PREDICTING OUTCOMES IN PEDIATRIC INFLAMMATORY BOWEL DISEASE

Martine Aardoom

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Predicting Outcomes in Pediatric Inflammatory Bowel Disease

Het voorspellen van het beloop van chronische darmontsteking op de kinderleeftijd

Proefschrift

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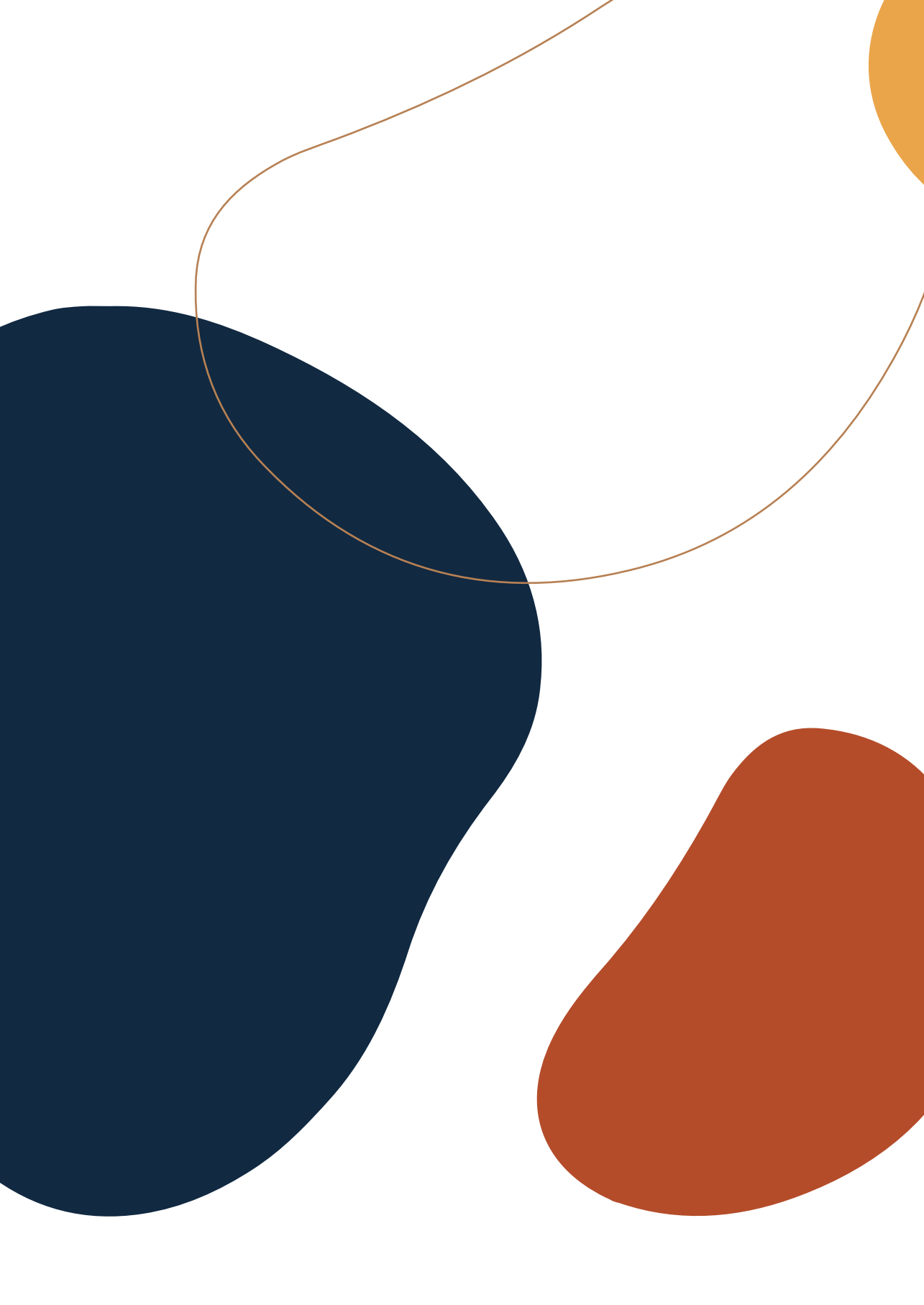

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General introduction and outline of this thesis

Parts of this chapter are published in Int J Mol Sci. 2019 May 23;20(10):2529, and the PIBD guideline (2019) by the Dutch Association of Pediatrics (NVK)

INTRODUCTION

Patients with inflammatory bowel disease (IBD) have a chronic inflammation of the gastrointestinal tract. The two most prevalent clinical forms of IBD are Crohn's disease (CD) and ulcerative colitis (UC). Although the peak incidence of IBD is around the age of 30 years, in around 10% of all cases the disease is diagnosed during childhood or adolescence.[1,2] For pediatric CD, prevalence rates in Europe range from 8.2 to 60 per 100.000, while for pediatric UC this is 8.3 to 30 per 100.000.[3] A recent study showed that the prevalence of IBD patient ≤17 years of age is 1.4% of all IBD cases.[4] In Europe, around two third of IBD diagnoses in children are CD.[5] Within the pediatric population, IBD can present at very young age, even in children <1 year of age. However, most often pediatric-onset IBD (PIBD) is diagnosed in teenagers.[6,7] In the past decades, the incidence of PIBD has increased and the disease has become more prevalent in parts of the world where IBD was previously quite rare.[1,8,9] PIBD differs from adult-onset IBD as it presents with a more extensive inflammation pattern. In addition, the onset of disease in an early stage of life may lead to insufficient growth, late pubertal development and psychosocial problems.[10] Many differences in the disease presentation and disease course of PIBD exist, but currently remain unexplained. Considering the increasing incidence and risk of complications due to this chronic IBD itself or its treatment, knowledge on factors that predict the disease course is urgently needed.

Clinical presentation and disease course

IBD has a relapsing and remitting pattern, which means that at a certain time during the disease course complaints can reoccur due to a disease flare. Being grouped under the term IBD, CD and UC share certain clinical characteristics. Both may present with abdominal pain, diarrhoea, weight loss and rectal bleeding. In general, these two subtypes of IBD can be discriminated based on the location of the inflammation and their histopathological features (Figure 1).

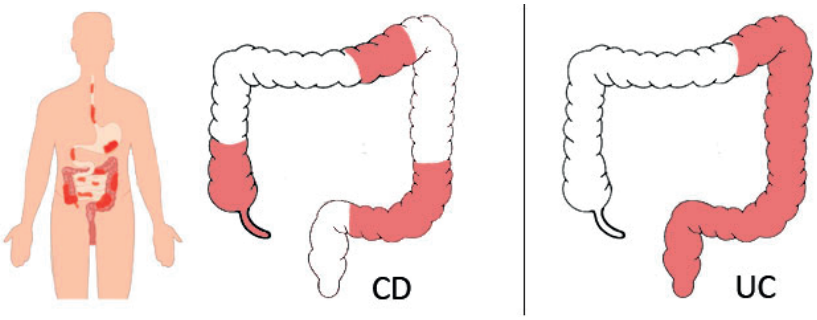

Figure 1. Parts of the gastrointestinal tract that can be affected in case of Crohn's disease (left) and ulcerative colitis (right).

CD is a granulomatous disorder that presents with transmural inflammation, often in a skip-lesion pattern. The inflammation can be located in all segments of the gastrointestinal tract and may result in the formation of strictures, abscesses and perianal or internal fistulas. The chronic inflammation in UC is more superficial and extends in a continuous pattern from the rectum to a more proximal part of the colon (Figure 2).

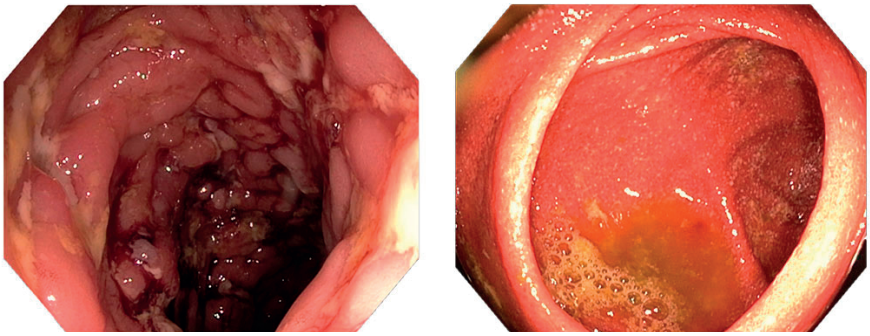

Figure 2. Endoscopic findings in a patient with Crohn's disease (left) and ulcerative colitis (UC)

Gastrointestinal inflammation is monitored by assessment of clinical disease activity scores, inflammatory markers in blood and stool and endoscopy. In some patients the disease remains in remission following their treatment directly after diagnosis, whereas others may have frequent flares or ongoing active disease despite treatment. The disease course may also be complicated by development of penetrating or stricturing disease in Crohn's disease patients and the need for surgery in both CD and UC. This is particulary relevant in children, as this age group has been shown to have a higher risk of complicated disease compared to adults.[11] A complicated disease course affects the child's growth, development, school attendance and quality of life. Classifing patients according to the risk of a complicated disease course should lead to more targeted treatment strategies.

Heterogeneity in children with IBD

Although the majority of patients can be classified as having either CD or UC there is a subset of patients with IBD type colitis that does not completely fit one of either disease types. Diagnosis of PIBD is performed according to the revised Porto criteria, which decribe the subtypes atypical UC and IBD-unclassified (IBD-U) next to CD and UC.[12] A proportion of the patients with colitis who are initially diagnosed with IBD-U are classified as CD or UC later on. The majority of these patients, however, remains being classified as IBD-U, showing that there is a group of patients that does not fit a CD or UC diagnosis. There may thus be more (sub)classes of IBD. Recently, an algorithm has been suggested to better classify patients with pediatric-onset IBD based on clinical, endoscopic and histologic findings at diagnosis. The value of this approach remains to be explored in

future studies.[13] The concept of more detailed IBD classification adds to the increasing evidence that UC and CD are very heterogeneous diseases. Both CD and UC are further classified by disease characteristics including extension, location and behaviour of the disease according to the Paris classification (Table 1).

Table 1. Paris classication *- Table adapted from Levine et al. IBD 2011 (14)*

Pediatric Crohn's disease		**Pediatric ulcerative colitis**	
Age at diagnosis	0 - <10 years	**Disease extension**	Proctitis
	10 - 17 years		Left-sided
			Extensive
			Pancolitis
Location	L1: Distal 1/3 ileum ± limited cecal disease		
	L2: Colonic	**Severity**	Never severe*
	L3: Ileocolonic		Ever severe*
	L4: Upper gastrointestinal disease**		
Behaviour	Non-stricturing, non-penetrating		
	Stricturing (B2)		
	Penetrating disease (B3)		
	Both penetrating and stricturing (B2B3)		
	Perianal disease modifier (p)		
Growth	No evidence of growth delay		
	Growth delay		

**Severe is defined as a Pediatric Ulcerative Colitis Activity Index (PUCAI) ≥65.(15)*
***Upper disease is further specified in disease proximal (L4a) and distal (L4b) to the ligament of Treitz but proximal to the distal third of the small intestine.*

As such, the Paris classification not only reflects disease at presentation but also associates with the disease course after diagnosis.[16] Despite the distinct differences between PIBD patients, current treatment strategies are mainly focused on the treatment of children with CD or UC in general.

Treatment strategies

Currently, PIBD cannot be cured and lifelong medical treatment is often needed. Treatment options for children with IBD can be categorized in nutritional therapy, medication and surgery.[17,18] In case of failure of medical therapy children with UC may need to undergo a total colectomy and children with CD may need an ileocecal resection or even a colectomy. First aim in the treatment of PIBD is to induce remission of disease, and secondly, to maintain remission. Maintenance therapy consists of immunomodula-

tors such as thiopurines or methotrexate. After diagnosis, children with UC are initally treated with 5-aminosalicylates or corticosteroids to induce remission. For treatment of UC, 5-ASA may also be used as single maintenance therapy. For children with CD, initial treatment options consist of exclusive enteral nutrition (EEN) or corticosteroids. EEN is a polymeric liquid diet that is nutritionally complete. This diet is given exclusively instead of usual solids and fluids for a period of 6-8 weeks. Although adhering to this diet is challenging for a child, the major benefit when compared to corticosteroids is the lack of side effects and positive effects on growth. Corticosteroid use in children can lead to growth delay and children may experience debilitating side effects such as weight gain and mood changes. In the past two decades, biologicals are incorporated in the treatment strategies for PIBD. Tumor necrosis factor alpha (TNF-α) inhibitors, so-called anti-TNF agents, were the first agents within the group of biologicals to be approved for use in the treatment of adult CD and UC in 1998 and 2005, respectively. In 2006, the anti-TNF agent infliximab (IFX) was approved for pediatric CD, followed by approval for pediatric UC in 2011.[19,20] Nowadays, more biological agents are available to physicians for treatment of PIBD. However, in contrast to adults, in children and adolescents the anti-TNF agents IFX and adalimumab are the only biologicals currently approved by the U.S. Food and Drug Administration or European Medicines Agency for treatment of IBD, others are under study and thus being used off-label (Table 2). Since 2021, adalimumab is approved for the treatment of children with CD and UC.[21,22]

Table 2. *Biologicals that are currently reimbursed or under study for treatment of pediatric IBD. Adapted from Aardoom et al.(23)*

Class	Name	Product (®)	Admission route	Status in PIBD
Anti-TNF	infliximab	Remicade	iv	Approved
	adalimumab	Humira	sc	Approved
	golimumab	Simponi	sc	Off-label
	certolizumab pegol	Cimzia	sc	Off-label
Anti-α4β7integrin	vedolizumab	Entyvio	iv	Off-label
Anti-α4β7 and αEβ7 integrin	etrolizumab	-	sc	Off-label
Interleukin 12/23 p40 inhibitor	ustekinumab	Stelara	iv/sc	Off-label
Interleukin 23p19 inhibitor	mirikizumab	-	iv	Off-label

Abbreviations: iv, intravenous; sc, subcutaneous.

