/or were treated episodically, were excluded.

Data on patient characteristics, disease history, previous and concomitant treatments were recorded. In addition, number and schedule of IFX infusions, outcome of IFX treatment, adverse events, surgery and treatment in case of IFX failure were extracted from the medical records. Data were collected until November 2009.

Definitions

The outcome of IFX treatment was defined as prolonged response, IFX requirement, loss of response, or non-response. Patients who maintained good clinical response minimally 3 months after IFX treatment stopped, were classified as having a prolonged response. Good clinical response was based on the judgment of the treating pediatric gastroenterologist. IFX requirement indicated that repeated IFX infusions were needed to maintain good clinical response. Adjustments in treatment schedule (dosage increase up to 10 mg/kg and/or shortening of the interval between two infusions) were allowed in these patients. Patients with loss of response had an initial good clinical response to IFX maintenance treatment, but eventually there was a need for surgery or withdrawal of IFX (including patients with recurrent allergic reactions despite prophylaxis) and switch to other medical therapy. Finally, non-response was defined as no clinical response to a three-dose IFX induction scheme and withdrawal of IFX after three infusions in total. Treatment outcome was considered successful in case of prolonged response or IFX requirement.

Statistical analysis

Data were collected and analyzed in SPSS (version 15.0, SPSS, Inc., Chicago, IL). Descriptive statistics were calculated as percentages for discrete data and medians with interquartile ranges (IQR) for continuous data. Kaplan-Meier analysis was used to estimate the cumulative probability of losing response to IFX treatment over time. Time to event was analyzed from the date of IFX initiation until the date of loss of response to IFX, or last known follow-up. To analyze predictive factors of IFX failure among categorical baseline characteristics (i.e. gender, disease location at diagnosis, initiation of IFX within one year after diagnosis, previous bowel surgery), univariate analyses with log-rank test were used. Multivariate Cox proportional hazards regression was used to identify independent variables predictive of IFX failure. The proportional hazards assumption was checked using log-minus-log survival

plots. To assess the relation between treatment outcome and adverse events, Fisher's exact test was used. All reported P-values are two-sided. P-values < 0.05 were considered significant.

RESULTS

Patient characteristics

Between October 1992 and November 2009, 188 pediatric patients in the Netherlands were treated with IFX in thirteen hospitals. Thirty-six patients were excluded because of the following reasons: follow-up < 3 months (n=6), no administration of a three-dose induction scheme (n=26), episodic treatment (n=3) and lost to follow-up (n=1).

Characteristics of the 152 included patients are shown in Table 1. The median age at start of IFX treatment was 15.0 years (IQR 13.1 – 16.4) after a median disease duration of 1.8 years (IQR 0.8 – 3.0). All patients but five were refractory to conventional treatment. These five patients received first-line IFX therapy because of severity of colonic disease at presentation (n=1)[16], perianal fistulas in the presence of juvenile idiopathic arthritis (n=1) and complex perianal fistulas at presentation (n=3).

The majority of patients (n=133) received a three-dose induction scheme at 0, 2 and 6 weeks followed by maintenance treatment. Sixteen patients (11%) received an induction scheme only. In three patients (2%) IFX was stopped after the induction scheme, but treatment was restarted when disease relapsed.

Outcome of IFX treatment

Median duration of IFX treatment was 16 months (IQR 7 – 34, range 2 – 132). In total, 2291 infusions were administered (median 10.5, IQR 6 – 21, range 3 – 86). Patients were followed for a median of 25 months (IQR 13 – 40, range 3 – 132) after start of IFX treatment, with 20 patients (13%) having a follow-up of more than 5 years.

Analysis of the entire cohort demonstrated that 15 patients (10%) had a prolonged response of at least 3 months after cessation of IFX therapy, 92 patients (61%) required repeated IFX infusions, while 40 patients (26%) had loss of response and 5 patients (3%) had no initial response to treatment.

Figure 1 shows follow-up of pediatric CD patients treated with IFX. The number of patients on IFX maintenance treatment decreased during the years due to discontinuation of treatment or reaching the end of the follow-up period. The majority of prolonged responders was treated with IFX because of isolated fistulizing disease (9/15), and received a three-dose induction scheme only (10/15). In the five remaining patients, IFX was stopped because of good clinical effect. CRP levels 3 to 7 months after cessation of IFX were available in nine patients, with a median level of 4 mg/L (IQR 3 – 10). Seven patients (47%) remained in remission during a median follow-up of 18 months (range 3 – 29 months). IFX was restarted

in three out of the eight patients with relapse of disease and this was successful in two of them.

Forty-six percent (42/92) of the patients who required repeated IFX infusions, received concomitant medication at the end of the follow-up period: thiopurines (n=26), methotrexate (n=8), 5-amino-salicylic-acids (n=7) and corticosteroids (n=1). Four of the six patients requiring IFX after 5 years continued IFX treatment until the end of the follow-up period (range 61 – 81 months). The remaining two patients lost response after 69 and 101 months, respectively.

Kaplan-Meier analysis showed that the cumulative probability of losing response to IFX in patients who required repeated infusions, was 13% (±3.1%), 40% (±5.5%), and 50% (±9.2%) after 1, 3 and 5 years, respectively (Figure 2).

Table 1 | Patient characteristics at start of infliximab treatment (n=152).

Gender (male), no. (%)	81 (53.3)
Age at start treatment (yr), median (IQR)	15.0 (13.1 – 16.4)
Disease duration before start of infliximab (yr), median (IQR)	1.8 (0.8 – 3.0)
Disease location at diagnosis, no. (%)	
Small bowel	13 (8.6)
Colon	43 (28.3)
Both	95 (62.5)
Isolated perianal fistulas	1 (0.7)
Previous surgery, no. (%)	32 (21.1)
Bowel surgery	16 (10.5)
Fistula correction	15 (9.9)
Both	1 (0.7)
Previous medication, no. (%)	
Corticosteroids	136 (89.5)
Exclusive enteral nutrition	63 (41.4)
Thiopurine	143 (94.1)
Methotrexate	38 (25.0)
5-Amino-salicylic acids	99 (65.1)
Indication for infliximab, no. (%)	
Refractory luminal disease	105 (69.1)
Refractory luminal disease and perianal fistulas	19 (12.5)
Refractory luminal disease and growth retardation	12 (7.9)
Perianal fistulas	11 (7.2)
First line	5 (3.3)

IQR=interquartile range

Adjustments in treatment schedule

Adjustments in treatment schedule at any time during follow-up were made in 74/152 (49%) of the patients. In 28 of the 40 patients who lost response to IFX (70%), an adjustment in treatment schedule was made before it was decided that IFX treatment had failed. Forty out of 92 (44%) patients with IFX requirement needed intensification of treatment, which was temporary in twelve patients. The median time to any adjustment in treatment schedule was 6 months (IQR 3 – 11). The timing of adjustments in treatment schedule is displayed in Figure 1.
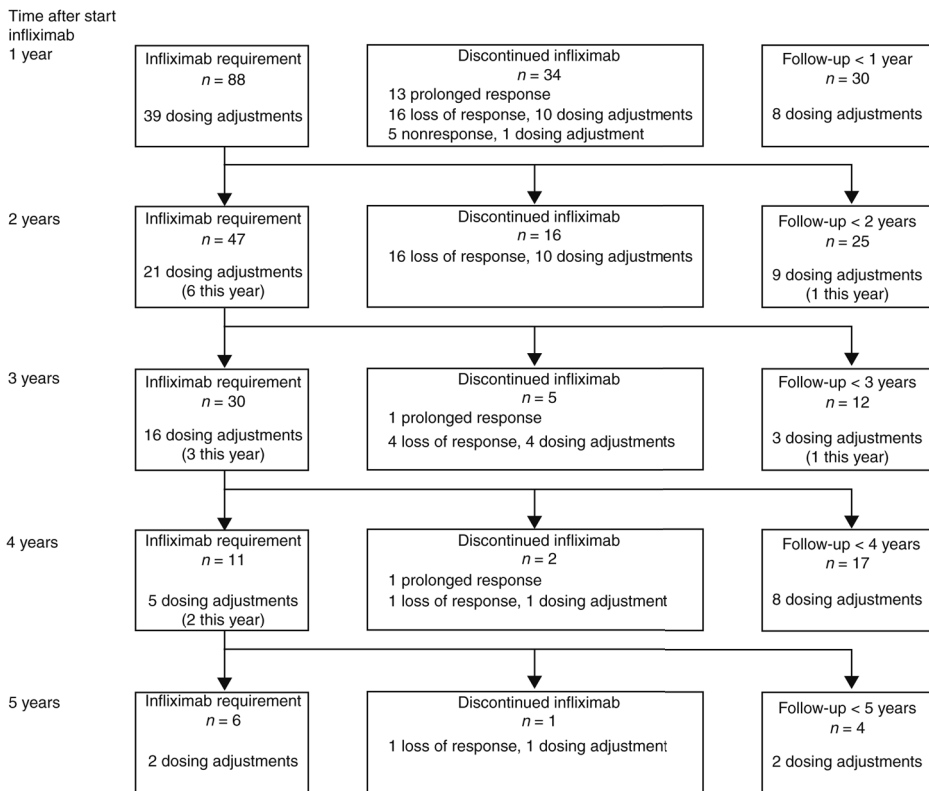

Figure 1 | Outcome of infliximab according to duration of treatment in 152 pediatric Crohn's disease patients. Patients with infliximab requirement drop out, because treatment is discontinued (prolonged response, loss or response), or end of follow-up is reached.

Fifty-four patients (73%) had initial adjustment with a decreased interval of 4 – 7 weeks between two infusions, in 16 patients (22%) the initial adjustment was a dosage increase

and in two patients both adjustments were made at the same time. In two patients, the sequence of the adjustments was unknown. Eventually, 32 of the 74 patients (43%) needed both a decrease in interval between two infusions and an increase in dosage.
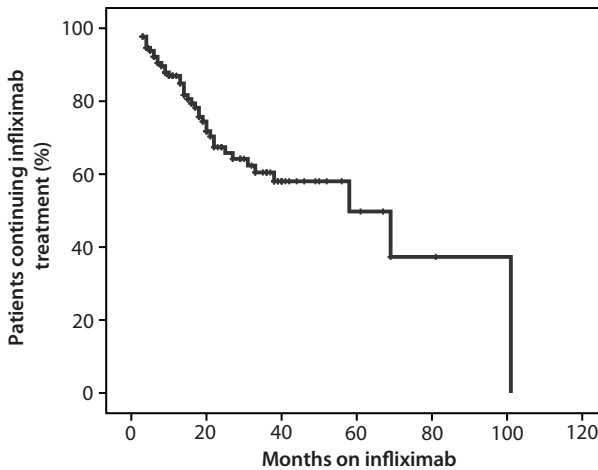

Figure 2 | Kaplan-Meier analysis of duration of infliximab treatment in pediatric Crohn's disease patients who initially required repeated infusions (n=132: patients with infliximab requirement (n=92) and loss of response (n=40)). Discontinuation of treatment is caused by loss of response to infliximab maintenance therapy.

Clinical predictors of IFX failure

None of the following factors were predictive of IFX failure in univariate analysis (log-rank test): disease location (p=0.75), initiation of IFX within one year after diagnosis (p=0.73), and previous bowel surgery (p=0.26). There was a trend toward a higher risk of IFX failure in females (p=0.063). Since gender did not meet the proportional hazards assumption, we had to perform a stratified multivariate proportional hazards analysis, as displayed in Table 2. Again, we found no independent predictors of IFX failure.

Treatment in case of IFX failure

Primary or secondary IFX failure was seen in a total of 45 patients. In most patients (n=35) maintenance treatment with an immunomodulator, including thiopurines (n=20) or methotrexate (n=15), was continued or restarted. Twenty-four patients underwent surgery (53%): bowel surgery in 19 patients, fistula correction in two patients and both bowel surgery and fistula correction in three patients. The median time between start of IFX treatment and surgery was 15.5 months (IQR 4 – 24). Despite the need for surgery, IFX

was continued in twelve patients: eight were still being treated with IFX at the end of the follow-up period, three patients eventually needed other medication and one patient was unsuccessfully treated with adalimumab and switched back to IFX treatment. There was a great variety in other treatment strategies used after IFX failure: adalimumab (n=20), corticosteroids (n=6), exclusive enteral nutrition (n=4) and/or restart of IFX (n=5). This latter treatment strategy was successful in two patients, but they required IFX again at the end of the follow-up period. A small minority of patients was treated with certolizumab (n=2), thalidomide (n=1) or anti-CD3 (n=2).

Table 2 | Predictors of infliximab failure (i.e. non-response or secondary loss of response) in stratified multivariate Cox proportional hazards regression analysis.

	HR	95% CI	P
Age at diagnosis	0.99	0.88 – 1.11	0.86
Disease location at diagnosis			
Small bowel	1		
Colon	1.68	0.38 – 7.40	0.50
Both	1.55	0.36 – 6.66	0.55
Initiation of IFX within 1 yr after diagnosis	0.83	0.40 – 1.70	0.61
Previous bowel surgery	1.41	0.61 – 3.25	0.42

Analysis was stratified according to gender.
HR = hazard ratio; CI = confidence interval; IFX = infliximab.

Adverse events

Among the entire cohort of patients, 17 patients (11%) experienced a type 1 allergic reaction during infusion. Reactions resolved spontaneously or after administration of intravenous corticosteroids and/or an antihistaminic. Treatment with IFX had to be discontinued in three patients because of recurrent allergic reactions despite prophylaxis. In total, 25 patients (16%) developed a mostly mild infection during treatment with IFX (e.g. gastroenteritis, upper respiratory tract infection, pneumonia, herpes infection, fungal infection, Clostridium colitis). However, one patient developed uncontrollable bacterial sepsis 5 months after start of IFX and died (previously published by de Ridder et al.[17]). Another serious infection (severe reactivation of EBV infection) was seen in a twelve-year old patient, which required temporary discontinuation of IFX treatment. A third patient refused further treatment with IFX because of a range of side effects (frequent upper respiratory tract infections, headache and mood swings). There was no significant difference in occurrence of infections between successfully treated patients and patients in whom IFX therapy failed (14% vs. 22%; p=0.24). Twelve patients (8%) reported a wide variety of skin eruptions (e.g. eczema, psoriasiform lesions) during the course of IFX treatment, but there was no need for discontinuation of

treatment. There was no significant relation between the occurrence of skin eruptions and treatment outcome (8% in successfully treated patients; 9% in patients in whom IFX therapy failed; p=0.75). No gender differences were found in the occurrence of allergic reactions, infections and skin eruptions (p=1.0; p=0.38; p=1.0).

One patient developed a basal cell carcinoma on the scalp 27 months after start of IFX therapy. Drug-induced lupus was seen in one patient, who discontinued treatment and switched to adalimumab. No other autoimmune phenomena were observed. Serum sickness-like disease, demyelination and heart failure[18] were not observed in this cohort of patients.

DISCUSSION

Our study describes the longest follow-up until now of a large, multicenter cohort of pediatric CD patients receiving induction with IFX followed by scheduled maintenance treatment in the majority of patients. Although IFX treatment is effective in children with refractory CD, our study shows that the therapeutic effect decreases over time with loss of response in 50% of patients who initially required repeated infusions, after 5 years. Adjustments in treatment schedule, decreased intervals and/or dosage increases, were required in 49% of the patients in order to maintain clinical response, with a median time to any adjustment of 6 months.

Recently, another large multicenter cohort study reported on the long-term outcome of IFX maintenance therapy in pediatric CD.[14] This study showed that 33% of patients discontinued IFX treatment after 3 years due to several reasons (elective, loss of response, primary non-response, allergy). The results on frequency and timing of dose adjustments were comparable with our results. Since our study only examined IFX discontinuation due to loss of response, these outcomes are somewhat difficult to compare. However, it seems that discontinuation of IFX due to loss of response occurred more frequently in our cohort of patients (40% loss of response after 3 years). An explanation for this difference could be the earlier introduction of IFX in the USA: the median interval between diagnosis and start of IFX was 9 months compared to 1.8 years in our study. This probably indicates more severe and complicated disease courses in our patients, which is reflected by the larger proportion of patients who underwent surgery before IFX initiation in our study (21% compared to 6% in the study of Hyams et al.). Another reason for the difference in loss of response could be the higher frequency of concomitant use of corticosteroids (9% at 3 years of follow-up compared to 1% in our study).

Our study found a trend toward a higher risk of IFX failure in females. Interestingly, male IBD patients seem to have the highest risk of developing HSTCL. It could be hypothesized that male patients achieve higher serum IFX concentrations compared to females. Pharmacokinetic differences have been found in male and female adult IBD patients treated

with IFX.[19] These findings warrant further investigation. In contrast with two previous studies[4, 7], we did not find an association between treatment outcome and disease duration before start of IFX. This may be explained by several factors. In the first study, only one IFX infusion was administered, while all patients in our study received induction with IFX usually followed by scheduled maintenance treatment. Current CD treatment guidelines[20-21] recommend a three-dose induction scheme and scheduled maintenance treatment, indicating that a single infusion is less effective for maintenance of response. In the second study, treatment effect was determined already after 18 weeks, while our study assessed treatment outcome after a median of 25 months. In addition to disease duration, disease location has been suggested as a predictor of response to IFX. Two adult studies have shown that patients with isolated colonic disease were more likely to respond to IFX, at least on the short term.[22-23] In our cohort, we did not find a relation between disease location and treatment outcome, which might have been caused by differences in distribution of disease locations between adults and children.[24] A recent study demonstrated that adult patients with objective evidence of inflammation (high CRP level and/or mucosal lesions at endoscopy) had the best clinical results with IFX.[25] These factors were not assessed in our study.

Infections and infusion reactions were the most frequently observed complications of IFX treatment in our study. Infections were seen in 16% of patients and were mild, except in two patients. Allergic reactions during IFX therapy occurred in 11% of our patients, which is comparable to previous reports.[9, 26] One young man developed a basal cell carcinoma on the scalp at 18 years of age, 27 months after start of IFX therapy. Before IFX monotherapy, he was treated with azathioprine and methotrexate. Non-melanoma skin cancer (NMSC) has been reported before in adult IBD patients on IFX treatment.[18, 27-29] A recent study showed that the increased risk for NMSC was especially associated with thiopurine use, but also, to a lesser extent, with biologic treatment.[30]

Hepatosplenic T cell lymphoma was not observed in our cohort; our patient population is relatively small and follow-up too short to detect this extremely rare complication. The alarming effect that reporting of HSTCL had on pediatric gastroenterologists probably caused a decrease in the concomitant use of thiopurines after initiating IFX therapy. In our study, only 28% of patients, who required repeated infusions, received concomitant thiopurines, compared to 64% of the patients in our previous study.[9]

Our data should be interpreted in the context of the following limitations. First of all, our study is observational and thus a reflection of daily practice. Decisions concerning adjustments in treatment schedule or discontinuation of IFX treatment were based on the judgment of the pediatric gastroenterologist and did not follow a standardized protocol. Since different schedules for patient visits were used, it was not possible to use the Pediatric Crohn's Disease Activity Index (PCDAI) or other clinical scores to determine disease activity at set time points. Furthermore, there could be an overlap between patients with a prolonged response to IFX

and IFX requirement. The majority of prolonged responders was treated with IFX before pediatric treatment guidelines were available and therefore only received a three-dose induction scheme. Current treatment guidelines do not recommend stopping successful IFX treatment, which has resulted in a decreasing number of prolonged responders in the last 2 years of our study. Vice versa, it was not routinely attempted to stop IFX in patients who required repeated infusions. Seven out of 92 patients (8%) with IFX requirement received IFX every 10 or 12 weeks at the end of the follow-up period. It is possible that these patients would have had a prolonged response after cessation of IFX. In the remaining 85 patients the risk of flaring was probably considered too high, which is supported by the finding that 46% of these patients required an adjustment in treatment schedule. Another limitation of our study is the absence of data on the formation of antibodies against IFX. Previous adult and pediatric studies have shown that the development of these antibodies is associated with a reduced duration of response to IFX treatment.[31-32] We are also unaware of the effect of changes in concomitant treatment during IFX on treatment outcome. Finally, our study does not include pediatric CD patients older than 16 years whose treatment was initiated by an adult gastroenterologist. However, there is no reason to assume that these patients are different from patients treated by pediatric gastroenterologists.

In conclusion, the present study underlines that IFX is an effective therapy in children with refractory CD. However, there are concerns regarding the durability of long-term IFX maintenance treatment, as 50% of patients on IFX maintenance treatment lose their initial therapeutic response after 5 years. Dose adjustments after start of IFX are frequently needed to regain therapeutic benefit. In contrast to previous studies, loss of response was not found to be associated with disease duration or disease location. These findings emphasize the need for effective long-term treatment strategies for pediatric CD, as well as the need for predictors of response to IFX treatment to select the most suitable patients for this treatment. This will prevent exposure and toxicity in patients who will not benefit from IFX.