Indication for treatment with biologicals

Anti-TNF

Ulcerative colitis

In the current treatment guidelines for pediatric UC, IFX is advised as second-line therapy for children with chronically active or steroid-dependent UC, uncontrolled by 5-ASA and thiopurines, for both induction and maintenance of remission.[17] When a patient initially

responds to IFX, but then develops intolerance or antibodies to IFX, adalimumab or golimumab may be considered.

Crohn's disease

In the treatment of children with CD, IFX is part of second-line therapy in a similar manner. It is being administered in case of chronically active luminal CD despite prior optimized immunomodulator therapy and to induce remission in children with active steroid-refractory disease. In children with CD there is also a role for anti-TNF therapy as first-line treatment. Studies have shown that children with active perianal fistulizing disease benefit from administration of IFX directly after diagnosis.[24] In addition, based on consensus guidelines, first-line IFX treatment should be considered in children with CD suffering from extensive disease, significant growth retardation, deep ulcerations in the colon seen at endoscopy, severe osteoporosis and stenosing or penetrating disease at diagnosis. More evidence on the beneficial effect of early anti-TNF treatment in children with CD is emerging. The RISK study showed in a propensity-score matched analysis that early anti-TNF treatment (within <3 months after diagnosis) was associated with higher corticosteroid free and surgery free remission rates at one year compared with early immunomodulator therapy.[25] Several other observational studies in children with CD show that primary IFX therapy may be very effective in inducing and maintaining clinical remission in pediatric patients with luminal CD.[26,27] A randomized controlled trial, in which adult patients with CD who had recently been diagnosed were included, showed that early treatment with IFX in combination with immunomodulators was more effective than conventional treatment with corticosteroids. However, a randomized controlled trial in therapy-naïve children with CD was still lacking.[28] Given the more severe phenotype of disease in pediatric-onset CD than in adult-onset CD,[11] pediatric patients with CD may benefit most from first-line anti-TNF treatment by preventing accumulating damage due to chronic uncontrolled inflammation.

Vedolizumab

For both CD and UC, vedolizumab is prescribed for children that are non-responsive or have lost reponse to an anti-TNF agent. Vedolizumab is a monoclonal antibody directed against α4β7 integrin. The α4β7 integrin is an adhesion molecule expressed on circulating memory T-helper lymphocytes allowing their migration into the intestinal tissue, which is an important component of the inflammation process in IBD.[29,30] Vedolizumab has been registered for treatment of adult IBD patients, but is being used off-label in children. For anti-TNF treatment, therapeutic drug monitoring is implemented in clinical practice by measuring trough levels and the presence of antibodies. Optimal serum concentrations for effectiveness have been described and several studies have shown that the use of therapeutic drug monitoring during anti-TNF therapy improves clinical

outcomes and reduces antibody formation.[31,32] For treatment with vedolizumab is still unclear whether therapeutic drug monitoring improve clinical outcomes. In a retrospective study of children with IBD who were treated with vedolizumab after primary or secondary failure of anti-TNF, corticosteroid free remission rates of 39% for UC and 24% for CD were achieved at last follow-up (median of 24 weeks).[33] Although vedolizumab treatment seems safe and effective, treatment optimization may result in higher remission rates and prevent these patients from needing surgery. A meta-analysis of ten adult IBD patient cohorts found that 54% with secondary loss of response to vedolizumab might benefit from dose optimization.[34] A few studies in adult patients with IBD have described serum vedolizumab levels and accumulating evidence regarding an exposure-efficacy relationship is emerging.[35-40] Clinical factors such as body weight and serum albumin level are suggested to be associated with these trough levels, but studies in children with IBD are lacking.[41,42]

Vedolizumab is not the only agent being used as second-line agent in the treatment of PIBD. The role of interleukin inhibitors (ustekinumab) and Janus Kinase inhibitors (tofacitinib) in the treatment of IBD is currently being explored.

The risk of developing severe complications

Optimizing and tailoring current treatment strategies requires information on the patient's individual risks. As mentioned earlier, the disease course of children with IBD may be complicated by frequent disease flares or ongoing inflammation despite several treatment strategies. Next to consequences such as growth failure, decreased quality of life and need for surgery, this may also lead to more rare but very severe complications. There are several severe disease-related or treatment-associated outcomes such as cancer, venous thromboembolisms and serious infection, that raise concerns. Reason for these concerns are studies in adults that have shown an increased cancer and mortality risk in IBD patients.[43,44] Longer disease duration, frequently combined with more extensive and severe colitis may put PIBD patients at a higher risk for developing colorectal cancer than patients with adult onset of disease.[11,45] The use of immunosuppressants has been associated with an increased risk of opportunistic infections, lymphomas, and even mortality.[46,47] Given the increasing use of immunosuppressants as maintenance therapy for IBD in children and the longer duration of treatment there is a rising concern that severe outcomes will affect pediatric patients as well. Despite these concerns, studies investigating these types of severe outcomes are scarce. International collaborations are required to gain insight in the incidence and characteristics of these oucomes in children with IBD and find out which patients are at risk.

Tailoring treatment to the individual patient risk

In adult IBD patients, several clinical risk factors have been identified for the development of a complicated disease course in IBD patients. Clinical factors such as extensive disease, ileal involvement, deep ulcerations and penetrating or stenosing behaviour were identified as factors associated with an increased risk for complications in CD patients. In UC patients extensive disease and presence of primary sclerosing cholangitis (PSC) are reported as prognostic factors.[48,49] In addition to these clinical factors, there is increasing data suggesting that serological, genetic and immunological biomarkers may help predict the disease course.[50-52] Although the aetiology of IBD is not completely understood, it is partly explained by a combination of a genetic predisposition, microbial factors and susceptibility of the immune system leading to an aberrant inflammatory immune response.[53-55] In IBD patients, a common disease denominator is the infiltration of $CD4^+$ T-cells in the intestinal tissue. However, it has proven to be very difficult to monitor the strength and phenotype of the inflammatory T cell response at an individual level. In consequence, it is difficult to monitor the effects of immune modulation. Studies investigating immune phenotypes suggest there may be a relation to certain clinical disease characteristics, but the available data is limited.[56] Investigation of immunological biomarkers from diagnosis onwards, combined with detailed clinical characterization of IBD patients, is warranted to further develop biomarker-based diagnostics, patient classification and therapeutic strategies.

AIM AND OUTLINE OF THIS THESIS

A better understanding of factors that affect the disease course of children with IBD should enable risk-stratified treatment, which may result in a beneficial effect on the course of disease and thus the lives of these children. The aim of this thesis is to identify predictors of disease course in PIBD patients and to select children with IBD who are at-risk for developing severe complications due to their disease or its treatment. Additionally, new treatment strategies, guided towards precision medicine in IBD, are tested and optimized.

In **Chapter 2** of this thesis, we summarize in a systematic review the existing literature on cancer and mortality in patients with pediatric-onset IBD. In **Chapter 3** we describe the characteristics of children with IBD who developed cancer or died based on a prospective international study. In **Chapter 4** the incidence and characteristics of another severe complication in children with IBD, venous thromboembolisms, are described based on the findings from a prospective PIBD safety registry. The study presented in **Chapter 5** focuses on the treatment strategies in a subgroup of patients with newly

diagnosed CD; children with moderate-to-severe CD. The results of a randomized controlled trial that compared first-line IFX treatment with conventional treatment (EEN or corticosteroids) are described in this chapter. **Chapter 6** shows our findings after studying a group of children with IBD that received vedolizumab therapy after non-response or loss of response to anti-TNF. In particular, we described the vedolizumab trough levels in these children and aimed to associate these levels with other disease characteristics. **Chapter 7** and **Chapter 8** present the findings of a systematic review and meta-analysis of clinical studies that investigated predictors of adverse outcomes of pediatric-onset IBD. Consensus statements were formulated based on the systematic review and meta-analysis, and results of the voting on these statements are included in these two chapters. **Chapter 7** focuses on pediatric CD and describes predictors of surgery, complications, chronically active disease, and hospitalization. In **Chapter 8** predictors of colectomy, acute severe colitis and chronically active disease in pediatric UC patients are described. **Chapter 9** describes the international prospective study we have designed with the aim to identify children with IBD that are most at risk to develop a complicated disease course or therapy non-responsiveness. Finally, in **Chapter 10**, the findings in this thesis are discussed and suggestions for future research are made.

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02

Malignancy and mortality in pediatric-onset inflammatory bowel disease: a systematic review

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ABSTRACT

Background: Cancer and death are the most severe outcomes that affect patients with inflammatory bowel disease (IBD). These outcomes are even more severe if they occur at a young age but are rare, even in the general population. We conducted a systematic review to provide an overview of all reported pediatric (PIBD) patients with severe outcome.

Methods: A literature search identified publications that reported development of cancer or fatal outcome in PIBD patients. Studies were eligible for inclusion when (1) article written in English, (2) original data, (3) individual patient information, (4) full text available, (5) study population consisting of patients diagnosed with IBD under the age of 19 years, and (6) who developed malignancy or fatality at any point later in life.

Results: A total of 98 included studies comprised data of 271 PIBD patients who developed cancer and/or fatal outcome at any point later in life. Meta-analysis demonstrated an increased risk for cancer in PIBD patients (pooled standardized incidence ratio 2.23, 95% CI: 1.98 – 2.52). The most frequent type of non-fatal cancer was lymphoma, whereas colorectal carcinomas were the most frequently reported type of fatal cancer in PIBD patients and were particularly associated with primary sclerosing cholangitis. The majority of patients with noncancer-related fatal outcomes were diagnosed with ulcerative colitis and most often died due to infectious complications or severe disease-associated complications.

Conclusions: The data in this review confirm that PIBD associated malignancy and mortality are rare and detailed clinical characteristics are limited. Prospective and international collaborations are needed to obtain more detailed patient-specific information, which is necessary to investigate the relationship between severe outcomes in PIBD patients and the currently used therapeutic strategies.

INTRODUCTION

The incidence of pediatric-onset inflammatory bowel disease (PIBD) has risen significantly in the past two decades in Europe and North America[1-3] and PIBD is becoming more prevalent in the rest of the world.[4] PIBD is characterized by extensive intestinal involvement and rapid disease progression.[5-7] Consequently, it is often accompanied by severe complications, such as growth failure and need for bowel surgery.[8] In addition, the longer disease duration, frequently combined with a more extensive and severe colitis, puts PIBD patients at a higher risk for developing colorectal cancer (CRC) than adult-onset IBD patients.[9] Even after adjusting for extent of disease, age at diagnosis was found to be an independent risk factor for CRC.[10, 11]

Despite their success in limiting persistent disease activity in IBD patients, immunosuppressant drugs can lead to serious and opportunistic infections and increase the risk of developing cancer.[12-14] The use of thiopurines has been shown to increase the risk for lymphoma[15, 16], non-melanoma skin cancers[17], and cervical cancer.[18] In addition, biological or non-biological immune suppression increases the risk of infectious complications, which may translate into an increased risk of mortality.[11, 19, 20] There is a growing concern that cancer and mortality will affect pediatric patients, as an increasing number of PIBD patients now are being exposed to immunosuppressant drugs over longer periods of time.

Due to the rarity of cases, few studies have investigated cancer and mortality in patients with PIBD. Much of the literature on severe outcomes in PIBD includes anecdotal case reports and case-series but very few population-based studies. To date, there is only one systematic review focussed on lymphoma and infections related to biological therapy[21], hence, a coherent overview of PIBD patients who develop cancer or fatal outcome is lacking. Better insight into the characteristics of these patients will help to identify predictive factors of severe disease course, which is ultimately needed to further optimize our therapeutic strategies. In this review, we conducted a systematic literature search to provide an overview of patients with IBD diagnosed at pediatric age who developed cancer or suffered a fatal outcome at any point later in life.

METHODS

Literature search

We conducted a literature search to identify all published studies that reported cancer or mortality in patients diagnosed with PIBD under the age of 19 years. A systematic search

up to June 1, 2017 was performed in the following databases: Medline, Ovid MEDLINE, Embase, Cochrane Central, Web of Science and Google Scholar. The detailed search strategy was developed in consultation with a research librarian and is outlined in the Supplemental Search Strategy. Reference lists of review articles and selected papers also were analyzed. To obtain full texts of potentially relevant papers, both electronic databases and libraries were accessed.

Selection criteria

All studies (prospective and retrospective cohort studies, case-control studies, cross-sectional studies, case series and case reports) that fulfilled the following criteria were included: (1) article written in English, (2) original data available in article, (3) individual patient information available, (4) full text article available, (5) study population consisting of patients diagnosed with IBD under the age of 19 years, and (6) who developed cancer or fatal outcome at any point later in life. No publication date restrictions were imposed. Animal studies, reviews, meta-analysis, editorials, and practical summaries or guidelines were excluded.

Data extraction and quality assessment

Systematic review has been performed according to PRISMA guidelines.[22] Two reviewers (Martine A. Aardoom and Maria E. Joosse) independently conducted an initial screen of identified abstracts and titles. Abstracts were eliminated in this initial screen if they did not meet the criteria as described above. Inconsistencies on inclusions were resolved by consensus. Abstracts meeting these criteria were eligible for full text review. The risk of bias was determined using the Newcastle-Ottawa Quality Assessment Scale for cohort studies. From the included articles the following information was retrieved using a standard data extraction form: gender, IBD type, age at IBD onset, IBD treatment, type of cancer or cause of mortality, age at cancer diagnosis and/or age at death. A random effects meta-analysis was performed to compute pooled standardized incidence ratios (SIR) for all types of cancer and CRC. Analyses were performed by a biostatistician using R version 3.4.2.