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Chapter

8

Antitumor necrosis factor treatment for pediatric inflammatory bowel disease

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ABSTRACT

Infliximab, adalimumab, and certolizumab are monoclonal antibodies against tumor necrosis factor-α (TNFα), a proinflammatory cytokine with an increased expression in the inflamed tissues of inflammatory bowel disease (IBD) patients. Currently, infliximab is the only anti-TNF drug that has been approved for use in refractory pediatric Crohn's disease (CD). Nevertheless, adalimumab and certolizumab have been used off-label to treat refractory pediatric IBD. Over the past 10 years, anti-TNF treatment has been of great benefit to many pediatric IBD patients, but their use is not without risks (infections, auto-immune diseases, malignancies). Despite the growing experience with these drugs in children with IBD, optimal treatment strategies still need to be determined. The purpose of this review is to summarize the current knowledge on the use of anti-TNF drugs in pediatric IBD and to discuss the yet unsolved issues.

INTRODUCTION

Inflammatory bowel disease (IBD) may present during childhood or adolescence in up to 20 – 30% of all patients.[1] There seems to be a worldwide trend toward increasing incidence rates of pediatric IBD.[2] Unique to pediatric-onset disease is the occurrence of linear growth impairment and delay in puberty, which can be present at diagnosis and may be a sign of ongoing inflammation during the course of disease. As in adults, the phenotypic spectrum of IBD in children and adolescents is variable. Nevertheless, specific demographic and phenotypic differences characterize early- versus later-onset disease.[3-4] For instance, Crohn's disease (CD) occurring prior to puberty affects a preponderance of males, whereas adult females are more commonly affected; most pediatric CD patients have ileocolonic disease, while adults more often present with isolated terminal ileal disease or isolated colonic disease; and ulcerative colitis (UC) presents with more extensive disease in children than in adults.

The treatment paradigm for pediatric IBD is quite similar to adult treatment, with induction and maintenance of remission as main treatment goals. In children, special considerations in treatment are needed regarding optimal growth and development.[4] In pediatric CD, both exclusive enteral nutrition (EEN) and corticosteroids are effective for induction of remission.[5] However, EEN has significant advantages over steroids due to its beneficial effect on growth, and fewer side effects. As in adult patients, thiopurines such as azathioprine (AZA) and 6-mercaptopurine (6-MP) are used for maintenance of remission, and are often introduced at the time of remission induction. Methotrexate (MTX) is an alternative to thiopurines when these drugs are ineffective or not tolerated. Pediatric UC is usually managed with aminosalicylates and corticosteroids, depending on disease extent and severity. Maintenance treatment consists of aminosalicylates, or thiopurines for patients with relapsing disease.[6]

Over the last decade, the introduction of anti-tumor necrosis factor (TNF) drugs has dramatically changed the treatment and management of IBD, especially in patients who are refractory to or intolerant of the conventional treatment regimens. Currently, there are three anti-TNF drugs that are licensed by the US Food and Drug Administration (FDA) to treat CD in adult patients: infliximab (IFX), adalimumab (ADA), and certolizumab pegol. IFX is also registered for use in adult UC. In pediatric IBD, IFX is the only anti-TNF drug that has been approved by the FDA, and only for use in refractory CD.[7] Nevertheless, all anti-TNF drugs have been used off-label to treat refractory pediatric IBD. In recent years, long-term follow-up data on IFX use in pediatric CD, increasing data on IFX use in pediatric UC, and on ADA use in pediatric CD have become available. This review will focus on the current evidence supporting the use of anti-TNF drugs in pediatric IBD patients. We will also address and discuss the yet unsolved issues regarding anti-TNF treatment in pediatric IBD.

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MECHANISM OF ACTION

TNFα, a cytokine produced by activated macrophages, monocytes, and T-cells[8], is a key mediator in immune responses, and has an increased expression in the mucosa of inflamed intestine.[9-10] This cytokine exerts its activity as either the cell surface-associated prepeptide (transmembrane TNFα), or as the cleavage product (soluble TNFα) generated by TNFα converting enzyme. Soluble TNFα mediates its biological activities through type 1 and 2 TNF receptors of remote tissues, while the biological activities of transmembrane TNFα are supposed to be mediated mainly through type 2 TNF receptors. Both receptors can bind intracellular adaptor proteins leading to the activation of a complex signaling cascade.[11] This cascade is responsible for a wide range of cellular responses, including cell death, survival, differentiation, proliferation, and migration.[8] Transmembrane TNFα also functions as a receptor that transmits outside-to-inside (reverse) signals back into TNFα producing cells.[11]

Currently, three anti-TNF antibodies are approved by the FDA for the treatment of adult IBD. IFX (Remicade®; Centocor, Malvern, Pennsylvania, USA) is a monoclonal chimeric anti-TNF antibody (75% human, 25% murine)[12], ADA (Humira®; Abbott Laboratories, Chicago, Illinois, USA) is a fully humanized monoclonal anti-TNF antibody, and certolizumab (Cimzia®; UCB, Brussels, Belgium) is a humanized monoclonal anti-TNF antibody Fab' fragment which is chemically linked to polyethylene glycol.[13] All three anti-TNF agents can bind and neutralize soluble and transmembrane TNFα.[14-15] However, neutralization of TNFα is probably not the sole mechanism of action of anti-TNF treatment in IBD, as etanercept and onercept (both human soluble TNF receptors) were ineffective in inducing remission in CD patients.[16-17] Several working mechanisms of anti-TNF treatment have been proposed that are independent of their TNFα neutralizing capacity, such as induction of apoptosis in T-cells and monocytes by binding of transmembrane TNFα[18-20], antibody-dependent cell-mediated cytotoxicity, and complement-dependent cytotoxicity.[11, 14, 21] Certolizumab does not have these functional properties, suggesting that they are not essential for the efficacy of anti-TNF drugs.[14] Recently, the importance of binding to Fc-receptors in the mechanism of action of anti-TNF antibodies was demonstrated by Vos et al.[22] In vitro, IFX, ADA, and certolizumab-IgG induced formation of a distinct macrophage subset in an Fc-region-dependent manner. These macrophages had immunosuppressive capacities, including the production of anti-inflammatory cytokines and inhibition of T-cell proliferation.

Understanding the exact mechanisms of action of anti-TNF drugs and their relationship with clinical effects will contribute to the optimization of these treatments, and to the development of new anti-TNF agents.

CLINICAL EFFICACY OF IFX IN PEDIATRIC CD

IFX as induction therapy

After the first use of IFX in 1992 in a 13-year old girl with severe colonic CD[23], randomized clinical trials in adult CD patients have confirmed the clinical benefit of IFX induction therapy.[24-25] In children, mostly small, non-randomized studies have reported on the outcome of IFX induction treatment.[26-36] The results of these studies are summarized in Table 1. It is somewhat difficult to compare the results of these studies because of different infusion schedules, different definitions for response and remission, and variable timing of evaluating treatment response, as well as differences in concomitant immunomodulator therapy. Overall, these studies demonstrated that IFX was very effective in the majority of pediatric CD patients, but relapse of disease was common after discontinuation of IFX treatment (despite continuous use of thiopurines or MTX). Additionally, IFX induction treatment proved to be successful in achieving mucosal healing.[28, 31] Results of pharmacokinetic assessments indicated that serum IFX concentrations in pediatric patients were similar to those in adults.[28]

IFX for fistulizing CD

Although the presence of fistulas (in combination with luminal disease) is often an indication to start IFX therapy, data on the efficacy of IFX in children with fistulizing CD are based on a small number of patients.[29-30, 36-38] Table 2 summarizes the results of these studies. Recently, Crandall et al. performed post-hoc analyses on the effect of IFX upon concurrent perianal disease in a subpopulation of 31 pediatric CD patients of the REACH study (28%).[38] Twenty-two patients had perianal disease at baseline. Two weeks after a single IFX infusion, 9 patients (41%) attained partial or complete response. At week 54, complete response was achieved in 15 patients (68%), and partial response in one patient (5%). Nine patients without perianal disease at baseline developed fistulas during IFX treatment: 7 had complete response, and 2 had no response at week 54.

IFX for treatment of enterovesicular fistulas in children has been described in only two case series.[39-40] In total, 8 children received a 3-dose induction schedule with a variable outcome. Despite closure of the enterovesicular fistulas, surgery of severe underlying bowel disease was still required in 2 patients. In 3 patients, IFX failed in closing the fistulas, and the remaining 3 patients had reduction of their symptoms.

Overall, the reported data suggest that IFX is effective in the treatment of children and adolescents with fistulizing CD.

IFX as maintenance therapy

Placebo-controlled trials have demonstrated that IFX is effective in maintaining remission in adult CD patients.[25, 41] In pediatric CD, there are no placebo-controlled, double-blind prospective studies on IFX maintenance therapy. The largest randomized study was the

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Table 1 | Overview of studies on the efficacy of infliximab induction therapy in pediatric Crohn's disease.

Study	N	Age (yr)	Concomitant IS	Infliximab	Treatment outcome	Definition used for treatment outcome
Hyams et al. [26]	19	Mean 14.4	74%	1 to 3 infusions (5 mg/kg)	*Wk 12:* significant decrease in PCDAI	
Kugathasan et al. [27]	15	Mean 12.8	87%	1 infusion (5 mg/kg)	*Wk 4:* 93% response *Wk 10:* 67% remission *Wk 52:* 21% prolonged response	Response: PCDAI improvement of ≥ 25 Remission: PCDAI ≤ 15
Baldassano et al. [28]	21	Median 15	71%	1 infusion (1, 5, or 10 mg/kg)	100% response, 48% remission at some point during a 12-wk follow-up	Response: PCDAI improvement ≥ 10 or modified CDAI decrease ≥ 70 Remission: PCDAI < 10 or modified CDAI < 150
Cezard et al. [29]	21	Mean 15	95%	3 infusions (5 mg/kg) on days 0, 15, and 45)	*Day 45:* 90% remission *Wk 52:* 10% prolonged response	HBI ≤ 4
Lionetti et al. [30]	22	Mean 13	64%	mean 3.3 infusions with an interval range from 2 – 12 wk	*Wk 18:* significant decrease in PCDAI	
Borrelli et al. [31]	18	Median 13	100%	3 infusions (5 mg/kg on wk 0, 2, and 6)	*Wk 8:* 56% remission	PCDAI ≤ 10
Lamireau et al. [32]	88	Median 14	82%	median 4 infusions	*Day 90 (±7):* 34% remission, 53% improvement in symptoms, 13% relapse	Remission: HBI ≤ 4 and ESR ≤ 20 mm, or fistula closure
Afzal et al. [33]	24	Median 13	100%	3 infusions (5 mg/kg on wk 0, 2, and 6)	*After induction:* 71% remission 82% relapse within 4 months of 3rd infusion	HBI < 4
Hyams et al. [34]	112	Mean 13.3	100%	3 infusions (5 mg/kg on wk 0, 2, and 6)	*Wk 10:* 88% response, 59% remission	Response: PCDAI improvement ≥ 15, with a total PCDAI score of 30 or less Remission: PCDAI ≤ 10
Wynands et al. [35]	38	Mean 13.8	84%	3 infusions (5 mg/kg on wk 0, 2, and 6)	*Wk 12:* 95% remission	HBI < 5
Ruemmele et al. [36]	40	Mean 13.9	100%	3 infusions (5 mg/kg on wk 0, 2, and 6)	*Wk 10:* 85% remission	HBI < 5 and/or complete fistula closure

IS: immunosuppression at start of infliximab treatment (use of thiopurines or methotrexate). PCDAI: Pediatric Crohn's Disease Activity Index. CDAI: Crohn's Disease Activity Index. HBI: Harvey-Bradshaw Index. ESR: erythrocyte sedimentation rate.

Table 2 | Overview of pediatric studies on the efficacy of infliximab in fistulizing Crohn's disease.

Study	N	Infliximab	Effect on fistula
Cezard et al. [29]	12	3-dose induction days 0, 15, 45	*Day 90*: 100% fistula closure
Lionetti et al. [30]	13	mean 3.3 infusions, interval range 2 – 12 wks	*Wk 18*: 54% fistula closure, 23% partial response, 23% minimal response
Ruemmele et al. [36]	13	3-dose induction wk 0, 2, 6	*Wk 10*: 69% complete fistula closure
De Ridder et al. [37]	16	Various treatment schedules Mean 7 infusions	*After a mean follow-up of 25 months*: 56% fistula closure or drainage cessation
Crandall et al.* [38]	22	3-dose induction wk 0, 2, 6 Randomization wk 10: infliximab every 8 or 12 wk	*Wk 2*: 41% partial or complete response** *Wk 54*: 73% partial or complete response**

* Post-hoc analyses of the REACH study [34]
** *Partial response:* initial perirectal subscore of 10 (active fistula, drainage, tenderness or abscess) decreasing to 5 (1 – 2 indolent fistula, scant drainage, no tenderness); *Complete response:* initial perirectal subscore of 5 or 10 decreasing to 0 (no symptoms or asymptomatic tags)

REACH study: an industry-driven prospective, open-label investigation of a 3-dose induction with IFX in moderate to severely active pediatric CD, followed by doses at either 8 or 12 week intervals for maintenance.[34] At baseline, 112 patients on concomitant immunosuppression (IS) received an induction regimen of 5 mg/kg IFX at weeks 0, 2 and 6. At week 10, 103 patients were randomized to receive IFX maintenance treatment every 8 weeks (n=52) or every 12 weeks (n=51). At the endpoint visit of 54 weeks, 29 patients (56%) in the 2-month interval group were in clinical remission (PCDAI (Pediatric Crohn's Disease Activity Index) ≤ 10) and not requiring dose adjustments compared with 12 patients (24%) in the 3-month interval group (p<0.001). Response to IFX was associated with improved quality of life. During the study, 32 patients (31%) needed dose adjustments due to loss of response: dosage increase to 10 mg/kg (n=9), reduction in dose interval to 8 weeks (n=10), or both adjustments (n=13). These adjustments were successful in 75% (24/32) of patients. Allowing for dose intensification in case of relapse, remission rates at week 54 were also superior with every 8 week dosing compared with every 12 week dosing (71% vs. 47%, p=0.02). In conclusion, the REACH study demonstrated that maintenance therapy every 8 weeks was superior to every 12 weeks in maintaining clinical response and remission in pediatric CD.

There is another randomized, open-label study (n=40) on the efficacy of IFX as maintenance therapy for active pediatric CD, which demonstrated the superiority of scheduled IFX maintenance treatment over episodic IFX treatment.[36] In addition, several observational studies, both prospective and retrospective, have been published on the efficacy of repeated use of IFX in pediatric CD.[35, 42-49] The results of all randomized and observational studies are summarized in Table 3.

Adjustments in treatment schedule (dose escalation, reduction in dose interval, or both) were frequently needed to maintain clinical remission, with rates varying from 27% to 49%.[35, 46-48] The median time to any dose adjustment was 6 to 9 months.[46-47] Intestinal surgery after initiation of IFX was performed in 25 – 35% of pediatric CD patients.[42, 45, 48] Crombé et al. estimated that the cumulative risk of intestinal surgery in children after initiation of IFX was 14% at year 1, 24% at year 3, and 30% at year 5.[48]

Taken together, IFX has proven to be an effective maintenance therapy for pediatric CD, but a substantial number of patients lose initial response and require dose adjustments to maintain clinical response. Current international treatment guidelines recommend IFX for induction and maintenance of remission in pediatric CD patients with moderate to severe disease, refractory to or intolerant of conventional treatment.[5] Current clinical practice is to administer IFX infusions (5 mg/kg) at 0, 2, and 6 weeks (induction therapy). When this 3-dose induction schedule has been effective, patients continue with scheduled maintenance infusions every 8 weeks. Dose escalation or reduction in dose interval may (temporarily) be required to prolong the duration of remission.

IFX and growth retardation

Growth retardation is a common complication of pediatric CD, and restoration of normal growth is considered a marker of therapeutic success.[50] Chronic undernutrition and direct effects of proinflammatory cytokines (such as TNFα, interferon γ, IL-6) are the two major and interrelated factors responsible for growth impairment in children with CD.[51]

IFX treatment has been reported to improve both height velocity and height for age SD scores (SDS) in children with refractory CD, especially in patients who were treated prior to or in early puberty.[52-53] The REACH study and the open-label extension study also reported on the positive effect of IFX on linear growth.[34, 49] Mean baseline height for age SDS of patients with at least one year delay in bone age improved significantly at both week 30 (mean improvement in SDS of 0.3) and week 54 (mean improvement in SDS of 0.5). Improvement in height status continued throughout the open-label extension, with median changes from baseline of the main study of 0.82 (n=15) at the end of 2 years of IFX therapy, 1.01 (n=10) at the end of year 3, and 1.56 (n=4) at the end of year 4. Significant increases in mean height for age SDS or height velocity SDS were also observed in four other studies.[29, 31, 36, 48] In contrast, three retrospective studies found no significant improvement of growth, but details on pubertal status were not available in these patients.[42, 44, 54] Other discouraging data have been reported by Pfefferkorn et al.: despite frequent use of immunomodulators and IFX, growth delay persisted in many children with CD in the first 2 years following diagnosis.[55]

IFX induction therapy can improve biomarkers of bone formation, as was demonstrated by Thayu et al.[56] Serum bone-specific alkaline phophatase (BSAP), N-terminal propeptide of type 1 collagen (P1NP), urine C-telopeptide of collagen cross-links (CTX-1), and

deoxypyrodinoline increased significantly during induction, and were associated with increases in height for age SDS at 54 weeks.

In conclusion, the majority of data suggest that IFX treatment has a beneficial effect on growth in children with growth impairment due to CD, especially in the prepubertal and early-pubertal patients.

CLINICAL EFFICACY OF IFX IN PEDIATRIC UC

In adult patients with moderate or severe UC, placebo-controlled studies have proven that IFX can be effective in inducing and maintaining remission, and in preventing colectomy in the short-term.[57-60] In children with refractory UC, data on the efficacy of IFX treatment are limited to two prospective cohort studies[61-62], and several small, retrospective case series.[63-69] Turner et al. described a prospective cohort of 128 children hospitalized for severe acute UC.[61] Thirty-three of 37 patients failing intravenous corticosteroids were treated with IFX. Short-term response (Pediatric Ulcerative Colitis Activity Index (PUCAI) < 35) was seen in 76% (25/33) of these patients, while 52% (13/25) had a sustained response during a 1-year follow-up period. Seven patients (28%) who initially responded to IFX and continued treatment after discharge, underwent colectomy within one year.

In the second prospective study, 52 of 332 (16%) pediatric UC patients (mean age 13.3 years, 54% male) were treated with IFX after a median disease duration of 9 months.[62] The indication to initiate IFX was steroid-refractory disease in 63% of patients, and steroid-dependent disease in 35% of patients. Most patients (65%) received a 3-dose induction schedule followed by scheduled maintenance treatment. Inactive disease (as assessed by the Physician's Global Assessment (PGA)) without use of corticosteroids was noted in 12/47 (26%) patients at 3 months, 12/44 (27%) at 6 months, 15/39 (38%) at 12 months, and 6/28 (21%) at 24 months. Dose adjustments were needed in 53% of patients on scheduled maintenance therapy. The likelihood of remaining colectomy-free after initiation of IFX treatment was 75% after 6 months, 72% after 12 months, and 61% after 24 months.

Retrospective case series have reported their experience with IFX treatment in 9 to 40 pediatric UC patients who were unresponsive to conventional treatment (i.e. steroid-dependent colitis, steroid-refractory colitis, acute severe colitis).[63-69] Using various definitions, response rates varied between 55% and 77% after differing periods of follow-up (range: 2 weeks – 27 months). Colectomy rates of 29 – 39% were reported.

A systematic review on the treatment of acute severe colitis in children pooled the results of six pediatric studies on the use of IFX in refractory severe UC.[70] The pooled short-term IFX success rate (in most cases indicating discharge from the hospital without the need for colectomy) was 75% (95% confidence interval (CI): 67% – 83%), and the long-term success rate (avoidance of colectomy) was 64% (95% CI: 56% – 72%).

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Table 3 | Overview of studies on the efficacy of repeated infliximab infusions in pediatric Crohn's disease.