RESULTS

The electronic search yielded a total of 10,187 articles, of which 6,984 potentially relevant articles remained after duplicates were removed (Figure 1A). An additional 43 articles were manually selected from reference lists. All records were screened on the basis of title and abstract to identify studies reporting development of cancer or fatal outcome in patients with IBD diagnosed at pediatric age. After screening, a total of 6,820

were excluded and 164 potential articles remained that were eligible for fulltext assessment. Of these, 66 articles were excluded. The most important reasons for exclusion were the lack of patient specific information (n=35) and the unavailability of fulltext after extensive online and medical library search (n=13). Six studies did not report any pediatric data, 5 studies did not describe IBD patient population, 7 studies were either retrieved twice due to publication in different sources or discussed data of an original article already included in the review. A total of 98 articles were included with a high interobserver agreement (Cohen's kappa κ= 0,92146).

Table 1 provides characteristics of the 98 included studies. Most identified studies were case reports (n=47), case series (n=20) and retrospective cohort studies (n=25). Only 4 prospective cohort studies, 1 cross-sectional study and 1 case-control study were retrieved with our literature search. Most retrospective cohort studies were single-center (68%). There were 2 prospective studies published by Hyams *et al.* that were both multicenter cohort studies, with data on PIBD patients [both ulcerative colitis (UC) and Crohn's disease (CD)] from the Pediatric Inflammatory Bowel Disease Collaborative Research Group[23] and the DEVELOP study.[24] Two prospective studies were single-center studies focusing on long-term outcomes in pediatric-onset CD patients.[25, 26] The follow-up period was reported in 18 studies of all cohort studies and case-control studies (60%, Table S1). The median time of follow-up was 13.0 years (IQR 5.6-17.7).

Table 1. Characteristics of included studies

	Type of study	No	References*
1	Retrospective study	**25**	1-25
2	Case report	**47**	26-72
3	Case series	**20**	73-92
4	Prospective study	**4**	93-96
5	Cross-sectional	**1**	97
6	Case control study	**1**	98
	Total:	**98**	

*See supplemental reference list

A total of 4 population-based studies (Figure 1) describe SIR for all types of cancer in PIBD patients over the last 3 decades. Of these, 3 were pooled in a meta-analysis demonstrating an increased risk for cancer in PIBD patients (pooled SIR 2.2, 95% CI: 2.0-2.5). Five studies reported SIR for CRC. One study reported a SIR for CRC in a PIBD cohort of 69 patients with 1602 patient-years of follow-up (25.7, 95% CI: 3.1-92.7).[27] However, as development of CRC is associated with colonic disease, most studies reported SIRs for CRC in CD and UC separately. Meta-analysis showed a strongly increased risk for CRC in

UC patients (pooled SIR 54.7, 95% CI: 26.0-115.4) and a lower but significantly increased risk in CD patients (pooled SIR 6.3, 95% CI: 3.9-10.2) (Figure S1).

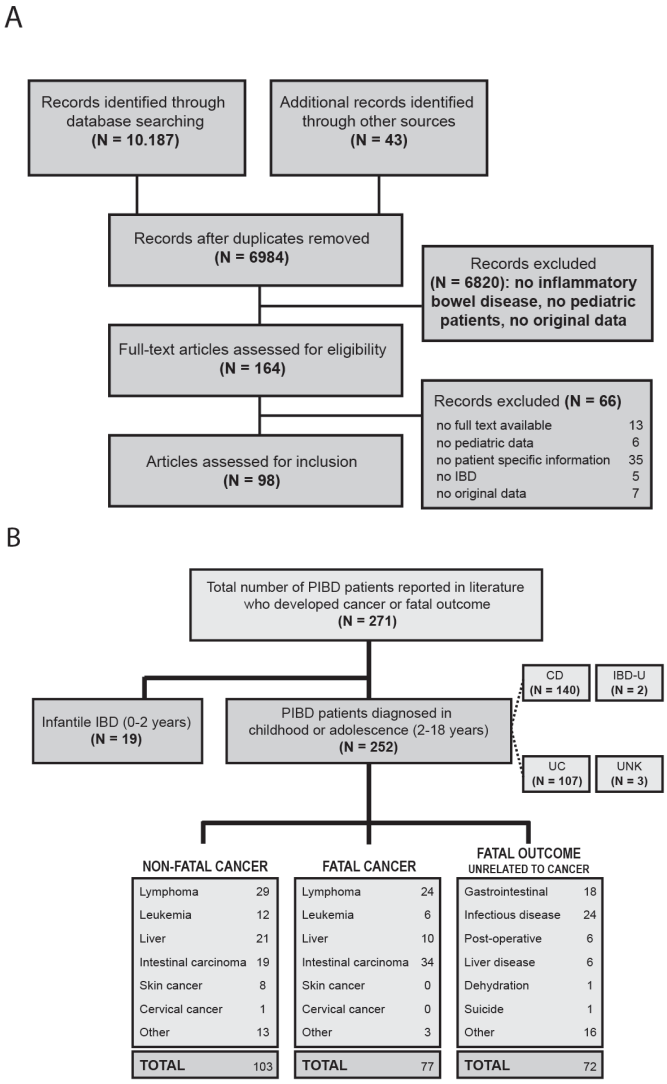

Figure 1. (A) Flow diagram of study selection and (B) overview of included patients.

No statistically significant increased standardized mortality ratios (SMR) in PIBD patients compared to the background population have been reported in the last 2 decades. Peneau *et al.* observed a 1.4-fold increased risk of mortality (95% CI: 0.5-2.9) in PIBD patients but this did not significantly differ from the background population. Likewise,

the SMR was not significantly increased in pediatric CD patients compared to the background population in the cohort studied by Jakobsen *et al.* (2.1, 95% CI: 0.6-5.4).

Study population

To gain further insight into the characteristics of PIBD patients who develop cancer or suffer a fatal outcome, detailed patient characteristics from all studies describing PIBD patients with cancer or fatal outcome were obtained. The 98 studies included in our review comprised detailed data of 271 PIBD patients who developed cancer and/or fatal outcome at any point later in life (Figure 1B). Eight reports described patients diagnosed with IBD under the age of 2 years; detailed characteristics of these infantile IBD patients are not further described in this manuscript. The remaining 92 studies comprised a total group of 252 PIBD patients with IBD diagnosed during childhood or adolescence. These patients were diagnosed with CD (65.2%, n=140), UC (43.0%, n=107) or inflammatory bowel disease unclassified (IBD-U) (0.8%, n=2) at a median age of 12.0 years (IQR 8.78-15.0; IBD type missing in 3 cases). The majority of those patients were male (63.4%, n=151). Median age at either diagnosis of cancer or occurrence of death was 18.00 years (IQR 15.0-25.0). All individual patient information of patients with PIBD diagnosed during childhood or adolescence can be reviewed in Supplementary Table 1.

Malignancy

Cases with cancer were reported in 80 of 92 studies (87.0%), comprising a total of 180 pediatric-onset IBD patients with a diagnosis of cancer. Of these patients, 77 (42.8%) were reported to have a fatal outcome. Patient characteristics of PIBD patients who developed non-fatal cancer or fatal cancer are described separately in Table 2 and Table 3, respectively.

Non-fatal cancer

A total of 103 patients with cancer but without a fatal outcome were reported in 42 studies. Of these studies 18 were case reports, 8 were cases series, 10 were retrospective studies, 4 were prospective studies, 1 was a case-control study and 1 was a cross-sectional study. Of the retrospective studies only 2 were multicenter.

In this patient group, patients were diagnosed with CD (63.7%, n=65) or UC (36.3%, n=37) at a median age of 12.00 years (IQR 10.00-15.00; IBD type missing in 1 case). The median age at diagnosis of cancer was 17.50 years (IQR 15.00-25.00). The majority of patients (64.2%) were male.

Most frequently reported non-fatal cancers were lymphomas (n=29), cholangiocarcinomas (CCA) (n=16), and CRC (n=19), as shown in Table 2. In the group of patients diagnosed

								Newcastle-Ottawa tool		
Study	Population	Size (N)	Period of diagnosis	Follow-up period	Malignancy (N)	SIR for cancer	95% CI	Selection	Comparability	Outcome
Peneau (2013)	Pediatric IBD patients < 17 years	698	1988-2004	Median 11.5 years	9	IBD: 3.0	1.3 □5.9	****	*	**
Kappelman (2014)	Pediatric IBD patients < 20 years	NR	1978-2010	NR	NR	CD: 2.3 UC: 2.0	1.5 - 3.4 1.4 - 1.7	****	*	**
Hyams (2017)	Pediatric IBD patients < 17 years	5,766	2007-2016	24,543 patient-years (median 4.7 years)	15	Drug exposed: 2.43 Non-drug exposed: 1.30	Drug exposed: 1.29-4.15 Non-drug exposed: 0.16-4.71	****	*	**
Olen (2017)	Pediatric IBD patients < 18 years	9,405	1964-2014	148,682 patient-years	497	Total: 2.2 UC: 2.6 CD: 1.7	Total: 2.0 - 2.5 UC: 3.2 - 3.0 CD: 1.5 - 2.1	****	**	**

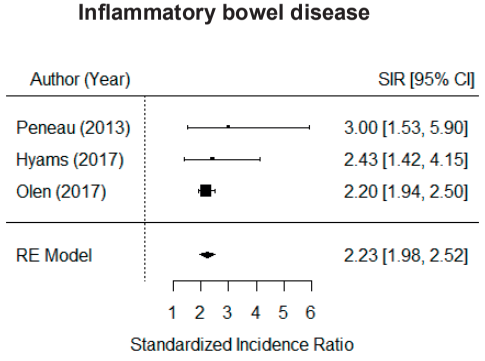

Figure 2. SIR for all types of cancer in PIBD patients over the last 3 decades. Table and graphs presenting SIRs by study including a pooled SIR for all types of cancer occurring in patients with PIBD following a random effects (RE) model. Kappelman *et al.* (2014) was not included in the meta-analysis as a SIR in the total PIBD population was not described. SIR, Standardized incidence ratio; RE, random effects; CI confidence interval; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; CRC, colorectal cancer.

Table 2. Clinical characteristics of PIBD patients with non-fatal cancer

	Type	Subtype (no.)	No.	Median age at IBD Dx (IQR, min-max) [no. missing]	Median age at cancer (IQR, min-max) [no. missing]	No. male (%) [no. missing]	No. UC (%) No. CD (%) [no. missing]
1	Lymphoma	1a NHL (17) 1b Hodgkin's (11) 1c UNK (1)	29	12.00 (10.50-15.00, 2.00-17.00) [0]	16.00 (14.50-17.00, 9.00-49.00) [0]	19 (65.5%) [0]	4 (13.8%) 25 (86.2%) [0]
2	Leukemia	2a ALL (3) 2b AML (3) 2c chronic leukemia (3) 2d UNK (3)	12	13.50 (11.25-15.00, 6.00-18.00) [0]	15.50 (14.25-20.75, 11.00-24.00) [0]	10 (83.3%) [0]	4 (33.3%) 8 (66.7%) [0]
3	Liver	3a CCA (16) 3b HCC (4) 3c UNK (1)	21	12.00 (5.00-14.00, 2.00-17.00) [4]	22.00 (17.50-32.00, 8.00-52.00) [0]	8 (57.1%) [7]	12 (57.1%) 9 (42.9%) [0]
4	Intestinal carcinoma	4a CRC (16) 4b Small intestinal adenocarcinoma (1) 4c Carcinoid (2)	19	12.50 (10.00-15.25, 5.00-18.00) [1]	24.00 (16.00-33.50, 13.00-69.00) [0]	11 (61.1%) [1]	14 (73.7%) 5 (26.3%) [0]
5	Skin cancer	5a Nonmelanoma skin cancer (6) 5b Melanoma (2)	8	12.00 (7.50-15.00, 7.00-16.00) [0]	17.00 (15.50-22.00, 14.00-27.00) [0]	5 (62.5%) [0]	1 (12.5%) 7 (87.5%) [0]
6	Cervical cancer		1	17.00 (NR) [0]	33.00 (NR) [0]	0 (0%) [0]	0 (0%) 1 (100%) [0]
7	Other		13	15.00 (11.50-16.50, 3.00-17.00) [0]	18.50 (15.00-34.75, 4.00-47.00) [1]	8 (61.5%) [0]	2 (16.7%) 10 (83.3%) [1]
	TOTAL		**103**	**12.00 (10.00-15.00, 2.00-18.00) [5]**	**17.50 (15.00-25.00, 4.00-69.00) [1]**	**61 (64.2%) [8]**	**37 (36.3%) 65 (63.7%) [1]**

NR, not relevant, UNK, unknown, NHL, non-Hodgkin lymphoma, ALL, acute lymphoblastic leukemia, AML, acute myeloid leukemia, CCA, cholangiocarcinoma, HCC, hepatocellular carcinoma, CRC, colorectal carcinoma