Study	N	Age (yr)	Concomitant IS	Infliximab	Treatment outcome	Definition used for treatment outcome
Hyams et al. [34]	112	Mean 13.3	100%	3-dose induction wk 0, 2, 6 Randomization wk 10: IFX every 8 wk (group A) IFX every 12 wk (group B)	*Wk 54:* 56% remission (group A), 24% remission (group B)	PCDAI ≤ 10
Ruemmele et al. [36]	40	Mean 13.9	100%	3-dose induction wk 0, 2, 6 Randomization wk 10: IFX every 8 wk (group A) IFX on demand (group B)	*Wk 60:* 83% remission (group A), 61% remission (group B)	HBI < 5 and/or complete fistula closure
Wewer et al. [42]	24	Median 15.4	92%	IFX on demand, scheduled IFX infusions Median 4 infusions	*90 days after intended cessation of IFX:* 29% prolonged response, 42% IFX dependency, 25% no response	Prolonged response: (total) regression of symptoms. IFX dependency: necessity of repeated infusions to maintain clinical response. No response: no regression of symptoms.
Duricova et al. [43]	82	8 – 18	91%	Induction only, IFX on demand, scheduled IFX infusions Median 7 infusions	*After 3 to 75 mo follow-up:* 22% prolonged response, 66% IFX dependency, 12% no response	See study by Wewer et al.
Wynands et al. [35]	38	Mean 13.8	84%	3-dose induction wk 0, 2, 6 (group A) 3-dose induction wk 0, 2, 6 followed by IFX every 8 wk for 1 year (group B)	*Wk 52:* 25% remission (group A), 58% remission (group B) *Wk 104:* 27% remission (after withdrawal of IFX in group B)	HBI < 5
Sinitsky et al. [44]	16	Mean 13.0	94%	3-dose induction wk 0, 2, 6 followed by IFX every 8 wk	*Yr 1:* 83% clinical remission; 58% relapse at some time during 1st yr	PCDAI < 15
de Ridder et al. [45]	66	Mean 4.5	98%	IFX on demand, scheduled IFX infusions Mean 15 infusions	*After mean follow-up of 41 mo:* 15% prolonged response, 56% IFX dependency, 29% loss of response	Prolonged response: maintenance of good clinical response minimally 90 days after last IFX infusion. IFX dependency: necessity of repeated infusions to maintain clinical response. Loss of response: initially good clinical response, but finally withdrawal of IFX and switch of medical therapy or surgery

Table 3 | *Continued*

Study	N	Age (yr)	Concomitant IS	Infliximab	Treatment outcome	Definition used for treatment outcome
de Bie et al.* [46]	152	Median 15.0	95%	3-dose induction wk 0, 2, 6 (usually) followed by scheduled IFX infusions Median 10.5 infusions	*After median follow-up of 25 mo:* 10% prolonged response, 61% IFX dependency, 26% loss of response, 3% no response Yr 1: 87% continuing IFX Yr 3: 60% continuing IFX Yr 5: 50% continuing IFX	See study by de Ridder et al.
Hyams et al. [47]	202	Mean 12.7	90%	IFX on demand, scheduled IFX infusions Median 10 infusions	Yr 1: 93% continuing IFX, 54% inactive disease Yr 2: 78% continuing IFX, 67% inactive disease Yr 3: 67% continuing IFX, 57% inactive disease	PGA=1, without requiring concomitant corticosteroids in the preceding quarter or surgery in the previous year
Crombé et al. [48]	120	Median 18	69%	IFX on demand, scheduled IFX infusions	*After median follow-up of 32 mo:* 54% IFX efficacy Yr 1: 82% continuing IFX Yr 3: 55% continuing IFX	Remission according to PGA
Hyams et al.** [49]	60	Mean 13.2	100%	5 mg/kg every 8 or 12 wk, or 10 mg/kg every 8 wk	Modified intention-to-treat analysis: Yr 2: 63% no disease Yr 3: 62% no disease Yr 4: 50% no disease	PGA=1

* Expanded patient cohort of the study by de Ridder et al. [45]
** Open-label extension of the REACH study [34]
IS: immunosuppression at start of infliximab treatment (use of thiopurines or methotrexate). IFX: infliximab. PCDAI: Pediatric Crohn's Disease Activity Index. HBI: Harvey-Bradshaw Index. PGA: Physician's Global Assessment.

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In summary, IFX has a role in the management of children with moderate or severe UC, but appears to be less effective than in pediatric CD. In the short-term, colectomy seems to be prevented in a significant proportion of children with UC, but long-term data are not available. Large multicenter trials are needed to determine the long-term benefit of IFX in different subgroups of pediatric UC patients.

CLINICAL EFFICACY OF ADA AND CERTOLIZUMAB IN PEDIATRIC IBD

ADA has been shown to induce and maintain response in adult CD patients who are naïve to anti-TNF therapy, intolerant of IFX, or have lost response to IFX.[71-74] Recently, a randomized controlled trial demonstrated that ADA was also effective for induction of remission in adult UC patients who failed treatment with corticosteroids and/or IS.[75] Although ADA is not (yet) licensed for use in pediatric IBD, this drug has been used off-label to treat children with refractory disease. Data on the efficacy of ADA treatment in pediatric CD are summarized in Table 4.[76-85] Taken together, ADA treatment seems to be efficacious for inducing and maintaining remission in pediatric CD patients, but follow-up periods have been relatively short. Preliminary results suggest that anti-TNF naïve patients benefit most from ADA treatment. As with IFX maintenance treatment, a significant number of patients lose response to ADA over time and require dose adjustments to maintain response. The optimal dosing scheme for children with CD is yet to be determined, but high-dose ADA for maintenance treatment seems to be more effective than low-dose ADA.

The effect of ADA on refractory pediatric UC has only been described in a few patients: 3 of 4 children with UC were successfully treated with ADA, with the non-responder requiring surgery. Multicenter trials are needed to determine the benefit of ADA in pediatric UC.

Data on the use of certolizumab in IBD are only available for adult patients. Placebo-controlled randomized trials have demonstrated that certolizumab is effective in inducing and maintaining remission in adult patients with moderate to severe CD, whether or not they had previously been treated with IFX.[86-88] Pediatric studies are currently underway to determine the safety and efficacy of certolizumab in children with CD.

ANTI-TNF TREATMENT FOR EXTRAINTESTINAL MANIFESTATIONS OF PEDIATRIC IBD

Approximately 30% of children with IBD will develop at least one extraintestinal manifestation after diagnosis, such as musculoskeletal, dermatological, ophthalmologic and/or hepatobiliary manifestations.[89-90] Anti-TNF treatment for children with extraintestinal symptoms has only been described in case reports and small case series. IFX seemed to be effective in cases of pyoderma gangrenosum, orofacial involvement, erythema nodosum, cutaneous metastatic CD of the penile and scrotal skin, primary lung involvement in IBD, primary sclerosing cholangitis in combination with pancreatitis, and clavicular

osteomyelitis.[91-95] Additionally, both IFX and ADA were effective for pediatric patients with peristomal pyoderma gangrenosum or uveïtis.[96-102]

Evidence from adult studies also suggests that both IFX and ADA can be effective for the treatment of extraintestinal manifestations.[103]

PREDICTORS OF RESPONSE TO ANTI-TNF TREATMENT

Although anti-TNF therapy is effective for the majority of pediatric IBD patients, about 10% of patients do not benefit from induction therapy (primary non-responders)[34, 36, 79], while other patients eventually lose their initial therapeutic response.[46-47, 62, 78] This inter-individual variation in response is likely to be caused by multiple host factors, such as disease and immune phenotype, and genetic background.

In children with CD, episodic IFX treatment has been associated with higher relapse rates compared with scheduled maintenance treatment.[36] Other clear risk factors have not yet been identified, although some interesting data have emerged. Two pediatric studies have suggested that anti-TNF therapy was more effective when therapy was initiated early in the disease course[27, 30], but other studies failed to demonstrate this association in pediatric CD.[29, 32, 46, 77-78] Duricova et al. reported that stricturing/penetrating disease behavior and intestinal surgery prior to IFX treatment were significantly associated with treatment failure.[43] Additionally, retrospective studies have found that young male patients and patients on concomitant IS were more likely to respond to ADA.[77-78] A recent study by Dubinsky et al. found six known susceptibility loci that were associated with primary IFX non-response in pediatric CD, as well as the presence of perinuclear antineutrophil cytoplasmic antibodies (pANCA).[104] In pediatric UC, data on potential predictors of response are scarce. Fanjiang et al. have found that IFX was less effective in patients with chronic steroid-dependent UC than in acutely ill patients[67], but this association was not confirmed by other studies.[62, 66, 68]

For adult IBD patients, an overview on examined predictive factors for successful anti-TNF therapy has been published in a recent review.[105] Factors possibly associated with a better efficacy in CD were: short disease history, younger age at diagnosis, objective evidence of inflammation at start of treatment (increased CRP and/or mucosal lesions at endoscopy), concomitant IS, isolated colonic disease, no previous abdominal surgery, no strictures, and not smoking. In adult UC, a pANCA+/ASCA- serotype and older age were associated with a suboptimal early clinical response to IFX.[106]

To conclude, in current clinical practice, there is no clear guidance as to which type of IBD patient may benefit most from anti-TNF treatment. It is important to find reliable predictors of response to optimize treatment and to improve the benefit-risk profile of anti-TNF drugs.

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Table 4 | Overview of studies on the efficacy of adalimumab therapy in pediatric Crohn's disease.

Study	N	Age (yr)	Prior IFX	Adalimumab	Treatment outcome	Definition used for treatment outcome
Hyams et al. [76]	192	64% ≥ 13 yr	44%	*Induction:* 160/80 mg (when ≥40 kg), 80/40 mg (when <40 kg) *Maintenance,* double-blind, randomization wk 4: Low-dose (per body weight) 20 or 10 mg eow High-dose (per body weight) 40 or 20 mg eow	*Wk 4:* 80% response (160/80 mg), 87% response (80/40 mg) *Wk 26:* 28% remission (low-dose), 39% remission (high-dose); higher remission rates in IFX naïve patients	Response: PCDAI decrease ≥ 15 from baseline Remission: PCDAI ≤ 10
Rosh et al. [77]	115	Mean 15.8	95%	*Induction:* 160/80 mg (19%), 80/40 mg (44%), 40/40 mg (15%), other (8%), unknown (14%) *Maintenance:* 80 mg (5%), 40 mg (88%), 30 mg (2%), 20 mg (4%); 85% eow, 12% weekly	*3 mo:* 21/66 (32%) remission *6 mo:* 18/42 (43%) remission *12 mo:* 16/33 (49%) remission *Dose adjustment:* 25%	Inactive disease according to PGA
Russell et al. [78]	70	Median 14.8	94%	*Induction:* 160/80 mg (4%), 80/40 mg (59%), 24 mg/m^2 (23%), other (14%) *Maintenance:* 80 mg (1%), 40 mg (91%), 24 mg/m^2 (4%), other (4%); 97% eow, 3% weekly	*1 mo:* 17/70 (24%) remission *6 mo:* 32/55 (58%) remission *12 mo:* 12/29 (41%) remission *Dose adjustment:* 35%	PGA
Viola et al. [79]	23	Median 16.1*	61%	160/80 mg and 80 mg eow (57%) 120/80 mg and 80 mg eow (9%) 80/40 mg and 40 mg eow (35%)	*Wk 12:* 31% remission *Wk 24:* 50% remission *Wk 48:* 65% remission *Dose adjustment:* 48%	PCDAI ≤ 10

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Table 4 | *Continued*

Study	N	Age (yr)	Prior IFX	Adalimumab	Treatment outcome	Definition used for treatment outcome
Wyneski et al. [80]	15	Median 17.9*	100%	160 mg and 80 mg eow (7%), 80 mg eow (7%), 80 mg and 40 mg eow (73%), 40 mg eow (7%), 40 mg and 20 mg eow (7%)	*After median follow-up of 6.5 mo:* 50% complete response, 14% partial response, 36% no response. *Dose adjustment:* 13%	Complete response: completely weaned from steroids, or steroid-free interval > 3 mo. Partial response: partially weaned from steroids, or some recurrence of symptoms. No response: no weaning from steroids, or need for surgery
Rosenbach et al. [81]	14	Median 13.9*	71%	*First dose:* 160 mg/1.73 m^3, *Second dose:* 80 mg/1.73 m^3, *Maintenance:* 40 mg/1.73 m^3 eow	*After median follow-up of 17.3 mo:* 50% complete response, 50% partial response. *Dose adjustment:* 57%	Complete response: HBI < 4, weight recovery, improvement of inflammatory markers. Partial response: HBI < 8
Noe et al. [82]	7	Median 16	100%	80 mg eow (14%), 80 mg and 40 mg eow (43%), 40 mg eow (43%)	*After 3 – 6 mo:* 86%**	PCDAI ≤ 10

In addition to the studies listed, there have been several case reports on the positive effect of adalimumab treatment in pediatric Crohn's disease. [83-85]

IFX: infliximab. eow: every other week. PGA: Physician's Global Assessment. PCDAI: Pediatric Crohn's Disease Activity Index. HBI: Harvey-Bradshaw Index.

* Inclusion of patients > 18 years ** 5 patients already in remission at start of adalimumab treatment

ANTI-TNF TREATMENT AND CONCOMITANT IMMUNOSUPPRESSANTS

Several pediatric studies have demonstrated short-term corticosteroid-sparing effects of IFX and ADA.[26, 29, 31-32, 34, 77, 79, 107-108] IFX was also associated with prolonged corticosteroid withdrawal over a 3-year period.[47] By 1, 2, and 3 years, less than 10% of patients continuing on IFX maintenance treatment were receiving corticosteroids.

In the first years after introduction of IFX, immunosuppressive therapy with thiopurines or MTX was usually continued during IFX maintenance therapy. The main rationale for this combined treatment was to improve short-term and long-term clinical outcomes by preventing the formation of antibodies to IFX (ATI, see paragraph 'Immunogenicity'), and achieving higher IFX serum levels.[109-110] However, this protective effect may not be present when patients are treated with scheduled maintenance infusions, as was demonstrated in adult studies.[111-112] In addition, results from a randomized trial in adult CD patients showed that withdrawing IS after 6 months of combination therapy did not affect clinical outcome during a 2-year follow-up, although median IFX trough levels were generally lower after withdrawal of IS.[113] In patients naïve to thiopurines or MTX, the additional value of combination therapy may be different, as was shown in the SONIC trial: a large randomized double-blind trial in 508 adult CD patients who were not previously treated with immunosuppressive or biological therapy.[114] Patients were randomly assigned to receive IFX and placebo, AZA and placebo, or both IFX and AZA. Steroid-free remission rates at week 26 were significantly higher in patients receiving both IFX and AZA than in patients receiving IFX monotherapy (57% vs. 44%, p=0.02), or patients receiving AZA monotherapy (57% vs. 30%, p<0.001). Similar trends were found at week 50. In addition, the total disappearance of mucosal ulcers was highest in the combined IFX and AZA group at week 26 (44% vs. 30% IFX mono vs. 17% AZA mono, p<0.001).

The downside of combination therapy may be an increased risk of toxicity. With the reports on hepatosplenic T-cell lymphoma (HSTCL, see paragraph 'Safety') in predominantly young male patients on combination therapy, many pediatric gastroenterologists converted to IFX monotherapy after a short duration of combination therapy, or combined therapy with MTX (instead of a thiopurine). In children with IBD, studies on the potential benefit of combination therapy are scarce, and more data on this important issue are therefore mandatory.

STEP-UP OR TOP-DOWN TREATMENT?

The great majority of IBD patients included in pediatric studies on IFX or ADA were treated according to a step-up strategy, indicating that conventional treatment had failed before anti-TNF therapy was initiated (steroid-dependency, steroid-resistance, intolerance or insufficient response to immunosuppressive therapy). However, it could be more effective to use anti-TNF drugs early in the disease course, as the early stages of immune-mediated

disease may be more susceptible to immunomodulation.[115-116] Preliminary evidence from adult studies suggests that a top-down strategy may alter the natural history of IBD. As the accumulation of tissue damage is a key factor of IBD and often leads to strictures and/or fistulas, irreversible destruction of the digestive tract requiring surgery might be prevented. In 133 adult CD patients, an open-label randomized trial has compared top-down treatment (3-dose IFX induction schedule and AZA) with step-up treatment (corticosteroids, and AZA in case of flaring or steroid-dependency).[117] After one year, steroid-free remission rates were significantly higher in patients treated with early combined IS (62% vs. 42%, p=0.03). In addition, median time to relapse was significant longer in the 'top-down group'.

Experience with a top-down approach is limited in pediatric IBD. In two case reports, IFX was used as first-line therapy in a 14-year old boy and 12-year old girl with CD. An impressive clinical improvement was seen after two IFX infusions, and they were still in clinical remission on combination therapy of 6-MP and Asacol after 5 months, and combination therapy of AZA and IFX after 7 months, respectively.[118-119] Recently, a South Korean study retrospectively compared three treatment strategies in 36 newly diagnosed pediatric CD patients with a minimal follow-up of 2 years.[120] Group A (n=10) received induction treatment with oral prednisolone and mesalamine maintenance treatment; group B (n=13) was treated with oral prednisolone and AZA; and group C (n=13) received induction with IFX, followed by IFX and AZA maintenance treatment for one year, and AZA monotherapy after that year. At one year follow-up, there were significant differences in relapse rates between group A and C (80% vs. 23%, p=0.012), and group B and C (62% vs. 23%, p=0.047). Relapse was defined by a PCDAI score > 10. After 2 years, relapse rates were 90%, 77% and 39% in group A, B, and C, respectively. This study was limited by the small number of patients, retrospective data collection, and potential biased assessment of treatment efficacy.

Although these limited data support the view that early use of potent immunosuppressive therapy can change disease course, they need to be confirmed in large, prospective trials to determine the benefit-risk ratio of this approach, as there are concerns about potential dangerous long-term side effects of anti-TNF medication (see paragraph 'Safety').

IMMUNOGENICITY

IFX therapy is associated with a risk of formation of ATI, which can partly be explained by the murine component of IFX. ADA treatment, being fully humanized, is associated with the same phenomenon, but to a lesser extent. The formation of antibodies to anti-TNF drugs may lead to acute infusion reactions (AIR), delayed hypersensitivity reactions, and decreased serum drug levels leading to a shorter duration of response.[109-110, 121] Concomitant use of IS may reduce the risk of antibody formation[110], whereas episodic treatment is associated with an increased risk of antibody formation.[121]

In three small pediatric studies, ATI were detected in about one third of CD patients.[35, 110, 121] In contrast, the REACH study observed ATI in only 3% of patients[34], which should be interpreted

with caution, as most patients (77%) had inconclusive test results for ATI. Adult studies have reported ATI rates varying from 14% to 61%.[25, 109, 122]

Data on formation of antibodies to ADA or certolizumab are only available from adult studies. Antibodies to ADA have been reported in 3 – 17% of CD patients with refractory disease[72, 123-124], and antibodies to certolizumab were present in about 9% of CD patients in the PRECISE studies.[86-87]

The most common symptoms of AIR are shortness of breath, flushing, nausea, headache, hypoxemia, and tachycardia. Pooling of 18 pediatric studies showed AIR in 168 of 1100 IFX treated patients (15%), and in 228 of 7137 infusions (3%).[26, 28-30, 32, 34-36, 42, 45, 49, 107, 110, 121, 125-128] Most reactions were mild and responded rapidly to treatment, temporarily stopping the infusion, and/or reducing the flow rate of the infusion. Premedication (antihistamines, antipyretics, or corticosteroids) did not seem to prevent the development of AIR.[125] In general, the rate of infusion reactions in children is similar to that in adults.[25, 129] However, a small study observed a significant difference in the rate of severe systemic reactions between adult (11/52, 21%) and pediatric patients (1/34, 3%, $p<0.02$).[128]

Delayed hypersensitivity reactions are usually defined as joint pain and swelling, associated with fever and/or rash, occurring more than one day post-infusion. These reactions occurred in 0 – 8% of IFX treated children with IBD[32, 34, 36, 42, 126-127], which is similar to the frequencies that have been reported in adults.[25, 129]

Formation of autoimmune antibodies has been described in pediatric CD patients treated with IFX. Positive antinuclear antibodies (ANA), without any clinical symptoms, were detected in 20 – 29% of patients.[29, 34, 36, 49] The incidence of formation of antibodies to double-stranded DNA varied from 0 – 10% of patients.[28-29, 34, 49] Development of a systemic lupus erythematosus-like syndrome is rare in the pediatric population, and has been described in case reports only.[130-131] In adults, ANA formation has been reported in 56% of IFX treated CD patients[132], and in 19% of ADA treated CD patients.[72] The clinical relevance of ANA induction by anti-TNF drugs is still unclear.

Another autoimmune disorder that has been described sporadically in pediatric IBD patients on IFX, is vasculitis.[32, 44, 133]

SAFETY OF ANTI-TNF TREATMENT IN PEDIATRIC IBD
Infections

Pooling of pediatric IBD studies shows serious or unusual infections in 49 of 1483 IFX treated patients (3.3%): sepsis (n=5), Listeria monocytogenes meningitis (n=1), herpes zoster or varicella infections (n=12), severe reactivation of Epstein-Barr virus (EBV, n=1), pneumonia (n=5), abscess (n=14), cutaneous tinea infections (n=3), opportunistic fungal infection (n=1), osteomyelitis (n=1), cellulitis (n=1), Pseudomonas infection of a gastrostomy site (n=1), pseudomembranous colitis (n=1), gastroenteritis (n=1), appendicitis (n=1), and in one

patient appendicitis and pancreatitis.[26-37, 42-48, 61-62, 64, 66-69, 107, 127] There was one sepsis-related death in an 11-year old boy with severe refractory CD who was also treated with parenteral nutrition, corticosteroids and AZA. The sepsis may have originated from an abscess located near a stenosis in the colon.[37]

In the relatively small pediatric studies on ADA use, serious or unusual infections were seen in 7 of 237 (3.0%) patients: sepsis (n=2), a severe case of Clostridium difficile, and abscess formation (n=4).[77-82, 85] There were two sepsis-related deaths in patients who were also on IS and home parental nutrition (coagulase-negative staphylococcal central venous catheter sepsis complicated by an invasive pulmonary aspergillosis; E. coli and Candida central venous catheter sepsis).[78]

Several case reports have also reported on serious or unusual infections in pediatric patients treated with IFX or ADA: Listeria moncytogenes meningitis, EBV-associated hemophagocytic lymphohistiocytosis, opportunistic fungal skin infection with Pityrosporum folliculitis, histoplasmosis, flare-up of an intramyocardial inflammatory process, and a fatal case of disseminated cytomegalovirus.[134-139]

IBD patients have an increased risk of opportunistic infections (e.g. invasive fungal infections, reactivation of latent tuberculosis), especially patients on a combination of immunomodulator therapies, and those with malnutrition.[140] Testing for tuberculosis (chest radiograph, skin test of purified protein derivative tuberculin) prior to anti-TNF therapy is recommended.

Neutropenia, occurring in association with anti-TNF therapy, has been described in a few pediatric IBD patients.[61, 78, 141]

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Malignancy

There are concerns that anti-TNF treatment may increase the likelihood of tumor development. Adult studies have yielded conflicting results. In contrast to clinical trial data with IFX and ADA in rheumatoid arthritis[142], several large IBD cohort studies did not find an increased risk of malignancy in patients treated with anti-TNF treatment compared with anti-TNF naïve patients.[129, 143] However, a meta-analysis on 8905 adult CD patients demonstrated that use of anti-TNF drugs with immunomodulators was associated with an increased risk of non-Hodgkin's lymphoma (NHL).[144]

One particular serious type of lymphoma, HSTCL, has been reported in IBD patients treated with anti-TNF therapy.[145] HSTCL is a rare form of NHL and presents with hepatosplenomegaly (in the absence of peripheral lymphadenopathy), and general symptoms such as fever, weight loss, and fatigue. The tumor is extremely aggressive, and overall median survival with maximal therapy is less than one year.[146] As of June 2008, 15 cases of HSTCL in IBD patients (13 CD, 2 UC) receiving combined IFX and thiopurine therapy have been confirmed.[145] Two of these cases were diagnosed after the patients had switched from IFX to ADA. HSTCL occurred predominantly in male adolescents and young adults (age 12 – 39 years; 14M/1F)

who received 1 – 24 IFX infusions. All but one patient had a fatal outcome. Recent data show that the number of reported HSTCL cases under combination therapy has increased to 20.[147] In addition, there have been at least 16 cases reported among IBD patients treated only with AZA or 6-MP.[145, 147] At present, it remains unclear whether the development of HSTCL is particularly associated with thiopurine monotherapy or combination therapy.

In children treated with anti-TNF drugs, 48 cases of malignancy were identified by the FDA as of April 2008 (31 following IFX use, 2 following ADA use, and 15 following etanercept use).[148] In early-onset IBD patients receiving IFX (n=24), HSTCL accounted for most cases (n=9), followed by NHL (n=4), and Hodgkin's lymphoma (n=2). The other cases included: leukemia, leiomyosarcoma, nephroblastoma, malignant melanoma, basal cell carcinoma, hepatic malignancy (undifferentiated), metastatic hepatocellular cancer, thyroid cancer, and colorectal cancer. All patients (16M/8F, aged 4 – 22 years) received concomitant IS. One case of HTSCL was reported in a 20-year old UC patient who was treated with ADA for 8 months. He had previously received IFX and 6-MP before switching to ADA. The reporting rate for malignancies and lymphomas in all children treated with IFX was higher when compared with background rates in the general US pediatric population.

Recent pediatric literature has reported on four additional cases of malignancies in children treated with anti-TNF drugs. A 17-year old female developed a bowel-associated Hodgkin's lymphoma approximately 1.5 years after discontinuation of IFX.[47] A second patient died of metastatic undifferentiated right colon carcinoma 7.5 years after discontinuation of IFX.[48] Thirdly, a case of basal cell carcinoma after 27 months of IFX therapy was reported.[46] The fourth patient (13-year, IBD-unclassified) died of an EBV-positive natural killer T-cell lymphoma with associated hemophagocytic lymphohistiocytosis after one year of IFX maintenance treatment.[149]

Large population-based studies and accurate registries are necessary to determine whether the development of malignancies is related to the severity and chronicity of the inflammatory disease, to the prolonged use of IS, or to a combination of both.

Miscellaneous

Anti-TNF treatment has been associated with rare cases of neurological disorders in adults, such as optic neuritis, seizures, and demyelinating disorders. In children, two cases of posterior reversible encephalopathy syndrome following IFX infusion have been described in a CD and UC patient.[150-151] In addition, a case of progressive multifocal leucoencephalopathy (PML) was described in a third patient.[152] This 16-year old CD patient developed a severe sepsis after the second IFX infusion. MRI examination after 3 months showed brain lesions related to PML. Six months after discontinuation of IFX, neurological symptoms and brain lesions had disappeared completely. Kachko et al. reported on a 16-year old CD patient who developed complex regional pain syndrome type I after his first IFX infusion.[153] To our knowledge, no other neurological disorders have been reported in pediatric patients.

Anti-TNF therapy has been associated with adverse outcomes in adult IBD patients with congestive heart failure.[154] Four pediatric studies have reported on the occurrence of cardiac symptoms during IFX treatment: one CD patient who suffered from a cardiac arrest secondary to cardiac arrhythmia associated with a long QT interval[47], one CD patient who developed cardiac insufficiency[48], one UC patient with a pericardial effusion with cardiomyopathy resolving after discontinuation of IFX[61], and one UC patient who developed familial cardiomyopathy.[67] In addition, a pilot study found asymptomatic cardiac involvement, as assessed by Doppler echocardiography, in 7 of 12 pediatric IBD patients receiving IFX.[155]

Dermatological symptoms such as eczema, or psoriasiform lesions, are an emerging observation in pediatric IBD patients treated with anti-TNF drugs. IFX-induced psoriasis was observed in 8% (6/73) of pediatric IBD patients[156], whereas another study reported a wide variety of skin eruptions in 8% (12/152) of pediatric CD patients.[46] In adults, skin eruptions occurred in 20% (150/734) of IBD patients.[129] Most lesions responded well to topical steroids.

Psychiatric side effects of anti-TNF drugs are reported to be rare. Recently, the open-label extension of the REACH study reported on suicide attempts in two pediatric CD patients on IFX maintenance treatment (intentional overdose with acetaminophen and alprazolam).[49] In adults, a case report described a 43-year old UC patient who developed a depression with psychotic symptoms during IFX treatment and made a suicide attempt 4 months after initiation of the infusions.[157] Another case of a suicide attempt during IFX treatment was reported in a 30-year old CD patient who experienced panic attacks 2 hours after each infusion. After the fifth infusion, she intoxicated herself with paroxetine.[158]

In conclusion, severe adverse events of anti-TNF treatment are reported in low frequency, but they may be severe and even fatal. By FDA and EMA (European Medicines Agency) mandate, Centocor initiated in 2009 a prospective long-term (20 years) observational registry of 5000 pediatric IBD patients in Europe and North-America. This registry intends to collect information on all serious adverse events associated with IFX, as well as other medical therapies for IBD.

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EXPOSURE TO ANTI-TNF DRUGS IN UTERO

IFX, ADA, and certolizumab are classified as category B agents by the FDA, indicating that there is no evidence of human toxicity in pregnancy. Limited data from two safety registries[159-160], two prospective cohort studies[161-162], and a retrospective case series[163] suggest that the rates of miscarriage and neonatal complications in women exposed to IFX or ADA during pregnancy are not different from those in non-exposed women. To our knowledge, there are no published data on the effect of certolizumab on pregnancy outcome in CD patients.

Placental transfer of IFX and ADA is unlikely during the early stages of pregnancy, but these immunoglobulines easily pass the placental barrier in the second and third trimester.[164] Case series have reported clinically significant IFX and ADA levels in the cord blood of the infant when these drugs were administered at the end of the second trimester or during the third trimester.[165-167] In all 13 cases, IFX or ADA levels on the day of birth were higher in the child than in the mother, and remained detectable for 2 – 6 months. The effects of these high drug levels on the developing immune system of the child are unknown, but the results of two case series showed that children with high IFX levels did not seem to have an increased risk of infections in their first year of life, and that they had normal responses to inactivated vaccines.[166, 168] However, a recent case report described a fatal case of a disseminated BCG infection in an infant vaccinated at 3 months of age.[169] His mother was treated with IFX throughout the pregnancy. The recent consensus of the World Congress of Gastroenterology therefore recommended that live-virus vaccines should not be given to infants exposed in utero to IFX or ADA, unless serum levels are undetectable.[170] Discontinuing IFX or ADA at the beginning of the second trimester (when possible) will probably prevent intra-uterine and postnatal exposure[166], but further studies are needed to determine the exact timing of discontinuation of IFX or ADA during pregnancy.

Certolizumab, a Fab' fragment, is assumed to cross the placenta by passive diffusion, resulting in less placental transfer compared with IFX and ADA. This was confirmed in four infants from mothers who used certolizumab during pregnancy with the last dose 1 – 4 weeks before delivery.[170-171] Mothers' levels on the day of birth ranged from 4.9 – 59.6 µg/ml, and infant levels varied from 0.4 – 1.0 µg/ml.

Taken together, IFX or ADA treatment during pregnancy seems to be relatively safe, but these results are based on small patient numbers. The long-term effects of the intra-uterine and postnatal exposure to anti-TNF drugs remain uncertain.

CONCLUSIONS AND FUTURE PERSPECTIVES

Over the past 10 years, IFX has been of great benefit to many pediatric CD patients. This biological drug has proven to be efficacious in inducing and maintaining remission, achieving mucosal healing, inducing perianal fistula closure, reducing corticosteroid exposure, promoting growth, and improving quality of life. IFX also has a role in the management of refractory pediatric UC, but appears to be less effective than in pediatric CD. ADA, although data are limited, seems to be effective for pediatric CD. The role of certolizumab in pediatric IBD is yet to be determined. Unfortunately, the use of anti-TNF therapies may not be without risks, such as opportunistic and serious infections, auto-immune diseases, and malignancies. To improve the benefit-risk profile of anti-TNF drugs, selecting patients with a high likelihood of response to these treatments is essential. However, reliable predictors of response are currently lacking. It is mandatory to continue the search for clinical parameters

(such as genetic polymorphisms, serologic markers, and cytokine profiles) that can identify those patients who are most likely to benefit from anti-TNF treatment.

Another problem is the secondary loss of response to IFX and ADA, which occurs in a substantial number of patients. Concomitant use of immunomodulators may improve the clinical outcomes, but this potential benefit needs to be weighed against a possibly increased risk of malignancies, especially of HSTCL. A randomized controlled trial examining the efficacy and safety of anti-TNF drugs as monotherapy versus combination therapy in pediatric IBD patients is needed to answer this important question.

A third point of discussion is the optimal timing for introduction of anti-TNF treatment. Early introduction of anti-TNF drugs in the disease course may prevent complications and surgery in the future, but, again, the long-term benefit-risk ratio of this approach needs to be determined. Future research has to focus on genetic and serologic markers that can stratify newly diagnosed IBD patients according to their risk of developing active disease or complications. This will enable the selection of patients who will benefit most from early biological treatment, leading to individually tailored therapeutic management.

Other issues that need to be sorted out are the optimal dosing schemes for IFX and ADA, the need for discontinuing anti-TNF treatment in patients with a long-term response, the benefit of therapeutic drug monitoring by measuring serum drug levels and antibodies to IFX and ADA, and the need to achieve mucosal healing in every patient. Finally, the optimal choice between IFX and ADA in anti-TNF naïve IBD patients may benefit a significant number of patients, and also reduce costs. A head-to-head comparison of the efficacy, safety, and cost-effectiveness of IFX and ADA in pediatric IBD is therefore essential.

8

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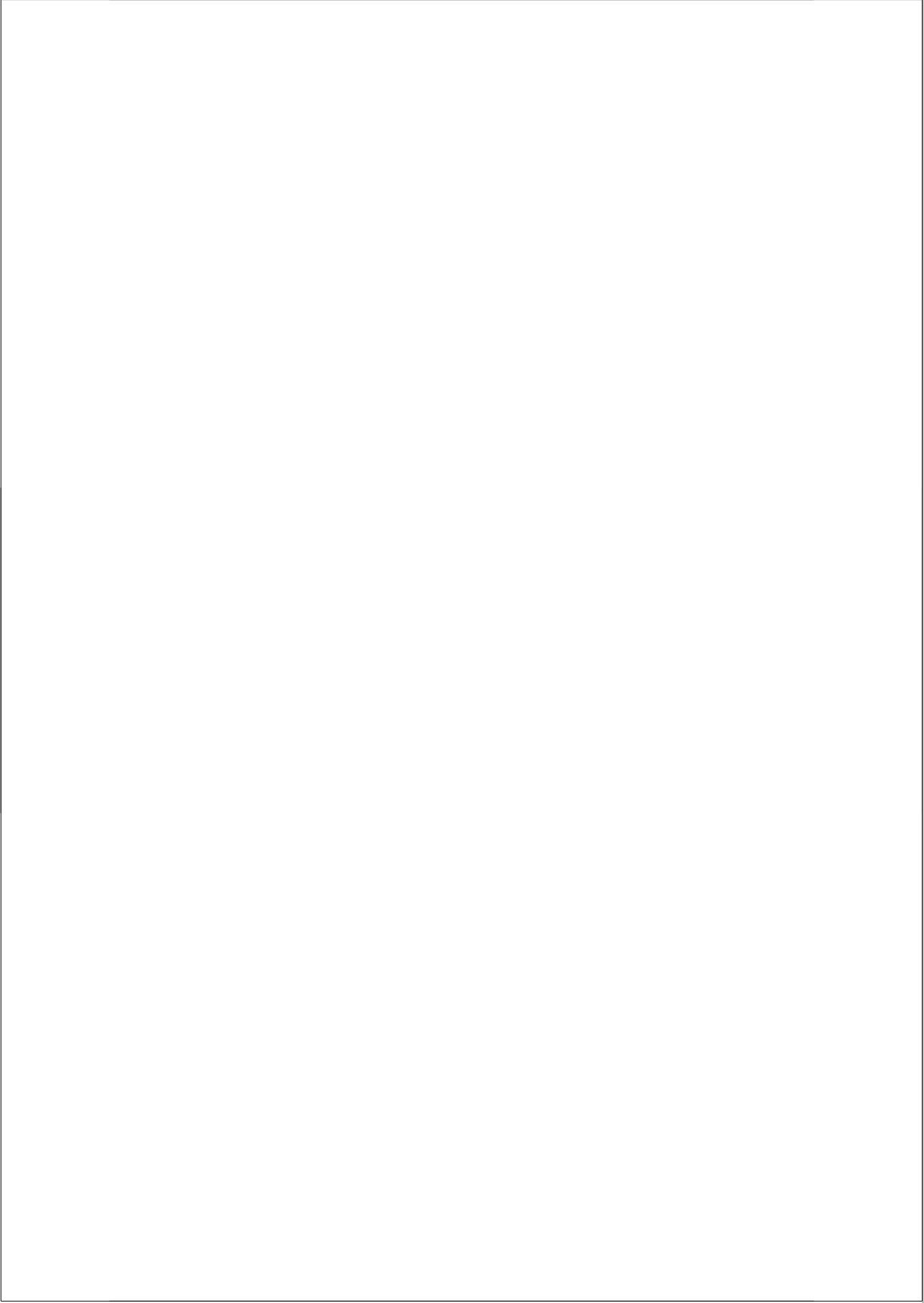
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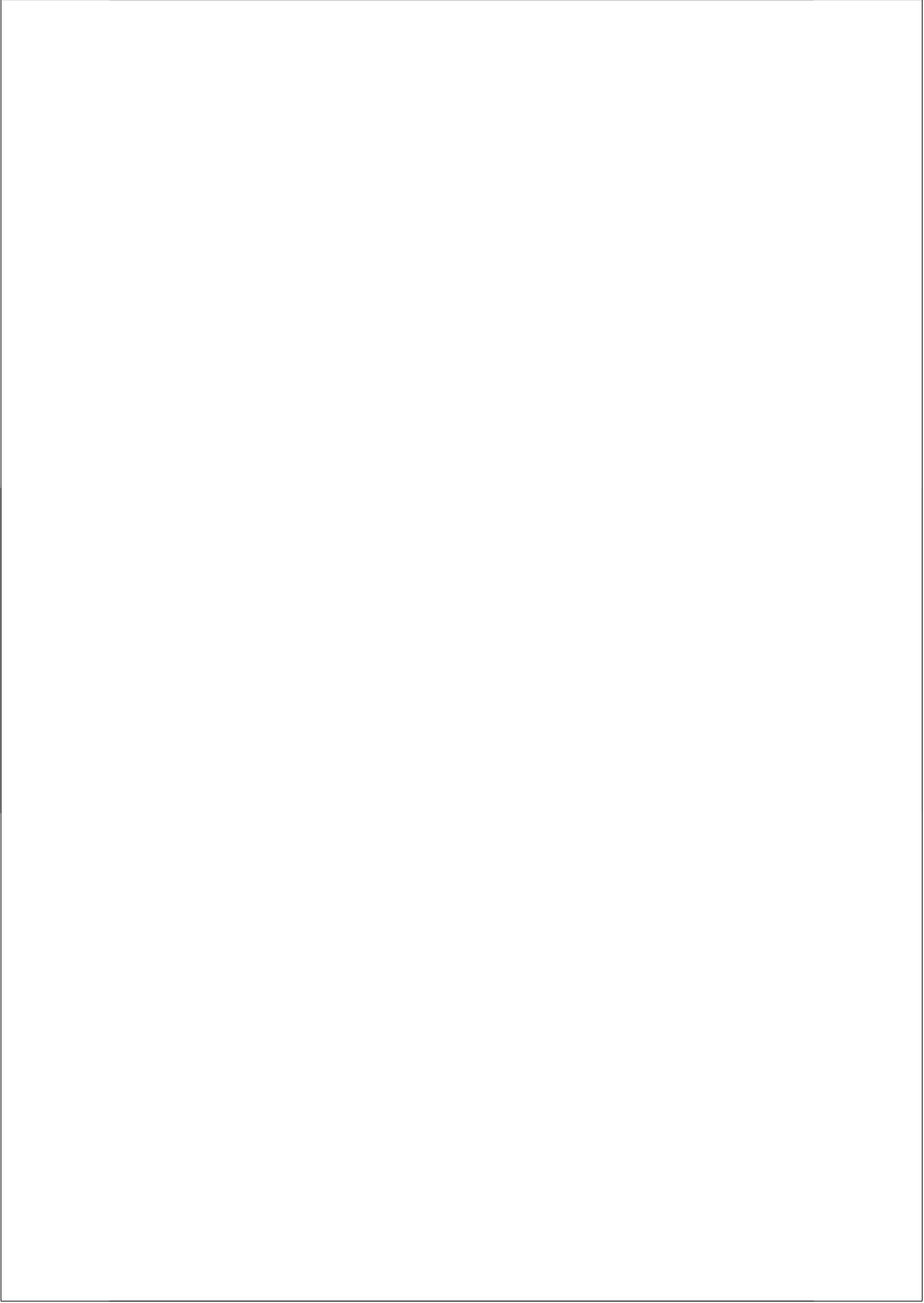
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8

Part IV

Transition from the pediatric to the adult gastroenterologist

C h a p t e r

9

Self-efficacy in adolescents with inflammatory bowel disease: a pilot study of the "IBD-yourself", a disease-specific questionnaire

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ABSTRACT

Background and aims

Successful transfer of adolescent IBD patients to an adult gastroenterologist requires anticipation of a changing role for patients and their parents. Self-efficacy has been demonstrated to be important for transfer readiness. We therefore developed an IBD-specific questionnaire (the "IBD-yourself") to assess self-efficacy in adolescent IBD patients visiting a transition clinic. Our aim was to evaluate the reliability of this questionnaire, and to describe the self-efficacy level of adolescent IBD patients, and the perceived self-efficacy level according to their parents.

Methods

In a cross-sectional design, 50 IBD patients (aged 14-18 years) and 40 parents completed the "IBD-yourself" questionnaire. Internal reliability was assessed by standardized Cronbach's α. Median self-efficacy scores per domain were calculated.

Results

The domains of the questionnaire for adolescents showed good to excellent internal consistency, with Cronbach's α ranging from 0.64 to 0.93. The domains of the parental questionnaire had Cronbach's α ranging from 0.47 to 0.93. Median self-efficacy scores of adolescents varied from 70 – 100%. In comparison with patient's self-assessment, parents thought that their child was more self-efficacious in knowledge of IBD and diagnostic tests, self-management of medication use, and transfer readiness. Length of time since first visit to the transition clinic was positively correlated with several domains of the questionnaire, such as independent behavior at the outpatient clinic, and transfer readiness.

Conclusion

The "IBD-yourself" questionnaire is a first step toward evaluating quality and efficacy of IBD transition programs. Pediatric gastroenterologists should be aware that parents do not always accurately assess the self-efficacy of their child.