Table 3. Clinical characteristics of PIBD patients with fatal cancer

	Type	Subtype (no.)	No.	Median age at IBD Dx (IQR, min-max) [no. missing]	Median age at mortality due to cancer (IQR, min-max) [no. missing]	No. male (%) [no. missing]	No. UC (%) No. CD (%) No. IBD-U (%) [no. missing]
1	Lymphoma	1a NHL (19) 1b Hodgkin's (2) 1c UNK (3)	24	14.50 (11.25-16.00, 2.00-18.00) [0]	18.00 (15.25-19.75, 12.00-52.00) [0]	20 (87.0 %) [1]	4 (16.7 %) 18 (75.0%) 2 (8.3%) [0]
2	Leukemia	2a ALL (2) 2b AML (2) 2c chronic leukemia (0) 2d UNK (2)	6	7.50 (2.00-14.75, 2.00-17.00) [0]	18.00 (2.00-33.75, 2.00-51.00) [0]	4 (66.7%) [0]	2 (33.3%) 4 (66.7%) [0]
3	Liver	3a CCA (8) 3b HCC (2) 3c UNK (0)	10	11.00 (8.00-13.00, 7.00-17.00) [2]	22.50 (19.50-31.00, 17.90-33.00) [0]	7 (70.0%) [0]	5 (50.0%) 5 (50.0%) [0]
4	Intestinal carcinoma	4a CRC (25) 4b Small intestinal adenocarcinoma (9) 4c Carcinoid (0)	34	12.00 (10.75-15.00, 2.00-17.00) [0]	25.50 (20.00-30.50, 7.00-48.00) [0]	22 (71.0%) [3]	19 (55.9%) 15 (44.1%) [0]
5	Skin cancer	5a Non-melanoma skin cancer (0) 5b Melanoma (0)	0	NR	NR	NR	NR
6	Cervical cancer		0	NR	NR	NR	NR
7	Other		3	8.00 (NR) [2]	19.50 (14.00-25.00, 14.00-25.00) [1]	1 (50%) [1]	0 (0%) 2 (100%) [1]
	TOTAL		**77**	**13.00 (10.00-16.00, 2.00-18.00) [4]**	**20.50 (17.00-28.75, 2.00-52.00) [1]**	**54 (75.0%) [5]**	**30 (39.5%) 44 (57.9%) 2 (2.6%) [1]**

NR, not relevant, UNK, unknown, NHL, non-Hodgkin lymphoma, ALL, acute lymphoblastic leukemia, AML, acute myeloid leukemia, CCA, cholangiocarcinoma, HCC, hepatocellular carcinoma, CRC, colorectal carcinoma

with a lymphoma, 17 patients had a non-Hodgkin lymphoma, including 2 hepatosplenic T-cell lymphomas (HSTCL). The majority of patients with a lymphoma had been exposed to thiopurines (n=18, 62.1%), of which 4 patients had also used a biological. Two-third (68.8%) of the patients with a CRC were male and 84.2% of these cases (n=16) were diagnosed with UC. Most patients with CRC were exposed to monotherapy, either of 6-mercaptopurine (n=3), aminosalicylates (n=2) or steroids (n=1). One patient received no treatment (n=1). Treatment was not reported in the remaining cases (n=12, 63.2%). Of the 19 CRC cases, 9 patients had a documented concomitant diagnosis of primary sclerosing cholangitis (PSC). The median duration of PSC to CRC was 4.0 years (IQR 1.0-8.0; n=5). Two patients were diagnosed with CRC before PSC diagnosis and in 2 patients age at PSC diagnosis was unknown. PSC was not mentioned in the studies reporting the other 7 CRC cases. The youngest 2 patients diagnosed with CRC were 15 years old, and had an IBD duration of 10 and 2 years respectively. In these 2 patients, no information on the presence of PSC was provided. Three of the patients with CRC also had a CCA. Of the group of patients with CCA, all but 1 patient had PSC (87.5%, n=14, not mentioned in 1 case) complementary to their UC (n=11) or CD (n=3). Of the 15 patients with CCA, 5 were male, 3 were female and in 7 patients the gender was not described, and 6 of the 15 (40.0%) developed CCA before 19 years of age. The youngest patient diagnosed with CCA was 8 years old and had been diagnosed with IBD since 3 years of age. All non-melanoma skin cancers in this group comprised basal cell carcinomas.

Fatal cancer

A total of 49 studies reported patients who developed cancer with a fatal outcome, including 19 case reports, 11 case series, 18 retrospective studies and 1 prospective study. Of the retrospective studies 4 were multicenter studies and the remaining 14 studies were performed in a single center. In total, the 49 studies comprised patient data of 77 PIBD patients who developed IBD at a median age of 13 years (IQR 10.0-16.0). In this patient group, 75.0% of patients were male. Most patients were diagnosed with CD (57.9%, n=44), followed by UC (39.5%, n= 30) and IBD-U (2.6%, n=2). In 1 patient the IBD type was unknown. The median age at death was 20.5 years (IQR 17.0-28.8). In 43 patients the duration from cancer to death was not mentioned. Of the remaining 34 patients, 20 died within one year after their cancer diagnosis and in 14 patients the median duration from cancer diagnosis to mortality was 2.00 years (IQR 1.0-15.0).

Intestinal carcinomas (n=34) and lymphomas (n=24) were most frequently reported in PIBD patients who died of cancer. Most intestinal carcinomas were CRC (73.5%, n=25). Treatment was not reported in 72.0% (n=18) of CRC cases (Table S1), whereas treatment information was available in the majority of patients who died due to a lymphoma (not reported in n=4, 16.7%). Two-third of the patients with a lymphoma had been exposed to

thiopurines (70.8%, n=17). In almost all patients diagnosed with lymphoma the duration of thiopurine use and the duration from diagnosis of lymphoma to moment of death was unknown (n=18, 75%). Non-Hodgkin lymphoma was diagnosed in 19 patients, of whom the majority (84.2%, n=16) had a HSTCL. All of the patients diagnosed with a HSTCL had been exposed to thiopurines. Detailed data on the use of biologicals was lacking in this group of patients. A strong male predominance was observed among HSTCL cases (87.5%, n=14). Two male patients developed Hodgkin's lymphoma and 1 of those was also diagnosed with CCA.

In total 8 patients with UC (n=5) or CD (n=3) were diagnosed with CCA (5 males). PSC was described in 5 of those patients (62.5%); 4 males and 1 female, who died at a median age of 21 years (IQR 18.0-24.5). The female patient was known to have CD, the male patients both CD (n=2) and UC (n=2).

Most patients with a fatal intestinal carcinoma had a CRC (73.5%, n=25). This was most frequently observed in males (60.0%, n=15) and patients with UC (72%, n=18; gender not described in 3 cases). Seven of the 25 (28.0%) developed CRC before 19 years of age. Information on concomitant PSC was provided in only 4 of the fatal CRC reports (16.0%; 2 cases without PSC and 2 cases with a documented concomitant PSC diagnosis). The 2 patients in whom PSC was mentioned developed IBD at 3 and 15 years of age and CRC at 16 and 28 years of age, respectively, after a PSC disease duration of 3 and 12 years. In this group of fatal cancer, no patients with skin cancer or cervical cancer were described.

Noncancer-related deaths

Cases with fatal outcome were reported in 63 of 87 studies (72.4%). Of these studies, 48 studies (76,2%) reported cases in which mortality was related to cancer (as described above), and 23 studies (36,5%) reported cases with fatal outcome due to other causes. Of these 23 studies, 8 were case reports, 5 were case series, and 10 were cohort studies, of which 7 were retrospective and 3 prospective. Most retrospective studies were single centre or multicentre but performed in a single country.

A total of 72 cases with fatal outcome unrelated to cancer were reported, of which 50.7% of patients was male (n=36, Table 4). Patients were diagnosed with UC (56.3%, n=40) or CD (43.7%, n=31) at a median age of 10.0 years (IQR 6.5-13.0; IBD type missing in 1 case). The median age at death was 15 years (IQR 13.0-20.0).

Infectious disease (n=24) and gastrointestinal complications (n=18) were the most common causes of non-cancer related deaths. A total of 16 patients died of sepsis; most of these were male (62.50%, n=10) and diagnosed with CD (68.6%, n=11). The majority of

Table 4. Clinical characteristics of PIBD patients with fatal outcome unrelated to cancer

	Type	Subtype (no.)	No.	Median age at IBD Dx (IQR, min-max) [no. missing]	Median age at mortality (IQR, min-max) [no. missing]	No. male (%) [no. missing]	No. UC (%) No. CD (%) [no. missing]
1	Gastrointestinal	1a Acute severe colitis (3) 1b Toxic megacolon (2) 1c Perforation (5) 1d UNK (8)	18	10.00 (6.50-14.00, 2.00-15.50) [0]	14.00 (9.50-16.25, 5.00-28.00) [5]	8 (47.1%) [1]	14 (77.8%) 4 (22.2%) [0]
2	Infectious disease	2a Neurologic (1) 2b Pulmonary (4) 2c Sepsis (16) 2d Other (3)	24	9.00 (5.10-12.00, 2.00-14.00) [3]	16.00 (13.13-18.75, 8.00-31.00) [4]	13 (54.2%) [0]	11 (45.8%) 13 (54.2%) [0]
3	Postoperative		6	6.00 (4.20-10.45, 3.00-10.90) [1]	16.55 (12.35-30.00, 7.40-36.00) [0]	3 (33.3%) [0]	4 (66.7%) 2 (33.3%) [0]
4	Liver disease		6	15.00 (10.40-18.00, 10.40-19.00) [1]	27.00 (20.70-36.00, 19.40-44.00) [1]	5 (83.3%) [0]	5 (100%) [1]
5	Dehydration		1	2.00 (NR) [0]	5.00 (NR) [0]	1 (100%) [0]	1 (100%) [0]
6	Suicide		1	15.00 (NR) [0]	24.00 (NR) [0]	Not applicable	0 (0%) 1 (100%) [0]
7	Other	7a Accident (1) 7b Underlying disease (2) 7c Neurological disease (2) 7d Cardiovascular disease (5) 7e MOF (3) 7f UNK (3)	16	9.50 (7.00-13.25,4.00-17.00) [0]	14.50 (13.25-20.00, 2.00-27.00) [0]	8 (50.0%) [0]	5 (31.3%) 11 (68.7%) [0]
	TOTAL		**72**	**10.00** **6.50-13.00, 2.00-19.00** **[5]**	**15.00** **[13.00-20.00, 2.00-44.00)** **[9]**	**36 (50.7%)** **[1]**	**40 (56.3%)** **31 (43.7%)** **[1]**

NR, not relevant, UNK, unknown, MOF, multi organ failure

the patients who died of sepsis was exposed to two immunosuppressants (43.8%, n=7). The remaining were exposed to one immunosuppressant (25.0%, n=4) or information on medication was not reported (31.2%, n=5). A central line was present in 4 patients (26.7%) who developed sepsis. Other underlying causes of sepsis were bowel perforation (n=2), peritonitis (n=2), abdominal abscess (n=2), disseminated varicella zoster infection (n=1), fulminant *Campylobacter jejuni* infection (n=1), pneumonia (n=1) and unknown (n=3). In the 8 patients who died due to infectious causes other than sepsis no information on medication was reported.

Refusal of medical treatment was reported in 2 of the 18 cases (11%) who died due to a gastrointestinal complication. Medication refusal or nonadherence was not mentioned in any of the other groups. Intestinal surgery was the most frequently reported cause of post-operative death (83.3%, n=5). Of these 5 patients, 4 patients (80%) died after colectomy and 1 patient died after an ileal resection (20%). One patient was reported who died after a renal transplantation.[26] A total of 7 patients were reported who died due to concomitant liver disease. Of these patients, the majority (71.4%, n=5) were male and diagnosed with UC (85.7%, n=6). Hepatic cirrhosis (n=2), PSC (n=1), liver failure (n=2) and noninfectious hepatitis (n=1) were mentioned as underlying causes for liver failure. PSC was reported in only one patient.

DISCUSSION

Over the last years the medical treatment of PIBD has changed considerably with a tendency for using more intensive immunosuppressive medications earlier in the disease course. There is a rising concern that these therapies may be associated with an increased risk of developing cancer and subsequently mortality. Following our meta-analyses we demonstrate an increased risk for all types of cancer in PIBD patients. However, although long-term follow-up studies are important to calculate incidence rates, these studies also illustrate that the absolute number of PIBD patients with cancer and mortality is low, resulting in limited detailed clinical characteristics of the group of PIBD patients of interest. Better insight into the characteristics of PIBD patients who develop cancer or have a fatal outcome will help to identify predictive factors of severe disease course. Therefore, with this review we aimed to provide an overview of patients with IBD diagnosed at pediatric age who developed cancer or suffered a fatal outcome at any point later in life.

The studies identified by our literature search report a wide variety of cancer types but show a strong predominance of CRC, CCA and HSTCL cases, which are usually very

uncommon among adolescents and young adults. Lymphomas were the most frequent type of non-fatal cancer in PIBD patients reported in the literature. The high frequency of lymphomas in this systematic review reflects the results of the retrospective study by de Ridder *et al.* who showed that 9 out of 18 PIBD patients with cancer were diagnosed with lymphoma.[28] In agreement, a study using the US Food and Drug Administration's Adverse Events Reporting System to identify malignancies associated with the use of biologicals[29], reported that 15 of the 24 PIBD patients that developed a malignancy were diagnosed with a lymphoma (62.5%). Recently, the large prospective DEVELOP study by Hyams *et al.* reported that 8 of 15 patients with a malignancy had either leukemia (n=3) or lymphoma (n=5).[24] These patients were more likely to be on current thiopurine monotherapy or combination therapy with a biologic and thiopurine, as there was only one case reported with TNF monotherapy (no thiopurine exposure). However, in the French population-based EPIMAD registry bowel-related carcinomas were most frequently observed and no lymphomas were reported after a median follow-up time of 11.5 years (IQR 7.0-15.0).[30] Possibly these discrepancies might be due to differences in study population size or duration of follow-up. The DEVELOP study demonstrated that SIR for malignancy among 5,766 patients was significantly elevated only for patients receiving combination therapy with thiopurine and biologic (SIR 3.06) but not with thiopurine or anti-TNF monotherapies.