INTRODUCTION

The incidence of inflammatory bowel disease (IBD) in children is increasing.[1] Most early-onset IBD patients present during adolescence, a critical period for physical and psychosocial development. In a few short years, the growing adolescent must shed the sheltered environment of childhood and achieve self-reliance and independent living.[2-3] In addition to all these changes, adolescents with IBD have to become independently responsible for their own medical care. At some point, usually around the age of 16 – 18 years, these patients will move from the pediatric to the adult healthcare system, an important milestone in the life of young IBD patients and their parents.[4-5]

There are several differences between pediatric and adult IBD health care.[5-7] Pediatric care tends to be more focused on growth and development, whereas adult gastroenterologists are facing other health issues, such as fertility, pregnancy, and cancer surveillance. There are also significant differences regarding use of sedation during diagnostic procedures, as well as amount of parental involvement. Additionally, the adult gastroenterologist expects his patient to be autonomous and independent. Successful transfer to the adult gastroenterologist requires anticipation of this changing role for the patient and his parents. The transition process should therefore consist of a stepwise program with age-appropriate checklists of tasks for the patient, as well as for the medical team.[3, 8-9] Currently, there are no tools to evaluate the effect of different IBD transition programs.[9]

In 2006, a transition clinic for IBD patients between 14 – 18 years was initiated in the Erasmus MC – Sophia Children's Hospital. The transition clinic is located in the adult department, and patients are seen together by both the pediatric and adult gastroenterologist during the first visit and once yearly thereafter. At all other visits, the pediatric gastroenterologist sees the patients alone. The main goal of the transition clinic is to get the adolescent ready for transfer to the adult gastroenterologist by increasing his/her knowledge of disease and treatment, as well as reaching a higher level of self-efficacy. Self-efficacy is a person's belief in his/her capability to organize and execute actions required to deal with prospective situations.[10] Self-efficacy is a prerequisite for self-management, and has been demonstrated to be of key importance in transfer readiness.[11]

We therefore developed an IBD-specific questionnaire to assess the self-efficacy of adolescents visiting our transition clinic, the "IBD-yourself" questionnaire. The primary aim of this pilot study was to evaluate the reliability of the "IBD-yourself" questionnaire, and to describe the level of self-efficacy of adolescent IBD patients visiting the transition clinic and the perceived level of self-efficacy according to their parents. In addition, we aimed to compare self-efficacy between disease groups and sexes, and to test for associations between self-efficacy and length of time since first visit to the transition clinic.

MATERIALS AND METHODS

Participants

Patients and their parents/caregivers were recruited from the transition clinic for adolescent IBD patients of the Erasmus MC – Sophia Children's Hospital, Rotterdam, The Netherlands. Adolescent IBD patients, who visited the transition clinic between March and July 2008, were eligible for this study. Exclusion criteria were mental inability to fill out a questionnaire, and not being able to read and understand Dutch. One accompanying parent of the patient and the pediatric gastroenterologist were also asked to participate. Data on patient characteristics, disease history, treatment, date of first visit to the transition clinic, and number of transition clinic visits were retrieved from the medical records after informed consent.

This study was approved by the local ethics committee of the Erasmus MC. Written informed consent was obtained from all patients and their parents/caregivers.

Measurements

The "IBD-yourself" questionnaire was developed as an instrument to measure self-efficacy of adolescents visiting the transition clinic. Questions of the "IBD-yourself" were generated from the available literature of general and disease-specific self-efficacy measures.[11-13] A pre-test of the questionnaire was completed by four adolescent IBD patients to determine whether the questionnaire was comprehensible and consistent.

The final version for adolescents contained 12 domains, addressed by at least 59 questions (depending on the patient's treatment; see Appendix). The questions on the perceived level of disease burden and independency in general were determined using a 100 mm visual analogue scale (VAS). The VAS on general independency ranged from "not independent" to "very independent", while the VAS on disease burden ranged from "no disease burden" to "heavy disease burden". Other domains of the questionnaire were: self-efficacy in knowledge of IBD, diagnostic tests and treatment, self-efficacy in medication use, actual behavior regarding medication use in the past week, skills for independent visits to the transition clinic, actual behavior during visits to the transition clinic, coping with IBD, knowledge of the transition process, and readiness for transfer to the adult gastroenterologist. Most of the questions were rated on a four-point Likert scale, ranging from 1 ("no, definitely not") to 4 ("yes, definitely"). Higher scores indicated higher levels of self-efficacy. As the total number of questions could differ between patients, it was not possible to generate a total self-efficacy score, only total scores per domain.

The parents of the adolescent IBD patients were invited to fill out an abbreviated version of the "IBD-yourself" questionnaire in order to determine how they perceived the self-efficacy of their child. Patients and parents had to complete the questionnaire in 20 minutes, separately from each other. The treating pediatric gastroenterologist was only asked to score patient's general independency on a VAS.

Statistical analysis

Data were collected and analyzed in SPSS (version 16.0, SPSS, Inc., Chicago, IL, USA). Descriptive statistics were calculated as percentages for discrete data and medians with interquartile ranges (IQR) for continuous data. VAS scores were obtained by measuring in millimeters the middle of the cross that patients, parents, and pediatric gastroenterologist placed on the VAS. Scale scores were linearly transformed to a 0 – 100 scale, with higher scores representing higher levels of self-efficacy or heavier disease burden.

Internal consistency of the individual domains was evaluated by calculating the standardized Cronbach's α. Homogeneity was considered to be good if α > 0.60, and excellent in case of values > 0.90. In addition, the standard error of the measurement (SEm) was calculated as another measure of reliability of the individual domains. The SEm estimates how repeated measures of the adolescent on the same questionnaire tend to distribute around his or her 'true' score. The SEm is calculated by using the Cronbach's α and the standard deviation (SD) of the domains: SEm = SD * $\sqrt{}$ (1- Cronbach's α). A low SEm indicates a reliable test. Reliability of the domain on perceived knowledge of treatment could not be analyzed due to the heterogeneity in number of questions per patient (due to variation in medication used).

Demographic and disease-related differences between participants and non-participants were analyzed using the Mann-Whitney test or χ^2-test. The Wilcoxon-signed rank test was used to test for differences in domain scores between adolescents, parents and pediatric gastroenterologist. Differences in total domain scores between gender and disease type were assessed by the Mann-Whitney test. Spearman's correlation coefficients were calculated to examine the correlation between total domain scores and length of time since first visit to the transition clinic. All reported P-values are two-sided, P-values < 0.05 were considered significant.

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RESULTS

Patient characteristics

A total of 57 patients was eligible for this study, of whom 50 (88%) were willing to participate. Patient demographics are presented in Table 1. Non-participants did not differ from participants with respect to age, gender, type of IBD, or disease duration.

As there were adolescents who visited the transition clinic alone, a smaller number of parents (n=40) filled out the questionnaire: 28 mothers (70%) and 12 fathers (30%), with a median age of 44 years (IQR 42 – 48).

Reliability of the "IBD-yourself" questionnaire

Table 2 displays the reliability of the "IBD-yourself" questionnaire for both patients and parents. The internal consistency was good or excellent for all analyzed domains of the

questionnaire for adolescents (Cronbach's α ranging from 0.64-0.93). The Cronbach's α of the domains of the questionnaire of the parents varied from 0.47-0.93. In both the questionnaires for adolescents and parents, the SEm was low for most of the domains, confirming the reliability of the questionnaire.

Table 1 | Patient characteristics of adolescent IBD patients visiting the transition clinic (n=50).

Gender (male), no. (%)	22 (44%)
Age (yr), median (IQR)	16.3 (15.4-17.0)
Disease type	
Crohn's disease	30 (60%)
Ulcerative colitis	18 (36%)
IBD-unclassified	2 (4%)
Duration of disease	
< 2 years	34 (68%)
> 2 years	16 (32%)
Time since first TC visit	
< 1 year	25 (50%)
> 1 year	25 (50%)
Number of TC visits	
1 – 6	38 (76%)
7 – 12	12 (24%)
Educational level	
Low	30 (60%)
High	20 (30%)
Current medication	
Mesalazine	16 (32%)
Salazopyrine/Sulfasalazine	3 (6%)
Mesalazine enema	3 (6%)
Azathioprine	24 (48%)
Methotrexate	4 (8%)
Prednisone	3 (6%)
Infliximab	13 (26%)
Calcium/Vitamin D	15 (30%)
Folic acid	5 (10%)
Other medication	4 (8%)

IQR: interquartile range.
TC: transition clinic.

Table 2 | Reliability of the "IBD-yourself" questionnaire for adolescent IBD patients and their parents.

Domains	No. of questions	Questionnaire for Adolescents (n=50)			Questionnaire for Parents (n=40)		
		Cronbach's α*	SEm	95 % CI	Cronbach's α*	SEm	95 % CI
Knowledge of IBD	5	0.76	1.1	14.7 – 18.9	0.88	0.8	16.2 – 19.4
Knowledge of diagnostics tests	6	0.76	1.4	17.3 – 23.0	0.92	0.9	19.4 – 23.2
Medication use	8	0.89	1.7	22.5 – 29.3	0.93	1.6	20.9 – 27.3
Actual behavior medication use	4	0.68	1.7	11.2 – 17.8	0.63	1.7	11.1 – 18.0
Skills for independent outpatient clinic visits	9	0.87	2.2	23.3 – 32.0	0.89	2.1	20.3 – 28.6
Actual behavior outpatient clinic	4	0.64	0.8	4.1 – 7.3	0.47	0.8	4.1 – 7.5
Coping with IBD	4	0.93	0.8	12.0 – 15.3	0.85	1.1	10.8 – 15.0
Knowledge of transition process (adolescents/parents)	14/15	0.74	3.7	42.8 – 57.5	0.86	3.2	45.3 – 58.1
Transfer readiness	2	0.86	0.5	5.2 – 7.2	0.88	0.5	4.6 – 6.8

SEm: standard error of the measurement. CI: confidence interval.
* Standardized, corrected for the number of items within the scale.

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Outcome of the "IBD-yourself" questionnaire

The median scores for the domains of the "IBD-yourself" questionnaire are listed in Table 3. Adolescents had a median VAS score on general independency of 69 (IQR 50 – 80) by self-assessment. Assessment by their parents resulted in a median score of 75 (IQR 60 – 89), and by the pediatric gastroenterologist in a median score of 72 (IQR 54 – 84). There was only a significant difference between the scores of the parents and the pediatric gastroenterologist (P=0.04). The median VAS score on disease burden according to the adolescent was 11 (IQR 4-51), with 13 adolescents (26%) reporting a score ≥ 50.

In general, adolescents reported high levels of self-efficacy with median scores varying from 70 – 100%. Patients and parents did not always agree on the level of self-efficacy. Parents thought that their child had more knowledge of IBD and diagnostic tests. They also scored significantly higher on self-management of medication use and readiness for transfer to the adult gastroenterologist. In contrast, adolescents found themselves more capable of independent behavior at the outpatient clinic.

Differences between gender and disease groups on self-efficacy

Male patients thought they had significantly more knowledge of their disease (median score 90% vs. 80%, P=0.03), were better able to tell friends and teachers about their disease (100% vs. 81%, P=0.048), and were more ready for transfer to the adult gastroenterologist compared with female patients (median score 88% vs. 75%, P=0.04). VAS scores on general independency and disease burden did not differ significantly between males and females. Ulcerative colitis (UC) patients had lower median domain scores compared with Crohn's disease (CD) patients, but these differences were not statistically significant, except for independent behavior during visits to the transition clinic (median score 5 (UC) vs. 6 (CD), P=0.04). There were only two patients with IBD-unclassified, which we did not include in our analysis.

Self-efficacy and the transition clinic

There was a significant correlation between length of time since first visit to the transition clinic and VAS scores on general independency filled out by the pediatric gastroenterologist (r=0.45, P=0.001) and the parents (r=0.35, P=0.03), but not by the adolescents (r=0.23, P=0.11). Length of time since first visit to the transition clinic was positively correlated with other domains of the questionnaire for adolescents: skills for independent transition clinic visits (r=0.29, P=0.04), actual behavior at the transition clinic (r = 0.53, P=0.001), and transfer readiness (r=0.33, P=0.02).

Table 3 | Median total domain scores of the "IBD-yourself" questionnaire for adolescent IBD patients and their parents.

Domain	Score range	Adolescents (n=50)		Parents (n=40)		P-value
		Median score (% of max score)	% with maximal score	Median score (% of max score)	% with maximal score	
VAS on general independency	0 – 100	69	5	75	7	0.09
VAS on perceived disease burden	0 – 100	11	2	NA	NA	NA
Knowledge of IBD	0 – 20	17 (85)	5	19 (95)	12	0.006
Knowledge of diagnostics tests	0 – 24	20 (83)	14	23 (96)	30	0.02
Medication use	0 – 32	27 (84)	11	27 (84)	7	0.01
Actual behavior medication use	0 – 20	16 (80)	2	16 (80)	2	0.20
Skills for independent outpatient clinic visits	0 – 36	28 (78)	9	24 (67)	4	0.02
Actual behavior outpatient clinic	0 – 8	6 (75)	9	6 (75)	5	0.10
Coping with IBD	0 – 6	16 (100)	44	13 (81)	18	0.45
Knowledge of transition process (adolescents/parents)	0 – 70/75	51 (73)	0	52 (69)	0	0.21
Transfer readiness	0 – 8	6 (75)	19	6 (75)	9	0.05

In both groups, minimal scores of 0 were not observed.
VAS: visual analogue scale. NA: not applicable.

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DISCUSSION

In this pilot study, we introduced the "IBD-yourself" questionnaire, the first self-efficacy measure for adolescents with IBD, which proved to be a reliable tool with a high internal consistency. Although additional validation and further domain and question reduction are necessary, this questionnaire is a first step toward evaluating quality and efficacy of IBD transition programs.

There is a clear need to evaluate and improve transition of adolescent IBD patients, as several studies have identified inadequacies in the preparation of adolescent IBD patients for transfer to the adult gastroenterologist. Deficiencies in knowledge of side effects of medications[14-15], disease location, surgical history, date of last colonoscopy, and previous results of small bowel imaging have been reported in adolescent IBD patients.[16] Additionally, adult gastroenterologists frequently report a lack of knowledge of the disease, treatment, and the impact of substance use on health in the young adults transferred to their practice.[17-19]

Increasing knowledge alone is, however, not sufficient for successful transition.[6] Self-efficacy in managing self-care has been demonstrated to be of key importance for transfer readiness.[11] Self-efficacy has also been associated with improved health behavior, as was reported in a study on adolescent sickle cell disease patients.[20] The patients with higher self-efficacy scores were more likely to attend outpatient clinic appointments after transfer to adult care. In our adolescent IBD population, levels of self-efficacy were high, with scores varying from 70-100%. Given the different disease-related domains, the "IBD-yourself" questionnaire can detect specific areas in which the individual patient needs extra attention. This will facilitate appropriate patient-tailored interventions, which could improve the transition to adult care. Future longitudinal studies in our IBD population will have to investigate the long-term outcomes of assessing and improving self-efficacy during the transition period.

The "IBD-yourself" questionnaire for adolescents proved to be a reliable tool, with good to excellent internal consistency for all domains. The domain on actual behavior during visits to the transition clinic consisted of four dichotomous questions, which could explain the lower internal consistency compared with the other domains. In a new version of the questionnaire, the response format of this domain will therefore be adapted into a four-point Likert scale (yes, always; yes, often; yes, sometimes; no, never). A current shortcoming of the questionnaire is the limited reproducibility, as it is not possible to generate a total self-efficacy score, emphasizing the need for further domain and question reduction in the future. Future studies will also need to investigate test-retest reliability, and further explore concurrent and predictive validity of the questionnaire.

Recently, self-efficacy has been assessed in adult IBD patients.[21] In an American study, the 29-item IBD Self-Efficacy Scale (IBD-SES) proved to be a reliable and valid tool for clinical and research utility. Some of the questions were comparable with the "IBD-yourself"

questionnaire regarding management of medical care. The IBD-SES however focused primarily on abilities to cope with stress, symptoms, and maintaining remission, while our questionnaire measured self-efficacy in knowledge of the disease and the transition process, independence in treatment, and independent behavior during consultations. Although results were preliminary, adult CD patients reported significantly lower levels of self-efficacy compared with UC patients, and disease duration was not associated with increased self-efficacy scores. Both results are in contrast with data from our study. We found no significant differences in self-efficacy between disease groups. Additionally, length of time since first visit to the transition clinic (which is correlated with disease duration) was positively correlated with several domains of the "IBD-yourself" questionnaire. These different outcomes are probably caused by differences in the questionnaires, as well as age of the study population.

We found several significant differences in self-efficacy scores of male and female patients. Remarkably, male patients found themselves better capable of telling friends and teachers about their disease compared with females. In contrast, a study about coping strategies in children demonstrated that girls were more likely to use strategies involving verbal expressions to others, to seek emotional support, and to ruminate about problems.[22] Questionnaires on self-efficacy or self-care management in adolescents with other chronic diseases, such as diabetes, sickle cell disease, and cystic fibrosis, did not demonstrate any gender differences.[23-25] In contrast, a review on the social psychology of self-efficacy reported on a greater sense of self-efficacy in boys.[26]

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Length of time since first visit to our transition clinic, which is highly correlated with a patient's age, was demonstrated to be positively correlated with several domains of the "IBD-yourself" questionnaire. Due to the cross-sectional design of the study, we do not know whether this positive correlation is a consequence of aging of the patient or really a beneficial effect of the transition clinic. Other studies on self-efficacy in children with chronic diseases have yielded conflicting results on the effect of age on self-efficacy. Older children with cystic fibrosis and asthma reported higher levels of self-efficacy and self-care management compared with younger children[24, 27], whereas age had no effect on self-efficacy scores of adolescent sickle cell disease patients.[25]

The results of the parental questionnaire suggest that parents may not always accurately assess the level of self-efficacy of their child. In general, parents reported higher levels of self-efficacy compared with their children. Discrepancies between adolescent IBD patients and their parents have also been observed in questionnaires on psychosocial and somatic symptoms.[28] Eight percent of the adolescents and 13% of the parents reported psychosocial problems, without the counterpart agreeing. Additionally, parents reported more somatic symptoms than their adolescent child. These findings illustrate the importance of gradually establishing an independent relationship between the pediatric gastroenterologist and the patient.

The most effective strategy to successfully transfer adolescent IBD patients to the adult gastroenterologist is yet to be determined. Based on the outcomes of a patient survey[29], the stepwise transition program in our hospital consists of yearly combined visits with both the pediatric and adult gastroenterologist. A single combined visit before transfer to the adult gastroenterologist has also been reported to be beneficial for subsequent care, and increased confidence in the new gastroenterologist. However, a substantial number of patients (30%) and parents (20%) felt that one visit had not been enough.[30] Developing a validated IBD transition tool will enable future studies to investigate the most effective transition strategy.

In conclusion, we have described a novel and valuable tool to assess self-efficacy of adolescents with IBD, which can be used to further improve IBD transition programs. Adolescent IBD patients report high-levels of self-efficacy, with several significant differences between male and female patients. Pediatric gastroenterologists should be aware that parents do not always accurately assess the self-efficacy of their child. Additional studies are needed to further improve and validate the "IBD-yourself" questionnaire.

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Appendix
The "IBD-yourself" questionnaire

Visual analogue scales

1. How independent are you concerning your disease?

0 |————————————————————————————————————| 100

Not independent   Very independent

2. How would you score your disease burden in the last week?

0 |————————————————————————————————————| 100
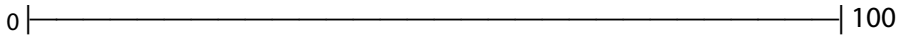
No disease burden   Heavy disease burden

Self-efficacy in knowledge of IBD

I am convinced that…	Yes, definitely	Yes, probably	No, probably not	No, definitely not
I can explain what kind of disease I have.				
I can explain which symptoms my disease can cause.				
I can tell which symptoms I have when my disease worsens.				
I can tell when the symptoms of my disease improve.				
I can clearly describe the future consequences of my disease.				

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Self-efficacy in knowledge of diagnostic tests

I am convinced that…	Yes, definitely	Yes, probably	No, probably not	No, definitely not
I can recall the diagnostic tests that I underwent when I was diagnosed with IBD.				
I know the diagnostic tests that I will have to undergo during the course of my disease.				
I can explain why my height and weight are measured during each visit to the outpatient clinic.				
I can explain why I have to undergo blood withdrawals during each visit to the outpatient clinic.				
I can explain what an abdominal ultrasound is.				
I can explain what an endoscopic examination is.				

Self-efficacy in knowledge of treatment

Which medication do you take?

	Which medication do you take to control your IBD symptoms?	Which medication do you take when your symptoms worsen?
Mesalazine, Pentasa, Salofalk, Asacol, Salazopyrine, Sulfasalazine		
Mesalazine enema		
Azathioprine		
Methotrexate		
Prednison		
Infliximab		

For each medication taken (also in case of calcium/vitamin D, and/or folic acid), please answer the following questions:

I am convinced that…	Yes, definitely	Yes, probably	No, probably not	No, definitely not
I am able to explain why I am treated with this medication.				
I am able to explain at what time of day I have to take this medication.				
I know the dosage of this medication (in milligrams).				
I know how often I have to take this medication (in number of pills/ enemas/injections/infusions per day/ week(s)).				
I am able to explain the side-effects of this medication.				
I am able to explain the consequences when I do not stick to my medication regimen.				