The group with the highest apparent risk for intestinal carcinoma appeared to be UC patients with PSC. UC was more prevalent in patients diagnosed with CCA and CRC (75.0% and 81.3%, respectively). All but one patient with CCA had a concomitant diagnosis of PSC, emphasizing the increased risk of neoplasia in this subgroup of PIBD patients. A strikingly large number of those patients were diagnosed with CCA before 19 years of age. These results are in line with literature in adults, which shows increased risk of CRC development in UC patients[31-33] and both CRC and CCA development in PSC-IBD patients.[34, 35]

CRC was the most frequently reported type of fatal cancer in PIBD patients. The median age at diagnosis of intestinal carcinoma was 25.5 years (IQR 20.0-30.5), which is a strikingly young age to develop this type of cancer. In line with this, recent data from the National Patient Register in Sweden over a period of 50 years (1964-2014) show that even before their 18th birthday, PIBD patients have an increased risk of cancer (hazard ratio 4.1; 95%CI 1.8-8.6) compared to the general population.[36] Gastrointestinal cancers were associated with the highest relative risks (hazard ratio 9.7; 95% CI 0.4-246), although absolute risks were low. Our review demonstrates a lack of information on therapy in patients with CRC, which limits conclusions on undertreatment in this population. Remarkably, most cases of HSTCL were fatal, as 16 PIBD patients with HSTCL

were reported to have a fatal outcome versus only 2 non-fatal HSTCL cases. Thiopurine exposure was reported in all patients with HSTCL, but details on current or previous thiopurine exposure and combination with biologicals were often limited. The duration from diagnosis of cancer to death was not reported in the majority of patients with fatal cancer. However, the available data suggest a short cancer duration at moment of death, as in 20 patients the median duration from cancer diagnosis to death was less than 1 year and in 14 patients the median duration was only 2.0 years (IQR 1.0-15.0). This could reflect the severity of cancers associated with IBD diagnosed at a pediatric age or might be caused by reporting bias.

In our review, mortality was most often due to infectious complications, followed by malignancy and disease associated complications. Disease-associated fatal complications were more common in UC than in CD. The median age of death in patients with non-cancer related mortality was 15 years (IQR 13.0-20.0). The majority of patients with non-cancer related fatal outcome were diagnosed with UC (56.3%). This is consistent with recent data from an adult population-based IBD cohort[37] and the retrospective study by de Ridder *et al*. that showed increased mortality mainly among UC patients (61%). The outlier for these pooled data was the French population-based study in which mortality occurred more commonly in CD patients.[30] Recent data by Olen *et al.* confirm that PIBD patients have an increased risk of mortality compared to the general population, with the highest hazard ratios observed in UC patients (hazard ratio 4.0; 95%CI 3.4-4.7). In our review, mortality was most often due to infectious complications of intestinal origin. Mortality primarily related to infections has been reported by de Ridder *et al.*[28] but was not observed in several large studies in pediatric[30, 38] and adult IBD patients.[37, 39, 40] Both in the pediatric[21] and adult IBD population[40], patients treated with steroids are more likely to develop serious infections. Most of the patients who died of sepsis reported in this review were exposed to at least two immunosuppressants, often including steroids, which suggests that much of the sepsis-related mortality in PIBD patients is drug-related and potentially avoidable. In addition, central venous lines were also a risk factor. Hence, it is important to closely monitor PIBD patients who develop fever and are using or have recently used more than one immunosuppressant drug. Surprisingly, no fatal cases due to hemophagocytic lymphohistiocytosis (HLH), a potentially fatal syndrome of pathologic immune activation that is associated with the use of immunosuppressants, were reported in the literature. It is plausible that certain cases of HLH in PIBD patients were not recognized as such due to diagnostic difficulties.[41] It is important to acknowledge that the association between thiopurine use and HLH in both adult and pediatric patients with IBD is well-established[16, 42, 43], and has recently been highlighted by the results from the DEVELOP study.[24]

Although this is the first systematic review to provide an overview of cases of PIBD patients who developed malignancy or fatality, it is impossible to ascertain that we captured all cases. It is likely that many cases are underreported. A second limitation is the quality of the reports. To be as inclusive as possible about these rare outcomes, we decided to include all types of studies with no restriction to the year in which the study was published. Moreover, it is likely that severe cases are reported more frequently, which is illustrated by the larger number of cases with fatal cancer compared to cases with non-fatal cancer in our data. Limited patient-specific information, in combination with heterogeneous study settings, precluded comparative analysis. Lastly, long-term follow-up of PIBD patients is difficult, as follow-up is often associated with transition to specialist adult care or private clinics. Studies reporting IBD patients who develop malignancy or mortality during adult care often do not provide individual patient data on age at IBD diagnosis. This leads to a risk of underreporting of malignancy and mortality in patients with a pediatric-onset of IBD. Moreover, the presenting age of cancer and/or death is likely to be biased towards a younger age due to limited long-term follow-up in most cohorts.

Overall, PIBD-associated malignancy and mortality is rare. To assess severe outcomes in PIBD patients long term follow-up and multicenter or population-based collaborations are indispensable. Furthermore, more detailed patient-specific information is necessary to investigate the relationship between severe outcomes in PIBD patients and the currently used therapeutic strategies. Obtaining this data is crucial to develop evidenced-based strategies that incorporate long-term risks and benefits.

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SUPPLEMENTARY DATA

Supplementary reference list of includes studies

Complementary to Table 1

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Supplemental search strategy

1st of June 2017

Database	*Retrieved refs*	*Refs after deduplication*
Embase.com	4578	4532
Medline Ovid	3660	1355
Web of Science	1706	900
Cochrane Central	43	22
Google Scholar	200	122
Total	***10187***	***6941***

Embase: ('inflammatory bowel disease'/exp OR enteritis/de OR ((inflammator* NEAR/3 bowel NEAR/3 diseas*) OR crohn* OR (ulcer* NEAR/3 colit*) OR IBD OR PIBD):ab,ti) AND (neoplasm/exp OR 'oncological parameters'/exp OR mortality/exp OR (neoplas* OR tumo* OR cancer* OR lymphoma* OR carcinoma* OR malign* OR adenoma* OR oncolog* OR melanoma* OR sarcom* OR leukem* OR leukaem* OR mortalit* OR death* OR fatal*):ab,ti) AND (child/exp OR adolescent/exp OR adolescence/exp OR pediatrics/exp OR childhood/exp OR 'child development'/de OR 'child growth'/de OR 'child health'/de OR 'child health care'/exp OR 'child care'/exp OR 'childhood disease'/exp OR 'pediatric ward'/de OR 'pediatric hospital'/de OR (adolescen* OR infan* OR newborn* OR (new NEXT/1 born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEXT/1 (age* OR aging)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool*

OR highschool*):ab,ti) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim) AND [english]/lim

Medline Ovid: (exp "Inflammatory Bowel Diseases"/ OR ((inflammator* ADJ3 bowel ADJ3 diseas*) OR crohn* OR (ulcer* ADJ3 colit*) OR IBD OR PIBD).ab,ti.) AND (exp neoplasms/ OR mortality/ OR mortality.xs. OR (neoplas* OR tumo* OR cancer* OR lymphoma* OR carcinoma* OR malign* OR adenoma* OR oncolog* OR melanoma* OR sarcom* OR leukem* OR leukaem* OR mortalit* OR death* OR fatal*).ab,ti.) AND (exp Child/ OR exp Infant/ OR exp Adolescent/ OR exp "Pediatrics"/ OR "Hospitals, Pediatric"/ OR (adolescen* OR infan* OR newborn* OR (new ADJ born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under ADJ (age* OR aging)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR high-school*).ab,ti.) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt. AND english.la.

Cochrane: (((inflammator* NEAR/3 bowel NEAR/3 diseas*) OR crohn* OR (ulcer* NEAR/3 colit*) OR IBD OR PIBD):ab,ti) AND ((neoplas* OR tumo* OR cancer* OR lymphoma* OR carcinoma* OR malign* OR adenoma* OR oncolog* OR melanoma* OR sarcom* OR leukem* OR leukaem* OR mortalit* OR death* OR fatal*):ab,ti) AND ((adolescen* OR infan* OR newborn* OR (new NEXT/1 born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEXT/1 (age* OR aging)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*):ab,ti)

Web of science: TS=((((inflammator* NEAR/2 bowel NEAR/2 diseas*) OR crohn* OR (ulcer* NEAR/2 colit*) OR IBD OR PIBD)) AND ((neoplas* OR tumo* OR cancer* OR lymphoma* OR carcinoma* OR malign* OR adenoma* OR oncolog* OR melanoma* OR sarcom* OR leukem* OR leukaem* OR mortalit* OR death* OR fatal*)) AND ((adolescen* OR infan* OR newborn* OR (new NEAR/1 born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEAR/1 (age* OR aging)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*))) AND DT=(article) AND LA=(english)

Google scholar: "inflammatory bowel disease"|crohn|"ulcerative colitis" cancer|neoplasms|tumor|tumour|mortality|death infants|children|child

Study	Population	Size (N)	Period of diagnosis	Follow-up period	Malignancy (N)	SIR for CRC	95% CI	Newcastle-Ottawa tool		
								Selection	Comparability	Outcome
Jakobsen (2009)	Pediatric IBD patients < 15 years	69	1962-1987	Total of 1,602 person-years	2	25.7	3.1 92.7	****	*	**
Ekbom (1990)	Pediatric UC patients < 15 years	266	1922-1983	4,220 person-years	13	118.3	63.0 - 202.3	****	*	*
Jess (2012)	Pediatric IBD patients 0-19 years	UC: 2,483 CD: 2,280	1979-2008	UC: 25,086 person-years CD: 27,014 person-years	UC: 17 CD: 1	UC: 43.8 CD: 2.35	UC: 27.2-70.7 CD: 0.33-16.7	****	*	**
Ekbom (1990)	Pediatric CD patients < 30 years	964	1983	12,025 person-years	5	9.5	3.1 - 23.3	****	*	*
Olen (2017)	Pediatric IBD patients < 18 years	9,405	1964-2014	148,682 patient-years	122	IBD: 19.5 UC: 33.3 CD: 5.8	IBD: 14.7 - 26.2 UC: 23.1 - 49.1 CD: 3.2 - 10.4	****	**	**

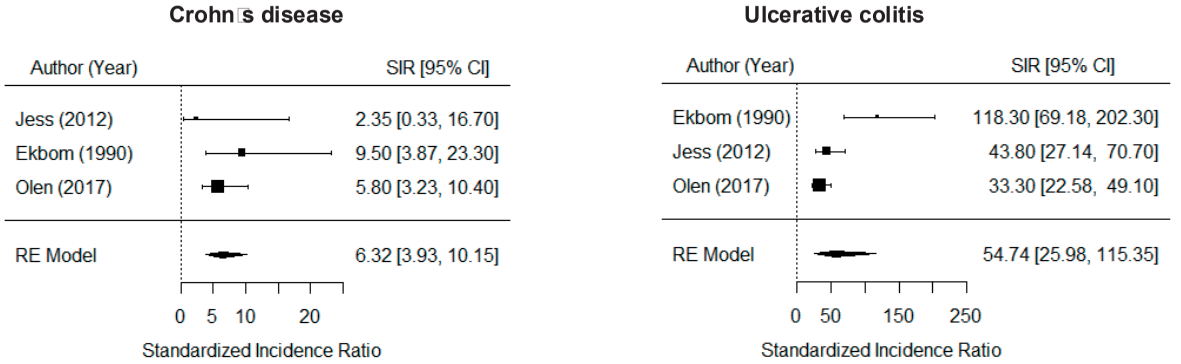
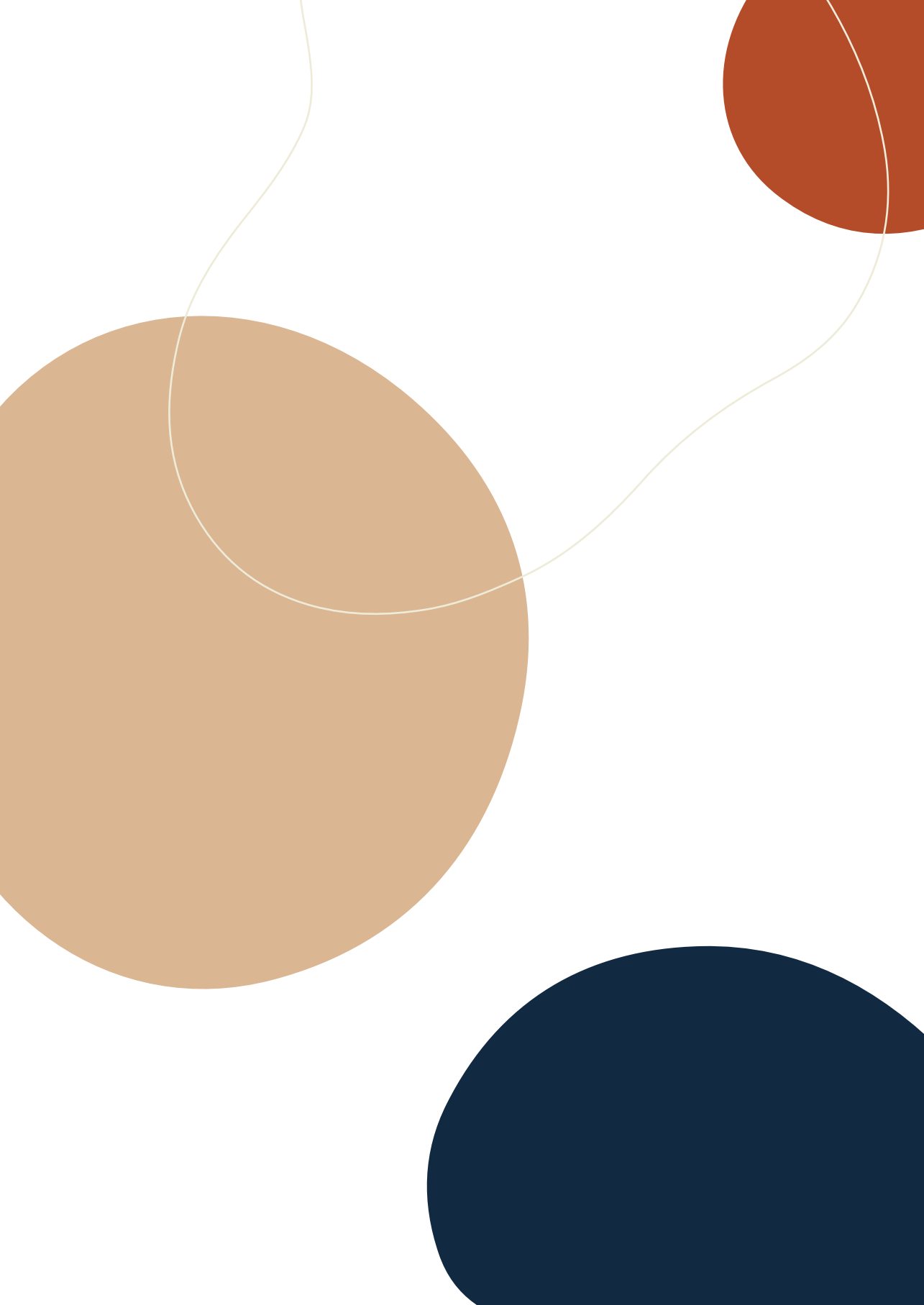


Figure S1. SIR for CRC in pediatric-onset CD and UC patients. Table and graphs presenting SIRs by study including a pooled SIR for CRC following a random effects (RE) model in both CD and UC patients. Jakobsen *et al.* (2009) was not included in the meta-analysis as only a SIR for CRC in the total PIBD population was described. SIR, Standardized incidence ratio; RE, random effects; CI confidence interval; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; CRC, colorectal cancer.



03

Malignancy and mortality in pediatric-onset inflammatory bowel disease: a 3-year prospective, multinational study from the pediatric IBD Porto group of ESPGHAN

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Aliment Pharmacol Ther. 2018 Sep;48(5):523-537.

ABSTRACT

Background: Risk benefit strategies in managing inflammatory bowel diseases (IBD) are dependent upon understanding the risks of uncontrolled inflammation versus those of treatments. Malignancy and mortality in IBD have been associated with disease-related inflammation and immune suppression, but data are limited due to their rare occurrence.

Aim: To identify and describe the most common causes of mortality, types of cancer and previous or current therapy among children and young adults with paediatric-onset IBD.

Methods: Information on paediatric-onset IBD patients diagnosed with malignancy or mortality was prospectively collected via a survey in 25 countries over a 42-months period. Patients were included if death or malignancy occurred after IBD diagnosis but before the age of 26 years.

Results: In total, 60 patients were identified including 43 malignancies and 26 fatal cases (9 due to cancer). Main causes of fatality were malignancies (n=9), IBD or IBD-therapy related nonmalignant causes (n=10; including 5 infections), and suicides (n=3). Three cases, all fatal, of hepatosplenic T-cell lymphoma were identified, all were biologic naïve but thiopurine-exposed. No other haematological malignancies were fatal. The six other fatal cancer cases included 3 colorectal adenocarcinomas and 3 cholangiocarcinomas (CCAs). Primary sclerosing cholangitis (PSC) was present in 5 (56%) fatal cancers (1 colorectal carcinomas, 3 CCAs and 1 hepatosplenic T-cell lymphoma).

Conclusions: We report the largest number of paediatric-onset IBD patients with cancer and/or fatal outcomes to date. Malignancies followed by infections were the major causes of mortality. We identified PSC as a significant risk factor for cancer-associated mortality. Disease-related adenocarcinomas were a commoner cause of death than lymphomas.

INTRODUCTION

Inflammatory bowel diseases (IBD) are associated with a long list of both treatment and disease-related complications and cancer. Paediatric-onset IBD is characterized by more extensive and aggressive disease, a longer disease duration, and a higher need for immune suppression early in the disease[1, 2], all of which may be risk factors for complications or cancer. Although, immune suppression may be associated with malignancy, hemophagocytic lymphohistiocytosis and opportunistic infections, it may reduce the risk of fibrostricturing disease, surgery and disease-associated tumors such as bowel adenocarcinoma.[3-8] Combination therapy with other immunosuppressive medications may increase the treatment success of biologics but is associated with an increased risk of adverse events. Hyams *et al.*[7] demonstrated that the standardized incidence ratio (SIR) for malignancy among 5766 paediatric-onset IBD patients included in the DEVELOP registry was significantly elevated for patients receiving combination therapy with thiopurine and biologics (SIR 3.06) but not with thiopurine or anti-tumor necrosis factor alpha (TNFα) as monotherapy. Several studies in adult IBD patients have shown that current exposure to thiopurines appeared to be more significantly associated with increased incidence of thiopurine-related malignancies than past exposure to thiopurines[9], while the DEVELOP registry did not delineate treatment as current or past.[7]

Given the rarity of some of these events, more detailed information on paediatric-onset IBD patients who develop cancer or have a fatal outcome is needed to obtain more insight in predictive factors of severe outcomes and to be able to optimize evidence-based treatment guidelines. The aim of this study was to identify and describe the most common causes of mortality, types of cancer and previous or current therapy among children with paediatric-onset IBD. We also aimed to describe the patient-specific and disease-specific characteristics of these groups and investigate the relationship between severe outcomes in paediatric-onset IBD patients and treatment exposure.

MATERIALS AND METHODS

Study design

This was a prospective multinational observational study performed in collaboration with the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN). We collected patients at all sites in 25 countries for 42 months from June 2013 to December 2016 (Table S1 tabulates all participating countries). The study was conducted in all sites according to the instructions of the local ethical committees. Some committees waived the need for informed consent due to the anonymous and non-interventional fashion of the study.

In each participating country, both a paediatric gastroenterologist and an adult gastroenterologist were appointed as national representatives. The representative paediatric gastroenterologist contacted paediatric gastroenterologists in each country through e-mail every 6 months throughout the study period in attempt to obtain all new cases of malignancy and/or mortality in patients with paediatric-onset IBD over the previous 6 month period. An explicit case report form (provided in supplementary material) was completed by the reporting paediatric gastroenterologist for all newly reported cases, using data from individual patient records. Cases that occurred prior to the study period were not included in our study. Existing IBD or cancer registries were not used to identify cases. In order to assess response rates, paediatric gastroenterologists were asked to actively respond negatively if no case was identified. When data were unclear the paediatric gastroenterologist was queried further by email. In order to identify cases that may have transitioned to adult care or developed malignancies after age 18 as a result of paediatric disease, the representative adult gastroenterologists followed the same procedures. Cases were ascertained by comparing and cross-checking all reported cases on country, year of reporting, sex and exact diagnosis.

Survey response rates per country were monitored throughout the study period to obtain insight into coverage (Table S1). Response rate was calculated as the number of physicians replying to the email call out of the total number of registered paediatric or adult gastroenterologists contacted in that country. Additional e-mails were sent out by ESPGHAN to increase awareness among gastroenterologists. The European Crohn's and Colitis Organisation (ECCO) provided logistical support and invited national representatives to nominate national coordinators. In addition, national patient organizations were informed on the study and every year investigators meetings were organized with national representatives from all participating countries.

Patient selection

Inclusion criteria for reported cases were patients with paediatric-onset IBD diagnosed according to the revised Porto criteria before 19 years of age[10], who died or were diagnosed with a malignancy after IBD diagnosis but before the age of 26 years. Patients with IBD-like inflammation due to proven monogenetic defects were excluded. Although infections are usually due to current immune suppression, malignancies may develop later after transition to adult care. In almost all European countries, paediatric-onset IBD patients < 16 years are cared for by paediatric gastroenterologists, and transition to adult care occurs after this age. As current guidelines for cancer surveillance in children and adults recommend surveillance starting from 8-10 years after disease-onset of paediatric-onset IBD, we extended follow up to 10 years after the age of 16 years to capture paediatric-onset IBD patients who developed cancer or mortality after transition to adult care.

Data collection

Data were collected by means of a case report form, which included 8 domains and 42 questions. The first 3 domains were divided into demographics, patient characteristics and disease characteristics, including questions on reporting physician, country, sex, IBD type, age at IBD diagnosis and comorbidities. The following domains of characteristics of malignancy and/or mortality included questions on type of malignancy and/or cause of death, age at malignancy and/or death, and IBD disease duration. The last domains contained questions on current and past therapy exposure, including thiopurines, biologics (agents blocking TNFα) or other immunosuppressant drugs (steroids, methotrexate and calcineurin inhibitors), as well as exposure to combination therapies and duration of exposure. Current exposure was defined as exposure in the 3 months prior to malignancy diagnosis or fatal outcome. Past exposure was defined as exposure previous to the last 3 months. "Ever exposed" was defined as exposure at any time prior to the malignancy or fatal outcome. Data was stored in a central database in the Erasmus Medical Centre in Rotterdam, The Netherlands.

Number of paediatric-onset IBD patients at risk (denominator)

Representative paediatric gastroenterologists of all European participating countries were requested to complete a survey that collected data stating which regions in their country as defined by the Nomenclature of Territorial Units for Statistics (NUTS) were covered during the years of data collection in this study (Table S2). Coverage was calculated for all European countries responding to the survey (Table S2). Full coverage was assumed for adults (20-26 years).

Eurostat most recent census data (2016) were used to obtain the total number of individuals covered in the general population (0-26 years) per country. This comprised the population from which the reported paediatric-onset IBD cases with cancer and/or mortality in our study were derived. In literature, paediatric-onset IBD prevalence among children (0-19 years) is around 30 per 100,000.[11-15] An estimated paediatric-onset IBD prevalence < 26 years of 60 per 100,000 was used to calculate the number of paediatric-onset IBD patients at risk for all countries. As this prevalence is likely an overestimation of the real prevalence[11-15], this is a conservative approach ensuring that the incidences of cancer and mortality in the paediatric-onset IBD patient population are not overestimated.

The total covered population (0-26 years) was multiplied by the estimated paediatric-onset IBD prevalence for this age group, resulting in an estimation of the true population that has the disease (number of paediatric-onset IBD patients 0-26 years at risk). As the study was conducted over 42 months, the number of paediatric-onset IBD patients at risk per year was multiplied by the years of exposure (3.5 patient-years).

Calculation of cancer and mortality incidence

Cancer and mortality incidences for paediatric-onset IBD patients < 26 years were calculated based on the number of patient-years (as described above) and the number of reported cases per country and in total (Table 1 and 2). Confidence intervals (CI's) were calculated using Byar's approximation based on a Poisson distribution. The relative risk (RR) and its 95% confidence interval (CI) were calculated according to Altman, 1991, in order to compare cancer incidence in paediatric-onset IBD patients with the general population. The average incidence for all countries was used to calculate the expected number of cases per country according to their covered population (Table 1 and 2, Figure 1). Poisson analysis was used to investigate the extent of variation in the number reported cases per country with statistical inference. Random-effects model for meta-analysis was used due to high heterogeneity in the results to investigate the incidences of cancer and/or mortality. The rare nature of the examined cases precluded comparisons between smaller regions and/or comparisons between sub-categories of the cases.

Table 1. Malignancy incidence in paediatric-onset IBD patients < 26 years in European countries

Country	No. malignancy cases reported	Paediatric-onset IBD patients in 3.5 years Denominator data[‡]	Annual incidence per 1.000.000 patients[†]	No. of expected cases[§]	Variation from expected
Austria (AT)	0	5,021	0	0.86	-0.86
Belgium (BE)	0	4,056	0	0.69	-0.69
Croatia (HR)	1	2,353	425	0.40	0.60
Czech Republic (CZ)	2	5,866	341	1.01	0.99
Denmark (DK)	0	3,737	0	0.64	-0.64
Finland (FI)	3	3,356	894	0.57	2.43
France (FR)	4	44,016	91	7.54	-3.54
Greece (EL)	2	5,800	345	0.99	1.01
Ireland (IE)	2	3,460	578	0.59	1.41
Italy (IT)	3	12,834	234	2.20	0.80
Poland (PL)	0	21,957	0	3.76	-3.76
Portugal (PT)	0	5,565	0	0.95	-0.95
Romania (RO)	0	11,332	0	1.94	-1.94
Sweden (SE)	3	6,461	464	1.11	1.89
Switzerland (CH)	1	4,118	243	0.71	0.29
Netherlands (NL)	6	10,722	560	1.84	4.16
UK - England	5	36,624	137	6.27	-1.27
UK - Scotland	1	3,338	300	0.57	0.43
UK - Wales	0	2,010	0	0.34	-0.34
Total	**33**	**192,625**	**171**	**33**	**NR**

IBD = inflammatory bowel disease, No = number of, NR = not relevant, UK = United Kingdom. [‡]See table S2 for calculation of denominator data. [†]Incidence calculation based on the number of patient-years and the number of reported cases. Incidence is reported in patient-years. [§]The average incidence for all countries was used to calculate expected number of cases per country.

Statistics

Data are presented as median and interquartile range (IQR) or percentages. Data analyses were performed using IBM SPSS version 24 (Armonk, NY, USA) and GraphPad Prism version 5.0 (San Diego, CA, USA). Baseline demographic and disease characteristics were evaluated for the entire cohort using descriptive statistics, including means and standard deviations (SD) or median and IQR for continuous variables, and frequencies and percentages for categorical outcomes. For comparison between 3 groups, the Fisher's exact test was used for categorical outcomes and the Kruskal-Wallis *H* test was used for continuous variables. If there was a statistically significant difference between the 3 groups, the Mann-Whitney test (continuous variables) or Fisher's exact test (categorical variables) was used to test differences between 2 groups as a follow up analysis. *P* values <0.05 were considered to present a statistically significant difference. In case of multiple comparisons, an adjusted significance level was used according to the Bonferroni correction (significance level = 0.05/number of comparisons).