When you have been treated with exclusive enteral nutrition in the past, please answer the following questions:

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I am convinced that…	Yes, definitely	Yes, probably	No, probably not	No, definitely not
I am able to explain what exclusive enteral nutrition is.				
I am able to explain why I was treated with exclusive enteral nutrition.				
I know for how long I was treated with exclusive enteral nutrition.				
I know how much nutrition I had to take each day.				

Self-efficacy in medication use

I am convinced that…	Yes, always	Yes, often	Yes, sometimes	No, never
I can manage to set out my medication each day, without help of others.				
I can manage to take my medication at the right time each day.				
I can manage to remember taking my medication, without help of others.				
I am able to ask for a new prescription when my medication runs out.				
I can tell when the medication has no effect on my symptoms.				
I can describe which effect a dosage reduction of my medication has on my symptoms.				
I can manage to take my medication at instructed times even when I am not at home.				
I can manage to bring my medication when I am planning to go out.				

Actual behavior regarding medication use in the past week

How many days of the past week did you…	Every day	5-6 days	3-4 days	1-2 days	None
remember to take your medication without help of others?					
set out your medication on your own?					
take your medication?					
experience side-effects of your medication?					

Self-efficacy in skills for independent outpatient clinic visits

I am convinced that…	Yes, always	Yes, often	Yes, sometimes	No, never
I can make hospital appointments on my own.				
I can talk to the doctor without my parents being present in the consultation room.				
I am able to discuss my problems with the doctor without help from my parents.				
I dare to ask the doctor any question.				
I dare to confess to the doctor that I did not stick to my medication regimen.				
I dare to tell the doctor if I should disagree with her or him.				
I am able to tell the doctor when my disease worsens/improves, without help of my parents.				
I know how to reach the doctor or nurse, if necessary.				
I can explain to others what was discussed in the consultation room.				

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Actual behavior at the outpatient clinic

	Yes	No	Not applicable
Did you make your own appointment for the most recent visit to the outpatient clinic?			
Did you enter the consultation room alone when you last visited the outpatient clinic?			
Were you able to ask the doctor a lot of questions during your last visit to the outpatient clinic?			
Were you able to influence changes in your medication regimen when you last visited the outpatient clinic?			

Self-efficacy in coping with IBD

I am convinced that…	Yes, always	Yes, often	Yes, sometimes	No, never
I can manage to tell friends about my condition.				
I can manage to explain my condition to friends.				
I can manage to tell my boyfriend/girlfriend about my condition.				
I can manage to explain my condition to my teacher or boss.				

Self-efficacy in knowledge of the transition process

Do you agree on the following statements?

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Stronly disagree
I can explain why the outpatient clinic is located in the adult gastroenterology department instead of the pediatric gastroenterology department.					
I know that this outpatient clinic is called the transition clinic.					
The transition clinic is easy to find.					
I am not able to explain why I have to visit a transition clinic.					
I know what happens when I will transfer to the adult gastroenterologist.					
I know who my adult gastroenterologist is going to be.					
I can explain the differences between pediatric and adult health care.					
I think it is important to know what happens after my transfer to the adult gastroenterologist.					
The transition clinic increases my self-management skills regarding my disease.					
The doctor has given clear information on the transfer to the adult gastroenterologist.					
I am happy to leave the children's hospital.					
I am able to discuss problems regarding sexuality with my doctor.					
Waiting times are short when I visit the transition clinic.					
The doctor and/or research nurse are easily reached, if necessary.					

Self-efficacy in transfer readiness

I am convinced that…	Yes, definitely	Yes, probably	No, probably not	No, definitely not
I am ready to make the transfer to the adult gastroenterologist.				
My parents are ready to make the transfer to the adult gastroenterologist.				

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Part V

General discussion, future perspectives, summary

C h a p t e r

10

**General discussion and
future perspectives**

In the present chapter, we will discuss the main findings of the reported studies, in the context of current literature. Additionally, we will make suggestions on directions of future research.

DIAGNOSTICS

Multicenter, multinational collaboration is needed when studying pediatric inflammatory bowel disease (IBD). In order to have consistent and reliable data, the essential first step is to ensure uniformity in the diagnostic workup and the criteria to diagnose IBD. In 2005, the IBD Working Group of ESPGHAN (European Society for Pediatric Gastroenterology, Hepatology, and Nutrition) therefore published consensus-based guidelines on the diagnostic workup of patients suspected of having IBD.[1] Subsequently, the EUROKIDS registry was established to evaluate the adherence to these Porto criteria in 44 centers in 17 European countries and Israel. Our study, presented in **Chapter 2**, demonstrated that adherence rates to the complete Porto criteria increased significantly from 45% to 64% between May 2004 and April 2009, illustrating the positive impact of the guideline audit on clinical practice. However, significant improvements are still needed, especially in the group of patients diagnosed with IBD-unclassified (IBD-U). IBD-U is a subgroup of IBD that cannot be characterized as either Crohn's disease (CD) or ulcerative colitis (UC) when upper gastrointestinal endoscopy, ileocolonoscopy, and small bowel imaging have been performed. Nevertheless, adherence rates to the complete Porto criteria were only 45% in our cohort of patients diagnosed with IBD-U. Although our prevalence rate (9%) was similar to rates reported in other large pediatric IBD cohorts[2-3], it might very well be that a diagnosis of IBD-U occurs less frequently when a full diagnostic workup is being performed in patients with a suspicion of IBD. Establishing a definite diagnosis is necessary for proper clinical follow-up, to define a suitable therapy, and to assess predictive risk of surgery. Future studies will have to evaluate whether the prevalence of IBD-U decreases due to increased diagnostic accuracy.

Colonoscopy with ileal intubation is the most important investigation to differentiate between CD and UC, and to identify localization and extent of disease.[1] However, intubation of the terminal ileum is not always successful because of its technical difficulties and time constraints. In our study, the diagnostic yield of ileocolonoscopy in diagnosing CD was estimated to be 13%, which was based on the incidence of isolated terminal ileitis (without perianal disease or granulomas in the colon) and the occurrence of granulomas solely confined to the terminal ileum. This yield is probably even higher, as ileal intubation is also important in the differential diagnosis of patients with pancolitis, which was not assessed in our study. The additional value of ileal intubation was also highlighted by other pediatric and adult studies.[4-6] In general, the success rate of ileal intubation was 72% in our study, with a significant increase of 17% during a 5-year period. As adult IBD literature has reported ileal

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intubation rates of 95% of all colonoscopies[7], we will aim to improve these rates further in the following years.

The routine use of upper gastrointestinal endoscopy at diagnosis is still controversial and clinical practice may vary among centers worldwide.[8] The rationale for performing upper gastrointestinal endoscopy is to help distinguish between CD and UC by finding specific endoscopic abnormalities or granulomas solely confined to the upper gastrointestinal tract, and to establish a diagnosis in patients with a normal ileocolonoscopy. Previous pediatric studies on the diagnostic role of upper gastrointestinal endoscopy have focused primarily on the isolated detection of granulomas in the upper gastrointestinal tract, with rates varying from 7 to 21%.[9-11] Our study evaluated the diagnostic yield of upper gastrointestinal endoscopy, using both endoscopic criteria (upper gastrointestinal tract abnormalities considered significant for CD, i.e. ulcerations, cobblestoning, stenosis) and histologic criteria (the presence of granulomas). We found that 4.5% of patients diagnosed with CD had ulcerations in the upper gastrointestinal tract without other characteristics of CD (perianal disease, ileocolonoscopic evidence of CD, granulomas in the gastrointestinal tract). Additionally, 3.0% of patients had granulomas solely confined to the upper gastrointestinal tract without the other characteristics of CD, which resulted in a total diagnostic yield of 7.5%. This yield will further increase in patients who have undergone colonoscopy, but where ileoscopy and small bowel imaging were not performed. A recent Hungarian study, which used definitions quite comparable with our study, demonstrated a diagnostic yield of upper gastrointestinal endoscopy of 9%.[12] These data demonstrate that upper gastrointestinal endoscopy reveals characteristic macroscopic and histologic abnormalities in a substantial number of patients that would be missed with (ileo)colonoscopy alone, justifying its use in the initial assessment of children suspected of having IBD.

DISEASE PHENOTYPE

CD and UC are complex disorders with a significant heterogeneity in disease presentation and course. A further classification in various sub-phenotypes is essential for a better understanding of the pathophysiology of these diseases and for an optimal therapeutic plan tailored to the patient. Classification of disease phenotypes in pediatric IBD has changed significantly during the years due to increasing diagnostic accuracy. Endoscopy skills and equipment are improving and, in most children and adolescents, procedures are now performed either under full anesthesia or analgo-sedation. Additionally, the use of more accurate imaging technologies such as MR enterography, CT enterography, capsule endoscopy, and ultrasound have led to better characteristics of both extent of inflammation and the degree of bowel damage. Reflecting these trends, IBD classification has been changed from the Vienna statement[13], through the Montreal classification[14], to the recent pediatric Paris classification.[15] In this recently modified classification of IBD, elements

of disease phenotype are age at diagnosis, disease location (including the proximal small bowel), disease behavior, and growth.

Age of disease-onset

In accordance with previous studies[3, 16-17], our results on disease phenotype in pediatric CD, presented in **Chapter 3**, clearly showed that disease location differs according to age of disease-onset. Younger children with CD have a tendency to isolated colonic disease, while older children more often present with ileal disease. In our study, disease behavior in pediatric CD also differed with respect to age at diagnosis, as older patients had a higher risk of stricturing disease complications. However, this association might be the effect of age on disease location, as older patients are more likely to have ileal disease, which in turn has been demonstrated to be associated with stricturing disease complications.[17] Thirdly, age at diagnosis has an effect on the disease course in CD patients, as was demonstrated by adult studies.[18-19] CD patients who were younger than 40 years at diagnosis, had an increased risk of a disabling disease course.

In UC, we also demonstrated that disease location was age-dependent, as was presented in **Chapter 4**. UC patients presenting with proctitis were significantly older than patients with more extensive disease, which is in line with a previous study that reported a trend toward fewer cases with proctitis in young children.[3] In contrast, rectal sparing seemed to occur more often in younger children with UC. To our knowledge, this association has not been previously reported.

Disease location

Accurately classifying disease location in IBD is important, as different subtypes may be associated with different types of complications. In keeping with other pediatric and adult data[17, 20], the EUROKIDS study showed that ileal disease in pediatric CD was associated with stricturing disease behavior, which in turn has been associated with an increased risk for surgery.[21-22] We also found an association between ileal disease (either isolated disease or ileocolonic disease) and esophagogastroduodenal disease. In contrast, an abstract from the North American Pediatric IBD Collaborative Research Group Registry only reports an association with ileocolonic disease.[23] These differences might be explained by the use of different definitions of disease involvement. Our study defined esophagogastroduodenal involvement by macroscopic criteria only (i.e. the presence of ulcerations, erosions/aphthae, cobblestones and/or stenosis), while the North American study used both macroscopic and microscopic criteria. Studies on the effect of esophagogastroduodenal disease on the disease course in CD patients have yielded conflicting results. Adult studies have demonstrated that upper gastrointestinal tract involvement is more frequently associated with an increased risk for relapse of disease and/or surgery[24-25], whereas pediatric studies did not find an increased risk for surgery.[21, 23] Again, there might be a disconcordance in definitions used for

upper gastrointestinal involvement. Besides the effect on disease course, disease location has been reported to influence treatment response. For instance, some pediatric evidence tends to favor exclusive enteral nutrition (EEN) in small bowel disease rather than in active colonic disease[26], while infliximab seems to have a better effect in adult CD patients with isolated colonic disease compared with ileal disease.[27]

In UC, a greater risk of colectomy in patients with more extensive disease has been noted in adult studies.[19, 28] In children, this association has not been confirmed,[29-30] which could be due to the differences in disease extent between newly diagnosed pediatric and adult UC patients.[31] Approximately 60 – 70% of pediatric UC patients present with pancolitis, as opposed to approximately 20 – 30% in adults. Furthermore, increased extent of colitis is a risk factor for UC-related colorectal cancer.[32]

Disease behavior

Disease behavior may have an impact on the disease course of IBD. As was mentioned earlier, the presence of stricturing and also penetrating disease in pediatric CD is associated with an increased risk for surgery.[22, 33] At diagnosis, the majority of pediatric CD patients (70 – 90%) has the uncomplicated nonstricturing, nonpenetrating phenotype, as was shown in the EUROKIDS study (**Chapter 3**), as well as in other pediatric studies.[17, 21] However, disease behavior is not stable over time, as nonstricturing, nonpenetrating disease progresses with the development of stricturing or penetrating complications in 15 – 38% of pediatric CD patients, depending on the duration of follow-up.[17, 21, 34]

Perianal disease was present in 9% of the pediatric CD patients in the EUROKIDS registry (**Chapter 3**), which is similar to rates reported in previous studies.[17, 21, 35] As is already known from adult CD patients[36], we showed that perianal disease was associated with disease involvement of the colon and penetrating disease behavior, suggesting an effect of perianal disease on the disease course of CD. In fact, adult and pediatric data have shown that CD patients presenting with perianal disease had an increased risk of developing disabling disease within the first five years after diagnosis.[18, 37]

In pediatric UC, classification of disease behavior is based on severity of disease as defined by PUCAI (Pediatric Ulcerative Colitis Activity Index) scores.[15] The EUROKIDS registry did not include data on disease activity or severity, but a previous study in pediatric UC patients has demonstrated that disease activity at presentation is a significant risk factor for colectomy during the first five years of follow-up.[38]

Growth

Growth failure is an important element of disease phenotype in pediatric CD, as this is present in 10 to 20% of children at diagnosis.[2, 39-41] In contrast, height of newly diagnosed pediatric UC patients does not seem to differ from healthy children.[42-43] Although our study, presented in **Chapter 5**, was not able to characterize growth by linear growth velocity

standardized for gender, age, and pubertal development (as is recommended in the Paris classification), our growth impairment rates for CD and UC based on national growth reference data were quite comparable with those reported in previous studies. In pediatric CD patients, disease location has been shown to affect the risk of impaired height, as small bowel involvement is more likely to disrupt normal nutrient absorption, and to cause stricturing disease and poor weight gain.[2, 44] Our study did not confirm this association, which might be explained by differences in diagnostic workup and definitions of disease location used in the other studies. In pediatric UC, the presence of pancolitis was negatively associated with both height and BMI.

Poor growth at disease-onset has also been demonstrated to be independently associated with an increased risk for surgery in pediatric CD patients.[33]

TREATMENT

The management of pediatric IBD has changed considerably over the last 15 years, mainly due to the introduction of biologicals. Despite the increased number of publications on treatment of pediatric IBD, there are still a lot of unsolved issues regarding the optimal treatment strategies in children.

Part III of this thesis has therefore focused on two induction treatments in pediatric CD: exclusive enteral nutrition (EEN) as induction treatment, and anti-TNF treatment as maintenance treatment. In most European countries, EEN is regarded as the first step in the step-up strategy of inducing remission in pediatric CD patients. Meta-analyses have demonstrated that EEN is as effective as corticosteroids for induction of remission in pediatric CD.[45-46] In contrast with corticosteroids, EEN induces mucosal healing and is more effective in improving nutritional status and linear growth recovery.[47] Nevertheless, EEN has not been universally adopted by centers worldwide. Adherence issues and lack of support from the patient and the family are seen as the main barriers to use EEN.[48] Our study, described in **Chapter 6**, confirmed the frequent occurrence of adherence issues in pediatric CD patients on EEN treatment, but also demonstrated the effectiveness of a completed six-week course of EEN. Although many aspects of EEN treatment are yet unknown (mechanism of action, duration of therapy, route of administration, food reintroduction regimen), this therapy should remain the first-line therapy in pediatric CD because it has fewer side effects than corticosteroids, and promotes growth.

When treatment with EEN, corticosteroids, and/or immunomodulators has failed, anti-TNF treatment can be used to induce remission in pediatric CD patients. Infliximab is currently the only anti-TNF drug that has been registered for use in pediatric CD. In line with previous studies[49-51], we showed that infliximab is effective in inducing and maintaining remission in children with refractory CD. However, a substantial number of patients loses their initial response and requires dose adjustments to maintain clinical response or switch to other

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therapies. In contrast to previous studies[27], the study presented in **Chapter 7** did not find an association between loss of response and disease duration or disease location. Finding reliable predictors of response to infliximab treatment will be essential to improve the risk-benefit profile of this drug, as its use may not be without long-term risks, such as opportunistic and serious infections, auto-immune diseases, and malignancies.[52] In 2009, Centocor (manufacturer of infliximab) initiated a prospective long-term (20 years) observational registry of 5000 pediatric IBD patients in Europe and North-America. This pharmacovigilance registry intends to collect information on all serious adverse events associated with infliximab, as well as other medical therapies for IBD. Adalimumab, a fully humanized anti-TNF drug, has also been demonstrated to be efficacious for refractory adult[53-54] and pediatric CD[55-57], but has not (yet) been registered for pediatric patients. The optimal choice between infliximab and adalimumab is yet to be determined.

TRANSITION

In 2002, the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) published experience-based recommendations on the transition of a patient with IBD from pediatric to adult care.[58] Subsequently, several authors have published data on the transition protocol used in their hospital.[59-61] However, surveys of adult gastroenterologists revealed that there continued to be gaps in a young adult's knowledge of medical history and medication.[62-64] Additionally, Canadian data demonstrated that most adolescents with IBD could not accurately localize their disease, were unaware of their surgical history, the date of their last colonoscopy, and previous results of small bowel imaging.[61] Our data, presented in **Chapter 9**, did not assess patient's knowledge on medical history, but focused on self-efficacy, which is a prerequisite for self-management. In general, levels of self-efficacy were high in our adolescent IBD population, but actual independent behavior during visits to the transition clinic and perceived knowledge of the transition process could be further improved. Taken together, the results from the aforementioned studies clearly demonstrate that IBD transition programs still require further improvements.

FUTURE PERSPECTIVES

The diagnosis and treatment of pediatric IBD have changed considerably over the past three decades, due to the availability of newer diagnostic modalities, and newer and powerful treatments such as biologicals. However, clinical outcomes are often still suboptimal and current treatment regimens need to be optimized.

During recent years, pediatric IBD studies have already increased in quality and quantity due to more extensive use of multicenter collaborations and large prospective databases. These databases will generate important knowledge, for instance on disease prognosis and risk

factors for a disabling disease course. Uniformity in diagnosis and classification of disease phenotype will then be essential to investigate associations with genetic, serologic, and other future biomarkers. This will eventually lead to novel tools that will enable pediatric gastroenterologists to stratify newly diagnosed pediatric IBD patients according to their risk of developing active disease or complications, resulting in patient-tailored interventions. For instance, patients who are more likely to develop complications may be treated more aggressively by early introduction of immunomodulators and biological therapy ('top-down strategy'), which might alter the natural course of disease. As a matter of fact, a multicenter randomized trial will be initiated in the coming year, in which the potential benefit of a 'top-down strategy' in newly diagnosed pediatric CD patients will be investigated.

The available evidence on treatment of pediatric IBD increased significantly during the last 10 years, but there is still a clear need for well-designed and well-conducted prospective trials on the safety and efficacy of drug treatments in children with IBD to further improve clinical outcomes. Studies should also focus on the efficacy of EEN, as this therapy has many benefits for pediatric CD patients who are often growth retarded and malnourished at disease presentation. It is important to determine the most effective EEN treatment regimen (duration of treatment, type of formula, etc.) and to elucidate the mechanisms by which EEN exert its effects. This will also lead to a better understanding of the interactions between the epithelium and foreign antigens in the intestinal lumen. Furthermore, future IBD research should focus on predictors of response to treatment, which would improve the benefit/risk profiles of drugs, especially of biologicals.

Development of Genome Wide Association (GWAS) analyses has greatly expanded the number of susceptibility genes implicated in the pathogenesis of IBD. Future studies will continue the search for new IBD susceptibility genes. Understanding of how these genes work will lead to a greater understanding of IBD pathogenesis. Hopefully, this will also allow for the development of more targeted therapies.

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Transfer to the adult gastroenterologist is an important milestone in the management of young IBD patients. Future research should focus on the most successful way to transition adolescent IBD patients to adult caregivers. Efforts should be made to determine universally accepted definitions that characterize a successful transition process, thereby not only focusing on patient's knowledge and self-management, but also on the effect on disease control, hospital admission and surgery, medical compliance, and quality of life.

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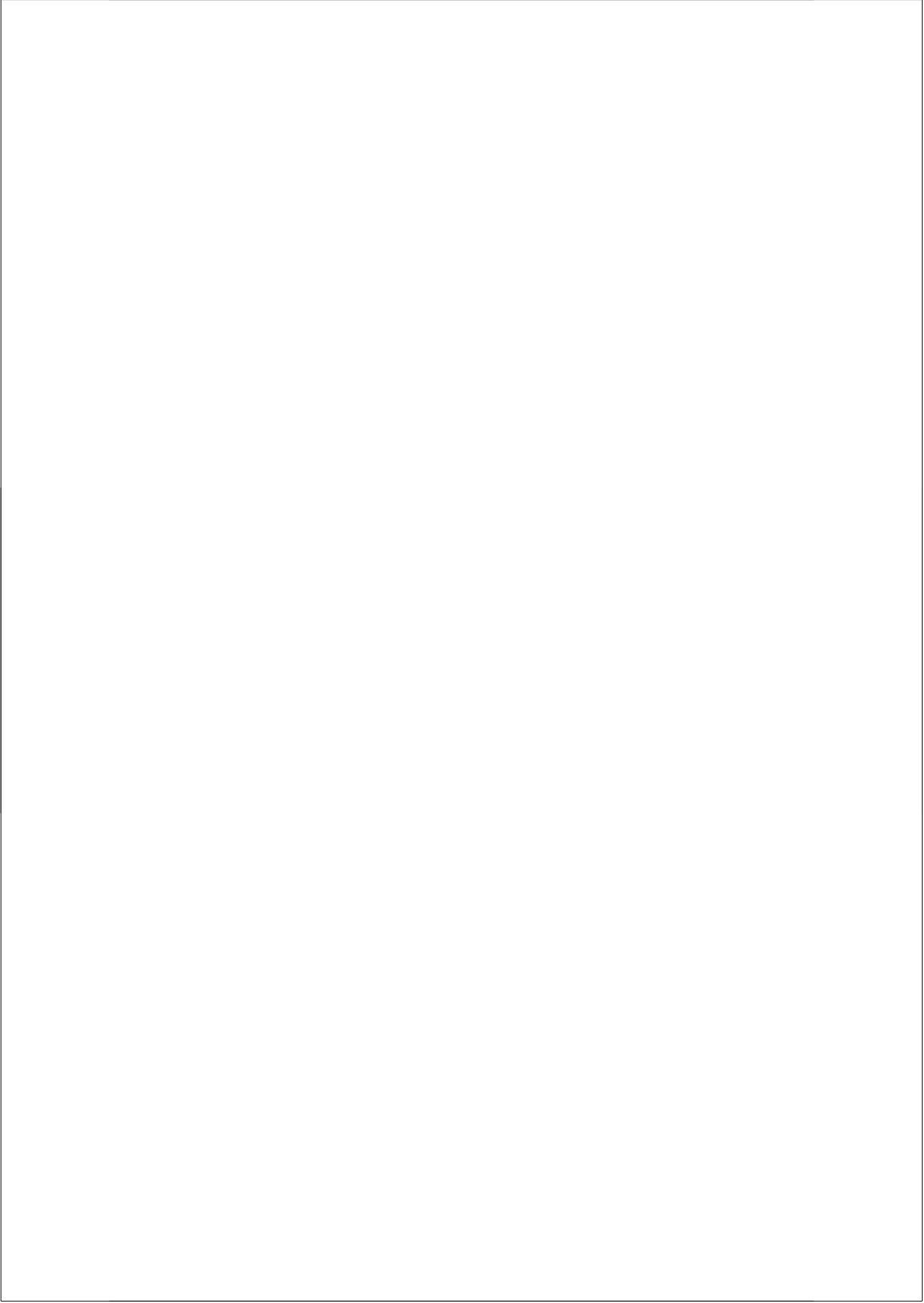
C h a p t e r

11

Summary

Samenvatting

Affiliations co-authors

SUMMARY

Inflammatory bowel disease (IBD) is a lifelong disease that presents during childhood and adolescence in up to 20% of all cases. Nevertheless, IBD in childhood and adolescence is rare, with incidence numbers of 5 – 8 per 100,000 children per year. With relatively small numbers of patients per center, (inter)national collaboration is mandatory.

The diagnosis of IBD and the differentiation into Crohn's disease (CD), ulcerative colitis (UC), and IBD-unclassified (IBD-U) is based on clinical, endoscopic, histopathologic, and radiologic findings. Establishing a correct diagnosis is essential when choosing therapeutic options, or when discussing long-term prognosis with a patient. At present, no therapeutic intervention can lead to a definitive cure of IBD. As in adults, treatment of children with IBD is therefore aimed at inducing and maintaining remission, but special considerations are needed regarding optimal growth and development. Both exclusive enteral nutrition and infliximab are treatments that have a beneficial effect on growth and nutritional status. Exclusive enteral nutrition is often used as induction treatment in children newly diagnosed with CD, while infliximab is usually reserved for refractory IBD patients. Besides prescribing the appropriate treatment, another important task of the pediatric gastroenterologist is to prepare the adolescent with IBD and his/her parents for the transfer to the adult gastroenterologist. A transition program allows adolescents to develop skills in communication, self-management, and assertiveness.

In this thesis, several aspects of pediatric IBD are evaluated, including diagnostics, clinical presentation, treatment, and transition. **Chapter 1** is a general introduction of these aspects, and also provides information on the national and international registries that were used in this thesis: the Dutch registry of infliximab use in pediatric CD, and the EUROKIDS registry, which is the first and only European pediatric IBD registry. This prospective registry includes data from pediatric IBD patients at diagnosis from 17 European countries and Israel. In this ongoing, web-based registry, patients are registered once, at the time of diagnosis.

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In **Chapter 2**, the first 5-year results of the EUROKIDS registry are presented. We investigated the adherence to consensus-based guidelines on the diagnostic workup of pediatric IBD patients (the Porto criteria) during a 5-year period (May 2004 – April 2009). Additionally, we evaluated the diagnostic yield of upper gastrointestinal endoscopy and ileal intubation during colonoscopy. Data from 2087 pediatric IBD patients (mean age 12.1 years, 56% males) were analyzed. Overall, the quality of the diagnostic workup in pediatric IBD patients increased steadily after the publication of the Porto criteria in 2005, with increasing numbers of upper gastrointestinal endoscopies and ileocolonoscopies being performed. Use of small bowel imaging by small bowel follow-through decreased significantly from 76% to 32% during the 5-year period ($P<0.001$), whereas use of MRI increased significantly from 9% to 50% ($P<0.001$), and CT abdomen from 3% to 9% ($P<0.001$). Adherence rates to a complete diagnostic workup according to the Porto guidelines were 59% in CD, 58% in UC, and 45%

in IBD-U patients, with a significant improvement over time for patients diagnosed with CD and UC. Using both endoscopic and histologic criteria, we found that the diagnostic yield of upper gastrointestinal endoscopy in diagnosing CD was 7.5%, and the yield of ileal intubation was 13%. These results underline the importance of a full endoscopic workup in children and adolescents with a suspicion of IBD.

Chapter 3 describes the variety of disease phenotypes of 582 newly diagnosed pediatric CD patients registered in the EUROKIDS database, who had a complete diagnostic workup according to the Porto criteria. Disease phenotype was assessed by the Paris classification, a pediatric modification of the Montreal classification of disease location in IBD. Isolated terminal ileal disease (±limited cecal disease) was seen at presentation in 16%, isolated colonic disease in 27%, ileocolonic disease in 53%, and isolated upper gastrointestinal tract disease in 4% of patients. In total, 30% of patients had esophagogastroduodenal involvement, and 24% jejunal/proximal ileal disease. We found that patients with isolated colonic disease were less likely to have esophagogastroduodenal involvement or stricturing disease complications compared with patients with disease involvement of the terminal ileum. Additionally, we demonstrated that disease phenotype was clearly dependent on the age of disease-onset, with older children (≥ 10 years) being more likely to have involvement of the terminal ileum, as well as stricturing disease behavior.

In **Chapter 4**, we investigated the occurrence of atypical disease phenotypes in 643 newly diagnosed pediatric UC patients registered in the EUROKIDS database (mean age 11.6 years, 50% males). Macroscopic rectal sparing was present in 5% of pediatric UC patients. Patients with rectal sparing were significantly younger at diagnosis than patients without rectal sparing (9.9 years vs. 11.8 years, *P*=0.02). Erosions or ulcerations in the upper gastrointestinal tract were present in 4% of UC patients, which were mostly located in the stomach. Backwash ileitis (in the presence of cecal inflammation) occurred in 10%, and a cecal patch in 2% of patients. We concluded that the occurrence of atypical disease phenotypes in children and adolescents should not preclude a diagnosis of pediatric UC. Recognition of atypical phenotypes in pediatric UC at disease-onset is crucial to prevent mislabeling of these patients as CD.

In **Chapter 5**, we present the EUROKIDS data on height and body mass index (BMI) at diagnosis, as assessed by different growth references. Additionally, we determined the effect of disease location on height and BMI. In 459 CD patients, mean height-for-age SDS was -0.11 (95% CI -0.21 to -0.001) according to WHO growth reference data, and -0.39 (95% CI -0.49 to -0.28) according to national growth references of 11 European countries. BMI-for-age SDS were -0.76 (95% CI -0.90 to -0.62) and -0.82 (95% CI -0.96 to -0.68), respectively. Growth retardation (height-for-age SDS ≤ 1.96 SDS) was present in 9%, and malnutrition

(BMI-for-age SDS ≤ 1.96 SDS) in 18% of pediatric CD patients. In 475 UC patients, height and BMI were significantly less affected compared with CD patients. The presence of pancolitis was negatively associated with both height and BMI of UC patients, while there was no effect of disease location or extent on height and BMI in pediatric CD. We concluded that the use of national growth references is more appropriate than the use of WHO growth reference data when analyzing a European cohort of children and adolescents.

Chapter 6 reports the results of a retrospective study on the effectiveness of a six-week course of exclusive enteral nutrition in 77 newly diagnosed pediatric CD patients (median age 13.9 years, 57% male) treated in two tertiary referral centers in the Netherlands. A completed six-week course of exclusive enteral nutrition was demonstrated to be effective, with complete remission rates of 71% and partial remission rates of 26%. Complete remission rates were found to be higher in children presenting with isolated ileal/ileocecal disease and malnutrition. Discontinuation of exclusive enteral nutrition before the intended treatment period occurred in 25% of patients due to worsening of symptoms (n=9) or adherence issues (n=10). Adherence issues seemed to occur more often in older children, females, children from non-Dutch parents, and patients receiving hyperosmolar sip feeds. These findings underline the importance of actively addressing adherence issues during a course of exclusive enteral nutrition.

In **Chapter 7**, the long-term efficacy of infliximab in the treatment of pediatric CD is discussed. Between October 1992 and November 2009, 152 pediatric CD patients (median age 15.0 years, 53% male) were treated with infliximab in 13 hospitals in the Netherlands. Patients received a median number of 10.5 infliximab infusions during a median follow-up of 25 months. We found that the cumulative probability of losing response to infliximab in patients who required repeated infusions, was 13%, 40%, and 50% after 1, 3 and 5 years, respectively. Dose adjustments (dosage increase to 10 mg/kg and/or shortening of the interval between two infusions) were needed in 74 patients (49%), with a median time to any adjustment of 6 months. These findings emphasize the need for effective long-term treatment strategies in pediatric CD.

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Chapter 8 is an extensive review of the current evidence supporting the use of antitumor necrosis factor (TNF) treatment in pediatric IBD. Infliximab, adalimumab, and certolizumab are monoclonal antibodies against TNFα, a proinflammatory cytokine with an increased expression in the inflamed tissues of IBD patients. Infliximab is a chimeric antibody, while adalimumab is a fully humanized antibody and certolizumab is a humanized anti-TNF antibody Fab' fragment. In children with CD, infliximab has proven to be efficacious in inducing and maintaining remission, achieving mucosal healing, inducing perianal fistula closure, reducing corticosteroid exposure, promoting growth, and improving quality of life.

Infliximab also has a role in the management of children with moderate or severe UC, but appears to be less effective than in pediatric CD. Adalimumab, although data are limited, seems to be effective for pediatric CD. The role of certolizumab in pediatric IBD is yet to be determined. Over the past 10 years, anti-TNF treatment has been of great benefit to many pediatric IBD patients, but their use is not without risks, especially in combination with immunomodulators (infections, auto-immune diseases, and possibly malignancies). Despite the growing experience with these biological drugs in children with IBD, optimal treatment strategies still need to be determined, such as the optimal timing for introduction of anti-TNF treatment, optimal dosing schemes, and the need for concomitant immunosuppressants.

Chapter 9 presents a study in which the reliability of a novel IBD-specific questionnaire on self-efficacy was evaluated in adolescent IBD patients and their parents who visited the IBD transition clinic of the Erasmus MC – Sophia Children's Hospital. In a cross-sectional design, 50 adolescent IBD patients and 40 parents completed the questionnaire, separately from each other. The questionnaire proved to be a reliable tool, with good to excellent internal consistency for all domains. In general, median self-efficacy scores of adolescent IBD patients were high, with scores varying from 70 to 100%. We demonstrated several marked differences between the self-efficacy scores of the patients and those assigned by their parents. Parents thought that their child was more self-efficacious in knowledge of IBD and diagnostic tests, self-management of medication use, and transfer readiness. Although additional validation and further domain and question reduction are necessary, this questionnaire is a first step toward evaluating quality and efficacy of IBD transition programs.

SAMENVATTING

Chronische inflammatoire darmziekten (in het Engels *inflammatory bowel diseases*, IBD) zijn levenslange aandoeningen, die zich bij ongeveer 10 – 20% van de patiënten al op de kinderleeftijd presenteren. IBD bij kinderen is relatief zeldzaam, met een incidentie van 5 tot 8 per 100.000 kinderen per jaar. Het aantal patiënten dat per centrum wordt behandeld is vaak klein. Daarom is het van groot belang dat onderzoek in (inter)nationaal samenwerkingsverband plaatsvindt.

IBD wordt onderverdeeld in de ziekte van Crohn, colitis ulcerosa, en 'niet te classificeren colitis' (in het Engels *IBD-unclassified*). Dit onderscheid wordt gemaakt op basis van klinische, endoscopische, histopathologische, en radiologische bevindingen. Het stellen van de juiste diagnose is belangrijk bij het bepalen van de behandeling en de prognose van een patiënt. Op dit moment is er geen behandeling die IBD kan genezen. De behandeling van kinderen met IBD is daarom, net als bij volwassenen patiënten, gericht op het induceren en behouden van remissie. Daarnaast wordt er extra aandacht besteed aan het bewerkstelligen van een normale groei en puberteitsontwikkeling. Voedingstherapie en infliximab zijn twee behandelopties die een positief effect hebben op de groei en voedingstoestand van een kind met IBD. Voedingstherapie wordt meestal toegepast als inductiebehandeling bij nieuw gediagnosticeerde kinderen met de ziekte van Crohn, terwijl infliximab over het algemeen gebruikt wordt bij kinderen met therapieresistente ziekte. Naast het voorschrijven van de juiste behandeling, is een andere belangrijke taak van de kinder MDL arts om de adolescente IBD patiënt en zijn/haar ouders voor te bereiden op de transfer naar de volwassen MDL arts. Gedurende het transitieproces moet de adolescent verschillende vaardigheden leren, zoals communicatieve vaardigheden, zelfmanagement, en ziekte-inzicht.

In dit proefschrift worden verschillende aspecten van IBD bij kinderen bestudeerd, namelijk de diagnostiek, de klinische presentatie, de behandeling, en het transitieproces. **Hoofdstuk 1** is een algemene inleiding over deze aspecten, en beschrijft daarnaast de nationale en internationale databases die zijn gebruikt voor dit proefschrift: de Nederlandse database van infliximab gebruik bij kinderen met de ziekte van Crohn, en de EUROKIDS database, de eerste en enige Europese database van kinderen met IBD. Deze prospectieve database bevat gegevens van nieuw gediagnosticeerde kinderen met IBD afkomstig uit 17 Europese landen en Israël. In deze doorlopende online database, worden patiënten eenmalig geregistreerd op het moment van diagnose.

In **Hoofdstuk 2** worden de eerste resultaten van de EUROKIDS database gepresenteerd. Gedurende de periode mei 2004 – april 2009 hebben wij onderzocht in hoeverre Europese richtlijnen ten aanzien van de diagnostiek bij kinderen met verdenking op IBD werden opgevolgd (de Porto criteria). Daarnaast werd de diagnostische waarde bepaald van gastroduodenoscopie en ileocolonoscopie. Gegevens van 2087 kinderen met IBD (gemiddelde leeftijd 12.1 jaar, 56% jongens) werden geanalyseerd. Sinds de publicatie

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van de Porto criteria in 2005 is het gebruik van gastroduodenoscopie en ileocolonoscopie significant toegenomen. Het gebruik van dunne darm passagefoto's nam significant af van 76% naar 32% (*P*<0.001), terwijl het gebruik van MRI significant toenam van 9% naar 50%, en het gebruik van CT abdomen van 3% naar 9% (beide *P*<0 .001). Een volledig diagnostisch programma volgens de Porto criteria werd uitgevoerd bij 59% van de patiënten met de ziekte van Crohn, 58% van de patiënten met colitis ulcerosa, en 45% van de patiënten met 'IBD-unclassified'. Het aantal patiënten met de ziekte van Crohn en colitis ulcerosa dat een volledig diagnostisch programma onderging, nam significant toe met de jaren. De diagnostische waarde (gebaseerd op endoscopische en histologische criteria) van gastroduodenoscopie voor het vaststellen van de ziekte van Crohn was 7.5%, en de waarde van ileocolonoscopie was 13%. Deze resultaten benadrukken het belang van een volledig endoscopisch onderzoek bij kinderen en adolescenten met verdenking op IBD.

Hoofdstuk 3 beschrijft de diversiteit aan fenotypes in een EUROKIDS cohort van 582 nieuw gediagnosticeerde kinderen met de ziekte van Crohn, die een volledig diagnostisch programma volgens de Porto criteria ondergingen. Ziektelokalisatie werd bepaald aan de hand van de 'Paris classification', die recent gepubliceerd is door een internationale groep van kinder MDL artsen. Deze classificatie is een uitgebreidere versie van de 'Montreal classification' voor ziektelokalisatie in volwassen IBD. Geïsoleerde ziekteactiviteit in het terminale ileum (±betrokkenheid van het coecum) werd gezien bij 16% van de patiënten, geïsoleerde ziekteactiviteit in het colon bij 27%, ziekteactiviteit in zowel het terminale ileum als het colon bij 53%, en geïsoleerde betrokkenheid van de bovenste tractus digestivus bij 4%. In totaal had 30% van de patiënten betrokkenheid van de oesophagus, maag, en/of duodenum, en 24% betrokkenheid van het jejunum en/of proximale deel van het ileum. We vonden dat patiënten met geïsoleerde ziekteactiviteit in het colon minder kans hadden op betrokkenheid van de oesophagus, maag en/of duodenum én minder kans hadden op fibrostenotische complicaties. Daarnaast hebben we aangetoond dat fenotype afhankelijk is van leeftijd bij diagnose. Patiënten ouder dan 10 jaar hebben een grotere kans op betrokkenheid van het terminale ileum, en op het ontwikkelen van fibrostenotische complicaties.

In **Hoofdstuk 4** onderzochten wij de incidentie van atypische fenotypes in een EUROKIDS cohort van 643 nieuw gediagnosticeerde kinderen met colitis ulcerosa (gemiddelde leeftijd 11.6 jaar, 50% jongens). Een macroscopisch normaal rectum was aanwezig in 5% van de kinderen met colitis ulcerosa. Deze kinderen waren significant jonger dan de kinderen waarbij het rectum macroscopisch wel was aangedaan (9.9 jaar vs. 11.8 jaar, *P*=0.02). Verder had 4% van de kinderen met colitis ulcerosa erosies of ulceraties in de bovenste tractus digestivus, waarbij met name erosies in de maag werden gevonden. 'Backwash ileïtis' (beschadiging en ontsteking in het distale deel van het ileum, in aanwezigheid van ontsteking in het coecum)

kwam voor bij 10%, en een 'cecal patch' (ontsteking rondom de appendix opening) bij 2% van de kinderen met colitis ulcerosa. Wij concludeerden dat atypische fenotypes kunnen voorkomen bij colitis ulcerosa op de kinderleeftijd. Het is dan ook belangrijk om atypische ziektelokalisaties bij colitis ulcerosa te kunnen herkennen, zodat voorkomen kan worden dat deze kinderen ten onrechte gediagnosticeerd worden met de ziekte van Crohn.