Table 2. Mortality incidence in paediatric-onset IBD patients < 26 years in European countries

Country	No. fatal cases reported[¶]	Paediatric-onset IBD patients in 3.5 years Denominator data[‡]	Annual incidence per 1.000.000 patients[†]	No. of expected cases[§]	Variation from expected
Austria (AT)	0	5,021	0	0.57	-0.57
Belgium (BE)	0	4,056	0	0.46	-0.46
Croatia (HR)	1	2,353	425	0.27	0.73
Czech Republic (CZ)	0	5,866	0	0.67	-0.67
Denmark (DK)	0	3,737	0	0.43	-0.43
Finland (FI)	2	3,356	596	0.38	1.62
France (FR)	0	44,016	0	5.03	-5.03
Greece (EL)	0	5,800	0	0.66	-0.66
Ireland (IE)	0	3,460	0	0.40	-0.40
Italy (IT)	3	12,834	234	1.47	1.53
Poland (PL)	1	21,957	46	2.51	-1.51
Portugal (PT)	0	5,565	0	0.64	-0.64
Romania (RO)	1	11,332	88	1.29	-0.29
Sweden (SE)	5	6,461	774	0.74	4.26
Switzerland (CH)	1	4,118	243	0.47	0.53
Netherlands (NL)	3	10,722	280	1.22	1.78
UK - England	5	36,624	137	4.18	0.82
UK - Scotland	0	3,338	0	0.38	-0.38
UK - Wales	0	2,010	0	0.23	-0.23
Total	**22**	**192,625**	**114**	**22**	**NR**

IBD = inflammatory bowel disease, No = number of, NR = not relevant, UK = United Kingdom.
[¶]Including fatal cancer and mortality due to other causes. [‡]See table S2 for calculation of denominator data. [†]Incidence calculation based on the number of patient-years and the number of reported cases. Incidence is reported in patient-years. [§]The average incidence for all countries was used to calculate expected number of cases per country.

RESULTS

Coverage and participation response rates per country

Except for 3 countries, all European countries responding to the survey claimed full coverage (Table S2). Response rates differed between the 25 countries (Table S1). Data collection among paediatric gastroenterologists was high in 15 out of 25 participating countries, with ≥ 70% of paediatric gastroenterologists responding to the semi-annual e-mails throughout the study period with a valid reply. Data collection from adult gastroenterologists had a ≥ 70% response rate in 9 of 25 countries, respectively (Table S1).

Patient characteristics

A total of 60 patients with either fatalities or cancer were identified during the study period (UC, n=21; CD, n=33; IBD-U, n=6). Of the 60 patients, 43 were diagnosed with malignancy and in 26 a fatality occurred; in nine (35%) of the latter the cause of death was cancer.

Malignancy and mortality incidence

The final estimated number of paediatric-onset IBD patients aged 0-26 years at risk in Europe was 192,625 patient-years. Since 33 cancer cases were reported in 192,625 patient-years (Table 1), the cancer incidence in paediatric-onset IBD patients aged 0-26 years was 171 per 1,000,000 (95% CI 120 – 238). Based on literature from national cancer registries, the cancer incidence in the general population aged 0-26 years is estimated at 210 per 1,000,000.[16, 17] Overall, the cancer incidence among paediatric-onset IBD patients was not found to be significantly different compared to the general population for this age group. The RR for malignancy in the paediatric-onset IBD population compared to the general population was found to be 0.816 (95% CI 0.57 – 1.18, *P*=0.277). However, cancer incidences among paediatric-onset IBD patients in specific countries, including the Netherlands, Finland and Sweden, were higher compared to the general population (Table 1).

To obtain insight in under-reporting per country, reported number of cases were compared to the average rate of reported rates (Table 1 and 2, Figure 1A). Five countries were found to have significantly different (lower or higher) number of reported cases compared to the average rate of reported rates (Figure 1B). A negative difference in variation was seen in France, Poland and Romania. Particularly, France and Poland reported a significantly lower number of cases than expected for both cancer and mortality (*P*=0.013 and 0.024 respectively, based on a Poisson distribution) which indicated potential under-reporting. When excluding these three countries, the cancer incidence in paediatric-onset IBD patients aged 0-26 years increased to 230 per 1,000,000 (95% CI 157 – 326). Sweden, Finland and the Netherlands presented significantly more cases than expected (p=0.007, 0.011 and 0.007 respectively).

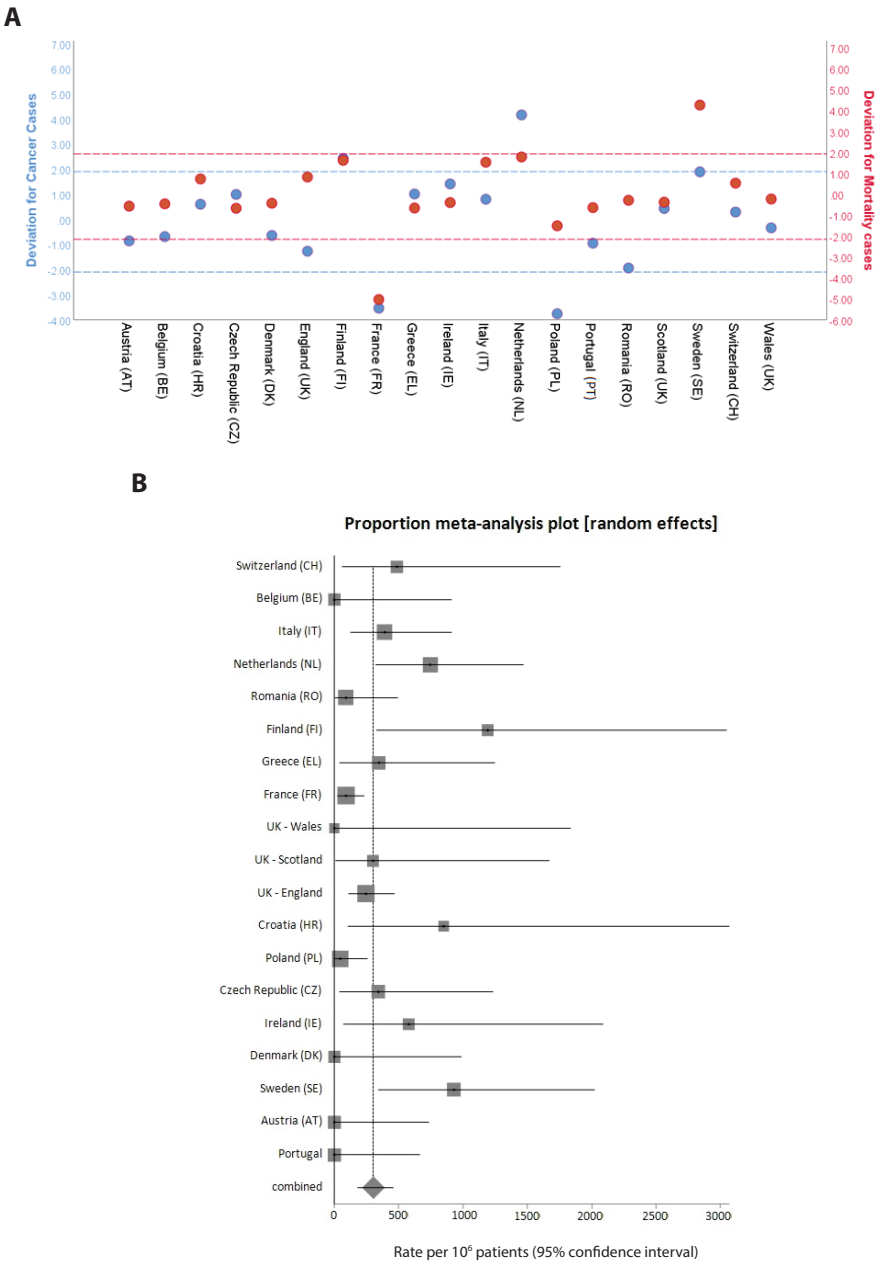

Figure 1. European incidence maps of malignancy and mortality in paediatric-onset IBD patients < 26 years. (A) The average incidence for all countries was used to calculate the expected number of cases per country according to their covered population. Deviation of the number of reported cancer and mortality cases from the expected number of cases is shown for European countries. (B) Forest plot with 95% confidence intervals for each country. Random-effects model for meta-analysis was used due to high heterogeneity in the results to investigate the incidences of cancer and/or mortality.

Malignancy

We identified 43 malignancies during the study period of which 24 (56%) occurred in patients with CD (Table 3). Patients who developed a fatal outcome due to their malignancy (6 males, 3 females) had been diagnosed with IBD at a median age of 12.9 year (IQR 8.3 – 15.4). They had significantly longer IBD disease duration to cancer than those with a nonfatal outcome (9.1 years [IQR 5.8 – 12.2] versus 4.3 years [IQR 2.0 – 9.0], *P*=0.019) and developed cancer at a higher median age of 20.0 years (IQR 19.0 – 23.5) versus 16.6 years (IQR 15.0 – 21.9) in patients with nonfatal cancer (*P*=0.012).

Hematopoietic tumours (n=21, 49%) were the most frequently reported type of malignancy (Figure 2). The median age at development of a hematopoietic tumour was 17.0 years (IQR 14.9 – 20.5), which was slightly lower compared to the other types of cancer (19.0 years, IQR 16.2 – 24.0, p=0.19). The majority of hematopoietic tumours included

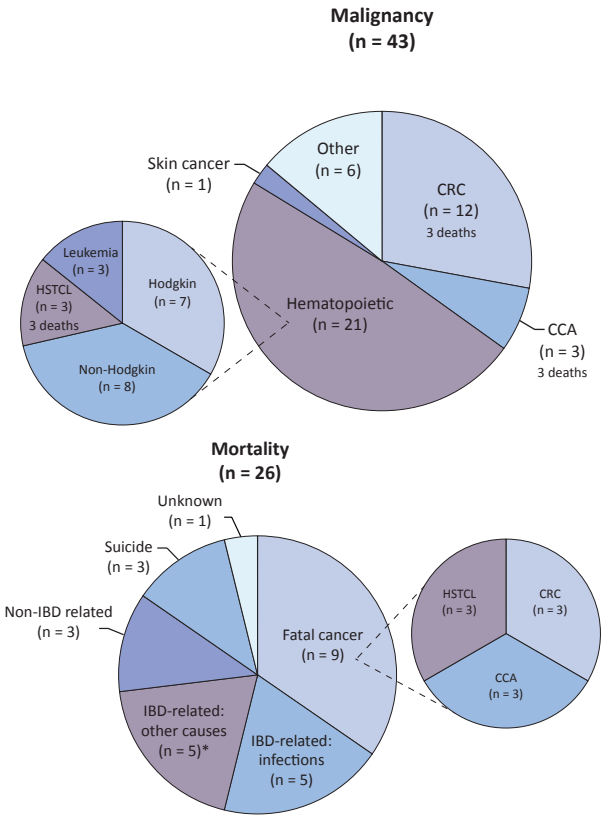

Figure 2. Causes of malignancy and mortality in paediatric-onset IBD patients (total cohort, n=60). A total of 43 malignancies and 26 mortalities were included in our cohort. Patients who died due to cancer were diagnosed with CRC (n=3), CCA (n=3) and HSTCL (n=3).

Table 3. Patient characteristics of paediatric-onset IBD patients who developed a malignancy and/or had a fatal outcome.

	Non-fatal cancer	Fatal cancer	Mortality due to other causes	Total	*P* value
Total patients, N	34	9	17	60	
Sex					NS
Male, N (%)	18 (52.9)	6 (66.7)	6 (35.3)	30 (50)	
Female, N (%)	16 (47.1)	3 (33.3)	11 (64.7)	30 (50)	
IBD diagnosis					NS
CD, N (%)	20 (58.9)	4 (54.4)	9 (52.9)	33 (55.0)	
UC, N (%)	11 (32.4)	5 (55.6)	5 (29.4)	21 (35.0)	
IBD-U, N (%)	3 (8.7)	NA	3 (17.7)	6 (10.0)	
Age at IBD diagnosis					NS
Mean (SD)	12.3 (4.1)	12.1 (4.3)	10.3 (4.2)	11.7 (4.2)	
Median (IQR)	13.5 (10.6 - 15.4)	12.9 (8.3 - 15.4)	11.8 (7.7 - 13.5)	12.7 (9.0 - 14.8)	
Duration of disease to cancer, y					**0.019**[g]
Mean (SD)	5.5 (4.0)	9.1 (3.5)	NA	6.2 (4.1)	*(non-fatal vs. fatal cancer)*
Median (IQR)	4.3 (2.0 - 9.0)	9.1 (5.8 - 12.2)	NA	5.5 (2.8 - 9.5)	
Duration of disease to death, y					**0.018**[h]
Mean (SD)	NA	9.5 (3.4)	5.3 (4.8)	6.7 (4.8)	*(fatal cancer vs. mortality)*
Median (IQR)	NA	9.9 (6.4 - 13.0)	3.6 (1.6 - 8.0)	7.0 (2.1 - 10.0)	
Age at cancer, y					**0.012**[g]
Mean (SD)	17.7 (4.2)	21.0 (2.4)	NA	18.4 (4.1)	*(non-fatal vs. fatal cancer)*
Median (IQR)	16.6 (15.0 - 21.9)	20.0 (19.0 - 23.5)	NA	17.4 (16.0 - 22.0)	
Age at death, y					**0.002**[h]
Mean (SD)	NA	21.9 (2.8)	15.2 (5.4)	17.5 (5.7)	*(fatal cancer vs. mortality)*
Median (IQR)	NA	20.0 (19.5 - 24.7)	15.1 (12.9 - 18.8)	17.0 (14.0 - 21.8)	
Comorbidities					
PSC, N (%)	2 (5.9)	5 (55.6)	2 (11.8)	9 (15.0)	**0.002**[a]; NS[b]; NS[c]
Perianal disease, N (%)	9 (26.5)[d]	1 (11.1)[e]	6 (35.3)[e]	16 (26.7)[f]	NS

For comparison between 3 groups, the Fisher's exact test was used for categorical outcomes and the Kruskal-Wallis H test was used for continuous variables. If there was a statistically significant difference between the 3 groups, the Mann-Whitney test (continuous variables) or Fisher's exact test (categorical variables) was used to test differences between 2 groups.