In **Hoofdstuk 5** worden de EUROKIDS resultaten over lengte en body mass index (BMI) bij diagnose gepresenteerd, waarbij gebruik werd gemaakt van verschillende groeireferenties. Daarnaast hebben we de invloed van ziektelokalisatie op lengte en BMI bepaald. In een cohort van 459 kinderen met de ziekte van Crohn was de gemiddelde lengte-naar-leeftijd SDS -0.11 (95% CI -0.21 to -0.001) wanneer gebruik werd gemaakt van WHO groeireferentie data, en de gemiddelde lengte-naar-leeftijd SDS was -0.39 (95% CI -0.49 to -0.28) op basis van nationale groeireferentie data van 11 Europese landen. BMI-naar-leeftijd SDS waren respectievelijk -0.76 (95% CI -0.90 to -0.62) en -0.82 (95% CI -0.96 to -0.68). Negen procent van de kinderen met de ziekte van Crohn presenteerde zich met groeivertraging (lengte-naar-leeftijd SDS ≤ 1.96 SDS), en 18% met ondervoeding (BMI-naar-leeftijd SDS ≤ 1.96 SDS). Kinderen met de ziekte van Crohn hadden significant lagere lengte- en BMI-naar-leeftijd SDS in vergelijking met een cohort van 475 colitis ulcerosa patiënten. Ziektelokalisatie had een significant effect op lengte en BMI van kinderen met colitis ulcerosa: kinderen met pancolitis hadden significant lagere lengte- en BMI-naar-leeftijd SDS dan kinderen met minder uitgebreide ziekte. Bij kinderen met de ziekte van Crohn bleek ziektelokalisatie geen effect te hebben op lengte en BMI bij diagnose. Wij concludeerden dat nationale groeireferentie data meer geschikt zijn dan WHO groeireferentie data voor het analyseren van een Europees cohort van kinderen en adolescenten.

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Hoofdstuk 6 beschrijft de resultaten van een retrospectieve studie naar de effectiviteit van 6 weken voedingstherapie, waarbij 77 nieuw gediagnosticeerde kinderen met de ziekte van Crohn (mediane leeftijd 13.9 jaar, 57% jongens) werden geïncludeerd in twee academische Nederlandse ziekenhuizen. Zes weken voedingstherapie resulteerde in complete remissie bij 71% en partiële remissie bij 26% van de kinderen met de ziekte van Crohn. Complete remissie werd vaker gezien bij kinderen met geïsoleerde ziekte van het terminale ileum (al dan niet met betrokkenheid van het coecum) of wanneer ondervoeding bestond bij diagnose. De behandeling met voedingstherapie werd voortijdig gestaakt bij 25% van de patiënten ten gevolge van verergering van de symptomen (n=9) of problemen met de therapietrouw (n=10). Problemen met therapietrouw kwamen vaker voor bij oudere kinderen, meisjes, allochtone kinderen, en patiënten die voedingstherapie kregen in de vorm van energieverrijkte drinkvoeding. Deze resultaten benadrukken het belang van het actief bespreekbaar maken van de therapietrouw tijdens een behandeling met voedingstherapie.

Hoofdstuk 7 beschrijft de lange termijn effectiviteit van infliximab behandeling bij kinderen met de ziekte van Crohn in Nederland. In de periode oktober 1992 – november 2009 werden 152 kinderen met de ziekte van Crohn (leeftijd mediaan 15.0 jaar, 53% jongens) behandeld met infliximab in 13 ziekenhuizen. Gedurende een follow-up van mediaan 25 maanden werden patiënten behandeld met mediaan 10.5 infliximab infusies. De cumulatieve kans op verlies van respons bij infliximab-afhankelijke patiënten was 13%, 40% en 50% na respectievelijk 1, 3 en 5 jaar. Gedurende follow-up hadden 74 patiënten (49%) intensivering van het behandelschema nodig (ophogen van de dosering tot 10 mg/kg en/of verkorten van het interval tussen twee opeenvolgende infusies). De periode tussen het starten met infliximab behandeling en 1^e aanpassing in het behandelschema was mediaan 6 maanden. Deze uitkomsten benadrukken het belang van effectieve, lange termijn behandelingsstrategieën voor kinderen met de ziekte van Crohn.

Hoofdstuk 8 geeft een uitgebreid overzicht van de bestaande literatuur over anti-tumor necrosis factor (TNF) behandeling bij kinderen met IBD. Infliximab, adalimumab en certolizumab zijn monoklonale antistoffen tegen TNFα, een proinflammatoir cytokine dat verhoogd tot expressie komt in ontstoken weefsels van IBD patiënten. Infliximab is een chimere (half mens, half muis) antistof, adalimumab is een volledig humane antistof, en certolizumab is een humaan Fab' fragment van anti-TNF. Infliximab wordt succesvol toegepast als inductie- en onderhoudsbehandeling bij kinderen met actieve ziekte van Crohn, en is tevens effectief voor de behandeling van perianale fistels. Daarnaast kan infliximab mucosale genezing bewerkstelligen, het gebruik van corticosteroïden verminderen, lengtegroei stimuleren, en kwaliteit van leven verbeteren. Infliximab wordt ook gebruikt voor de behandeling van kinderen met matige tot ernstige colitis ulcerosa, maar lijkt voor deze indicatie minder effectief te zijn dan voor de ziekte van Crohn. Adalimumab wordt succesvol toegepast bij kinderen met de ziekte van Crohn, maar de follow-up van effectiviteitsstudies is nog relatief kort. Data over certolizumab behandeling bij kinderen met IBD zijn op dit moment nog niet beschikbaar. In de afgelopen 10 jaar zijn veel kinderen met IBD succesvol behandeld met anti-TNF, maar het gebruik van deze geneesmiddelen, vooral in combinatie met immunomodulatoren, is niet zonder risico's (bijv. het optreden van infecties, auto-immuun ziektes, en mogelijk maligniteiten). Ondanks de toenemende ervaring met anti-TNF behandeling, is er nog relatief veel onduidelijkheid over het optimale behandelschema, zoals het optimale moment om te starten met infliximab/adalimumab, het optimale doseringsschema, en de noodzaak van combinatietherapie.

In **Hoofdstuk 9** werd de betrouwbaarheid van een nieuwe IBD-specifieke vragenlijst naar de zelfredzaamheid van adolescente IBD patiënten onderzocht. Tijdens een bezoek aan de IBD transitiepoli van het Erasmus MC – Sophia Kinderziekenhuis werden adolescenten

(n=50) en hun ouders (n=40) gevraagd de vragenlijst in te vullen, onafhankelijk van elkaar. De vragenlijst bleek een betrouwbaar instrument om zelfredzaamheid te bepalen, met een goede tot uitstekende interne consistentie van alle domeinen. Mediane zelfredzaamheid scores waren hoog, variërend van 70 tot 100%. Er werden duidelijke verschillen gevonden tussen de zelfredzaamheid scores van de patiënten en de scores toegekend door hun ouders. Ouders gaven hogere zelfredzaamheid scores dan hun kinderen op het domein van kennis van IBD en de diagnostiek, zelfmanagement van medicatie gebruik, en het gevoel klaar te zijn voor de transfer naar de volwassen MDL arts. Nadat verdere validatie van de vragenlijst en reductie van het aantal domeinen/vragen heeft plaatsgevonden, kan dit instrument een belangrijke rol gaan spelen bij het evalueren van de kwaliteit en de effectiviteit van IBD transitieprogramma's.

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A P P E N D I C E S

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Curriculum Vitae

List of publications

PhD portfolio

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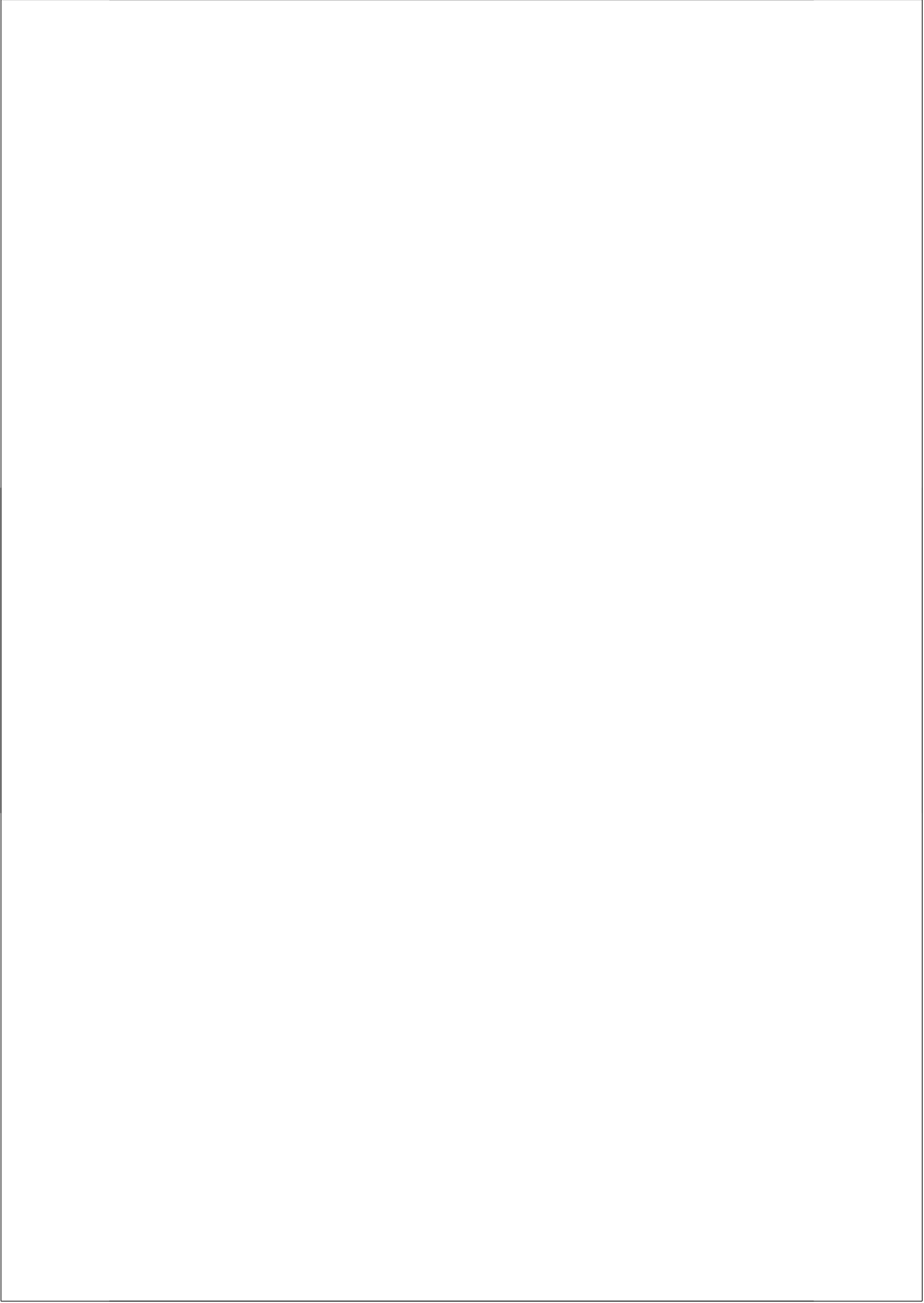
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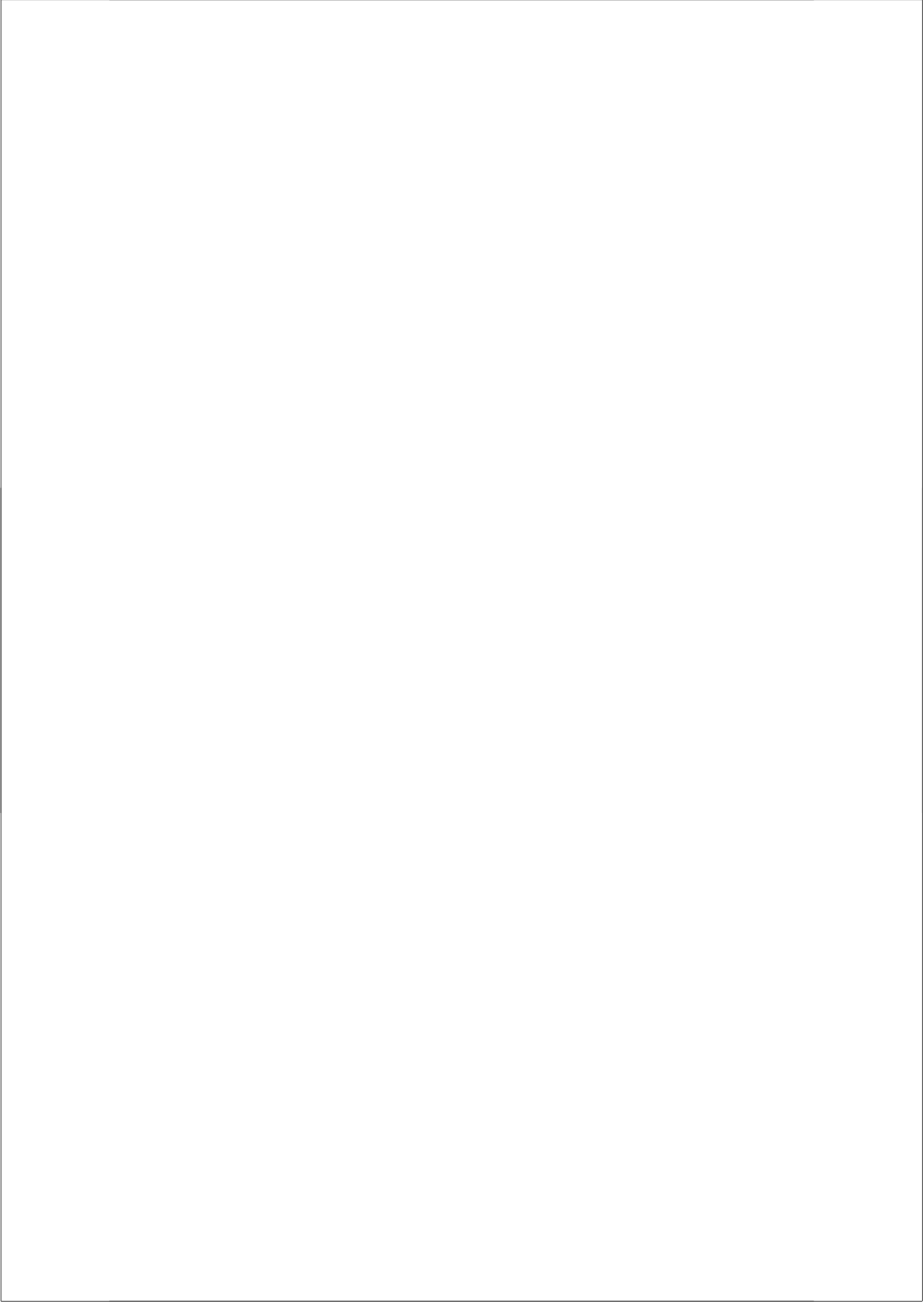
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CURRICULUM VITAE

Charlotte de Bie was born on December 7th, 1984 in Gorinchem. In 2002, she passed her secondary school exam (cum laude) at the Gymnasium Camphusianum in Gorinchem. In the same year, she started her medical training at the Medical Faculty of the Erasmus University Rotterdam. In May 2008, she completed her Master thesis on 'Enteral nutrition in pediatric Crohn's disease' at the Department of Pediatric Gastroenterology of the Erasmus MC – Sophia Children's Hospital (supervisor: Dr. J.C. Escher), which eventually resulted in a first manuscript for this thesis. Subsequently, she did an elective internship at the Department of Internal Medicine of 'het Diakonessenhuis' in Paramaribo, Suriname. Her final 12-week internship was performed at the Department of Pediatrics, Maasstadziekenhuis, Rotterdam (head of Pediatrics: Dr. C.R. Lincke). After obtaining her medical degree (cum laude) in November 2008, she worked for 5 months as a resident at the Department of Pediatrics, Maasstadziekenhuis, Rotterdam. In June 2009, she returned as a PhD student at the Department of Pediatric Gastroenterology of the Erasmus MC – Sophia Children's Hospital to continue her research on pediatric inflammatory bowel disease, under supervision of Dr. J.C. Escher. The research performed during this period is described in this thesis. As of July 2012, she will start her residency in clinical genetics at the Department of Medical Genetics, University Medical Center Utrecht (head of Medical Genetics: Prof. dr. N.V.A.M. Knoers).

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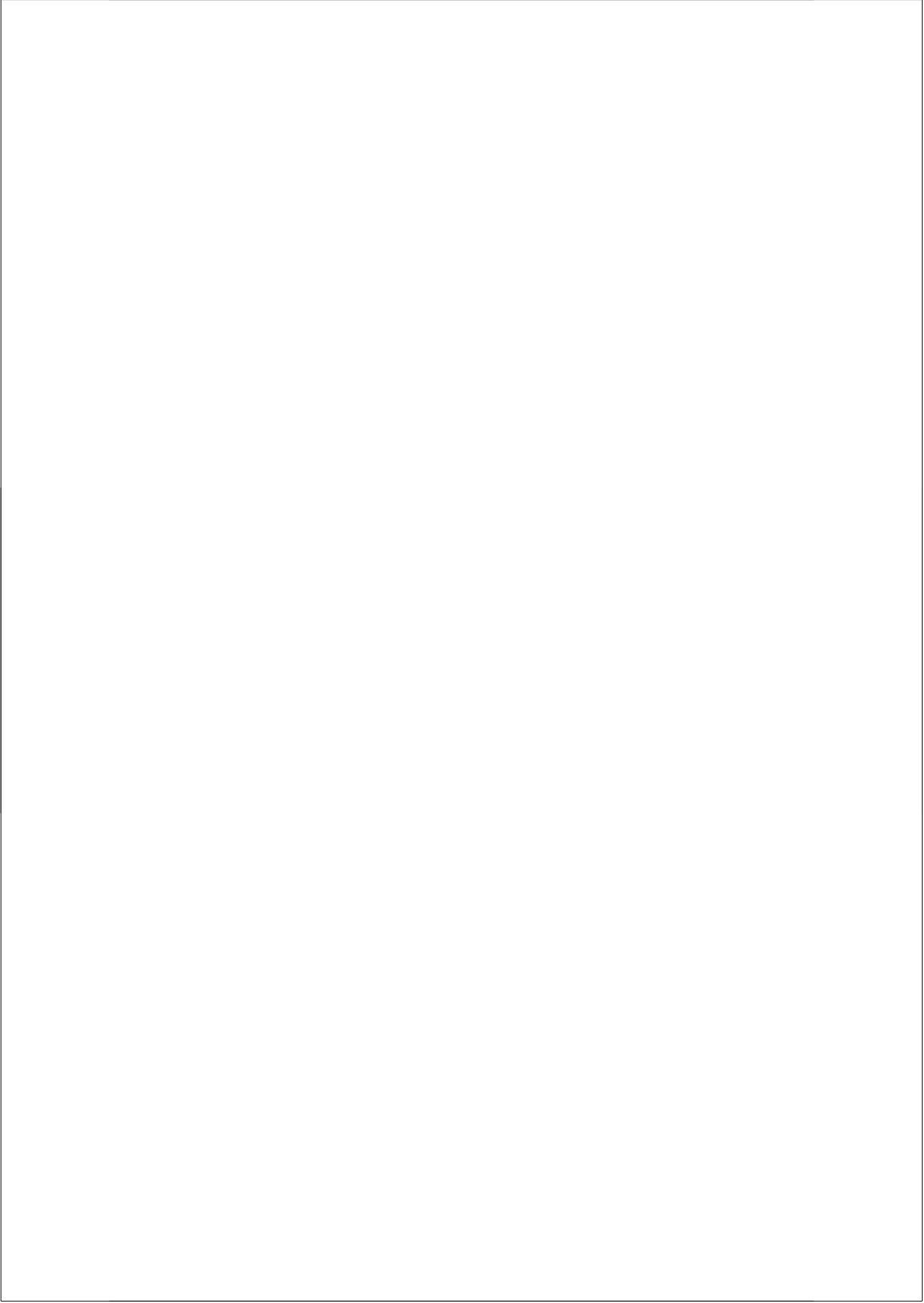
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PHD PORTFOLIO

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Research School:	Molecular Medicine
PhD period:	June 2009 – June 2012
Promotor:	Prof.dr. A.J. van der Heijden
Copromotor:	Dr. J.C. Escher

General academic courses	Year
Good Clinical Practice	2010
Biostatistics for clinicians	2010
Regression analysis	2010
Biomedical English Writing and Communication	2011
Research Management for PhD students	2011
Basic Human Genetics Course	2011
Research meetings, Department of Pediatric Gastroenterology	2009-2012

Seminars, workshops, symposia	
CPO mini-course: Methodology of patient orientated research and preparation for subsidy application	2011
Workshop Career Orientation	2011
KiCC-off symposium (oral presentation)	2012

(Inter)national conferences	
Pediatric Inflammatory Bowel Disease, Paris, France	2009
8th Research Day Pediatrics, Rotterdam, Netherlands (oral presentation)	2009
Spring meeting NVGE, Veldhoven, Netherlands (oral presentation)	2010
Young Investigators Forum ESPGHAN, Schliersee, Germany (oral presentation)	2010
Digestive Disease Week, New Orleans, USA (poster presentation)	2010
43rd annual meeting of ESPGHAN, Istanbul, Turkey (2 oral presentations)	2010
National Pediatrics Congress, Veldhoven, Netherlands (oral presentation)	2010
Clinical Observation Program, Erasmus MC, Rotterdam, Netherlands	2010-2012
7th congress of ECCO, Barcelona, Spain (poster presentation)	2012
Spring meeting NVGE, Veldhoven, Netherlands (oral presentation)	2012
ESPGHAN update meeting, Stockholm, Sweden (poster presentation)	2012

Teaching activities	
Regionale bijscholing Kinder MDL: Infliximab	2010

Other	
Peer review of manuscripts for scientific journals	2011-2012