NS, nonsignificant; NA, not applicable; PSC, primary sclerosing cholangitis; CD, Crohn's disease; UC, Ulcerative colitis; IBD-U, IBD unclassified; IQR, interquartile range; SD, standard deviation; N, number; y, year.

[a]*P value calculated with Fisher's Exact Test comparing non-fatal cancer versus fatal cancer groups;*

[b]*Non-fatal cancer vs mortality;*

[c]*Fatal cancer vs mortality;*

[d]*One missing value;*

[e]*Two missing values;*

[f]*Three missing values;*

[g]*P-value calculated with Mann-Whitney test comparing nonfatal cancer vs fatal cancer;*

[h]*P-value calculated with Mann-Whitney test comparing fatal cancer vs mortality.*

Hodgkin and non-Hodgkin lymphomas (n=7 and n=8 respectively). Two patients with non-Hodgkin lymphomas were Epstein-Barr-virus (EBV) positive (25%), 4 patients were EBV negative (50%) and the EBV status was unknown in 2 patients. None of the patients with Hodgkin lymphoma or NHL died. Three male patients (1 UC; 2 CD) were diagnosed with a hepatosplenic T-cell lymphoma (HSTCL, n=3, 14.3%). All of the patients with HSTCL died. These three patients developed HSTCL at the age of 20.0, 18.0 and 23.0 years, after an IBD disease duration of 5.2, 6.0 and 5.3 years respectively. In all cases death occurred within a year after the HSTCL diagnosis at the age of 20.3, 19.0 and 23.5 years.

In patients diagnosed with colorectal carcinoma (CRC, n=12, 29%), UC was the most frequent type of IBD (UC, n=6; CD, n=4; IBD-U, n=2). The 4 CD patients who developed CRC all had disease confined to the colon (L2; Paris classification[18]). IBD disease duration to cancer in patients with CRC was significantly longer than in patients who developed a hematopoietic tumour, with a median duration of 9.3 years (IQR 4.3 – 11.8) versus 3.7 years (IQR 2.0 – 7.8, *P*=0.034, Table S3). The youngest reported CRC patient was a female who developed CRC at the age of 14.5 years, 4 years after her initial IBD diagnosis. CRC was fatal in 25% of cases (n=3), always within 1 year after cancer diagnosis. The youngest patient with a fatal outcome due to CRC was 19.5 years old when CRC was diagnosed, 9.0 years after her IBD disease diagnosis, and died after a period of 6 months.

Cholangiocarcinoma (CCA) was the third group of most frequently reported malignancies (n=3, 7%, all male UC patients). Notably, all CCA cases were fatal and all patients had a concomitant diagnosis of primary sclerosing cholangitis (PSC). CCA was diagnosed after a median IBD duration of 12.9 years (IQR 5.0 – 16.0). The youngest reported CCA patient was 19 years old when his cancer was diagnosed and died within the same year, 14 years after his IBD diagnosis and 11 years after his PSC diagnosis. Of all patients who died due to an adenocarcinoma (CRC, n=3, and CCA, n=3), 67% (n=4) had concomitant PSC.

Other causes of cancer were melanoma (Clark's level 1) at the age of 12.4 years (n=1), myeloid sarcoma (n=1), neuroendocrine tumour with liver metastasis (n=1), alveolar rhabdomyosarcoma (n=1), thyroid carcinoma (n=1), brain glioblastoma grade IV (n=1) and renal cell carcinoma (n=1).

Malignancy and treatment: current exposure

Overall, virtually all patients who developed a hematopoietic malignancy (n=21) had ever been exposed to thiopurines (n=20, 95%, Table 4). With regard to the 3 months prior to their cancer diagnosis, the majority of these patients were exposed to thiopurine monotherapy (n=12, 57%). Four patients with a hematopoietic malignancy used

Table 4. Medication exposure in paediatric-onset IBD patients who developed a malignancy

	Total (n=60)	**Hematopoietic (n=21)**	HSTCL (n=3)	Non-HSTCL (n=18)	**Adeno-carcinoma (n=15)**	CRC (n=12)	CCA (n=3)	*P* value
CURRENT EXPOSURE								
Thiopurine monotherapy, N (%)	25 (41.7)	12 (57.1)	3 (100)	9 (50.0)	4 (26.7)	4 (33.3)	0 (0)	0.096
Biologic monotherapy, N (%)	11 (18.3)	4 (19.0)	0 (0)	4 (22.2)	2 (13.3)	2 (16.7)	0 (0)	1.00
Combination: Thiopurine + Biologic, N (%)	7 (11.7)	4 (19.0)	0 (0)	4 (22.2)	2 (13.3)	2 (16.7)	0 (0)	1.00
No medication, N (%)	9 (15.0)	1 (4.8)	0 (0)	1 (5.6)	3 (20.0)	1 (8.3)	2 (66.7)	0.287
Other medication, N (%)	8 (13.3)	0 (0.0)	0 (0)	0 (0)	4 (26.7)	3 (25.0)	1 (33.3)	0.023
PAST EXPOSURE								
Thiopurine monotherapy, N (%)	25 (41.7)	9 (42.9)	3 (100)	6 (33.3)	5 (33.3)	4 (33.3)	1 (33.3)	0.732
Biologic monotherapy, N (%)	2 (3.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA
Combination: Thiopurine + Biologic, N (%)	17 (28.3)	8 (38.1)	0 (0)	8 (44.4)	4 (26.7)	4 (33.3)	0 (0)	0.721
No medication, N (%)	8 (13.3)	3 (14.3)	0 (0)	3 (16.7)	3 (20.0)	2 (16.7)	1 (33.3)	0.287
Other medication, N (%)	9 (15.0)	1 (4.8)	0 (0)	1 (5.6)	3 (20.0)	2 (16.7)	1 (33.3)	0.677
TOTAL EXPOSURE								
Thiopurines (ever exposed, N (%)	**49 (81.6)**	20 (95.2)	3 (100)	17 (94.4)	10 (66.6)	9 (75.0)	1 (33.3)	0.063
Biologics (ever exposed), N (%)	**22 (36.7)**	9 (42.8)	0 (0)	9 (50.0)	5 (33.3)	5 (41.7)	0 (0)	0.732
Methotrexate (ever exposed), N (%)	**9 (15.0)**	3 (14.2)	0 (0)	3 (16.7)	2 (13.3)	2 (16.7)	0 (0)	1.00
Steroids (ever exposed), N (%)	**44 (73.3)**	16 (76.2)	3 (100)	13 (72.2)	11 (73.3)	9 (75.0)	2 (66.6)	1.00
Calcineurin inhibitor (ever exposed), N (%)	**5 (8.3)**	2 (9.5)	0 (0)	2 (11.1)	1 (6.7)	1 (8.3)	0 (0)	1.00
DURATION OF TOTAL EXPOSURE								
Duration thiopurine (y, median + IQR)	2.5 (0.9-5.7)[†]	2.6 (0.9-4.8)	4.2 (4.0-5.0)	1.9 (0.9-4.5)	6.0 (1.5-8.6)	6.0 (1.3-8.8)	6.0 (NA)	0.13
Duration biologic (y, median + IQR)	2.2 (0.6-4.0)[a]	3.0 (2.1-4.8)	NA	3.0 (2.1-4.8)	2.0 (0.3-2.5)	2.0 (0.3-2.5)	NA	0.083

P values are from Fisher's Exact Test for categorical variables. Definitions: Thiopurine monotherapy, exposure to thiopurines without any biologic exposure; Biological monotherapy, exposure to biologics without any thiopurine exposure; Combination therapy, combined exposure to thiopurines or biologics, either at the same time (n=18 for the total group) or in consecutive fashion (only in 1 patient for the total group); Other medications, consisting of MTX, CAI and steroids; No medication, not using thiopurines, biologicals, MTX, CAI or steroids; Current exposure, exposure in the 3 months prior to malignancy diagnosis or fatal outcome; Past exposure, exposure previous to the last 3 months; Ever exposed, exposure at any time prior to the malignancy or fatal outcome. CAI, calcineurin inhibitors, MTX, methotrexate, NA, not applicable; CD, Crohn's disease; UC, Ulcerative colitis; IBD-U, IBD unclassified; IQR, interquartile range; SD, standard deviation; N, number; y, year. [a]two missing values.

thiopurines in combination with a biologic (n=4, 19%), while others were exposed to biologic monotherapy (n=4, 19%) or were not using any medication (n=1, 5%) in the 3 months prior to their cancer diagnosis (Figure 3).

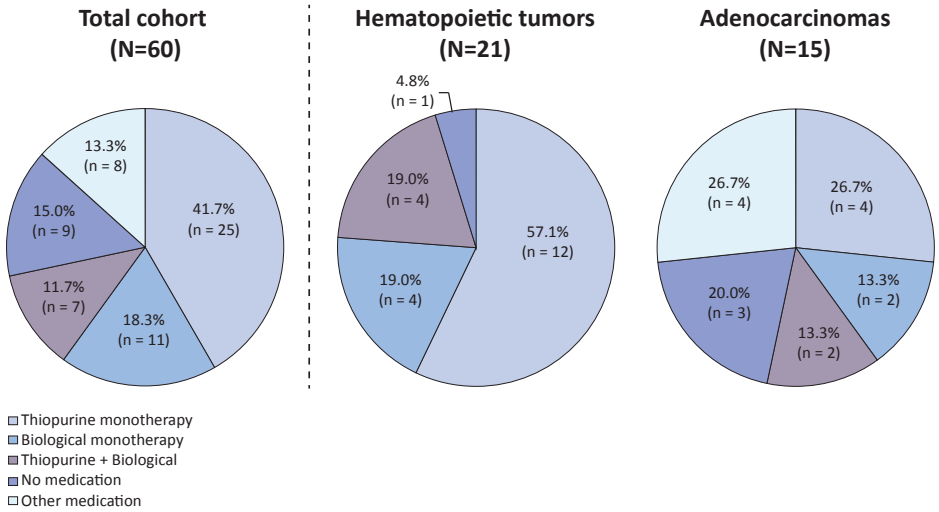

Figure 3. Medication exposure in paediatric-onset IBD patients in the 3 months prior to malignancy or mortality diagnosis. Current exposure (in the 3 months prior to severe outcome) was divided in 1) thiopurine monotherapy, 2) biologic monotherapy, 3) combination therapy of thiopurine with a biologic, 4) no medication or 5) other medication consisting of steroids, methotrexate, calcineurin inhibitors. Numbers and frequencies for the total cohort and patients who developed a hematopoietic malignancy or adenocarcinoma are shown.

Analysis of subgroups of hematopoietic tumours demonstrated that all patients who developed a HSTCL were exposed to thiopurines in the 3 months prior to their cancer diagnosis without concurrent or prior biologic exposure. We observed a numerically lower frequency of current exposure to thiopurine monotherapy in patients diagnosed with an adenocarcinoma compared to patients with a hematopoietic tumour (n=4, 27% vs. n=12, 57%, respectively, *P*=0.096). Curiously, none of the 3 patients who developed a CCA were receiving a thiopurine or biologic.

Malignancy and treatment: past exposure

There were no significant differences in percentage of patients with past exposure when comparing patients with hematopoietic cancer to patients who developed an adenocarcinoma (Table 4). Total duration of thiopurine exposure was numerically higher in the group of patients with an adenocarcinoma compared to patients who developed a hematopoietic tumour (median duration of 6.0 years (IQR 1.5 – 8.6) and 2.6 years (IQR 0.9 – 4.8), respectively; *P*=0.13). This observation can be explained by the significantly

longer IBD disease duration in patients diagnosed with an adenocarcinoma compared to patients with a hematopoietic tumour (9.5 years [IQR 5.0 – 12.0] versus 3.7 years [IQR 2.0 – 7.8], respectively, *P*=0.0064).

All 3 patients with a HSTCL had been previously exposed to thiopurines. The median duration of thiopurine exposure in the 3 HSTCL patients was 4.2 years (IQR 4.0 – 5.0) compared with 1.9 years (IQR 0.9 – 4.5) in the patients with other hematopoietic malignancies.

Other risk factors

Fatal cancers consisted of CRC (n=3), CCA (n=3) and HSTCL (n=3). In this total group of fatal cancers (n=9), 56% of patients (n=5) had a concomitant diagnosis of PSC, compared to 6% in the group of patients with nonfatal cancer (n=2, p=0.002; Table 3). The majority of patients with fatal cancer and a concomitant PSC diagnosis died due to adenocarcinomas (CCA, n=3, CRC, n=1, HSTCL, n=1). CCA was diagnosed at a median duration of 4.9 years after the initial PSC diagnosis (IQR 0.04 – 8.9 years). The PSC patient who died of CRC was a male patient who developed IBD at the age of 14 years. He was diagnosed with both PSC and CRC at the age of 24 years.

Only a small number of patients who developed a malignancy had a positive family history for cancer (n=5, 12%), consisting of 3 patients with a hematopoietic tumour (1 Hodgkin lymphoma, 1 non-Hodgkin lymphoma, 1 leukaemia) and 2 CRC patients. None of the patients who developed a malignancy had had a previous cancer diagnosis.

Mortality

A total of 17 non-cancer related deaths were reported during the study period (28%, Table 3). Patients who died due to non-cancer related causes were significantly younger than patients who died due to cancer (15.1 years [IQR 12.9 – 18.8] vs 20.0 years [IQR 19.0 – 23.5], *P*=0.002, Table 3). Infections (29%, n=5) were the main cause of noncancer related deaths. These included 4 patients with sepsis and 1 patient who developed disseminated tuberculosis on anti-TNFα therapy (Figure 2 and Table 5). In addition to infectious causes, another 5 patients died due to IBD- or IBD therapy-related causes that were of non-infectious origin. Death due to liver failure occurred in a 16-year-old female with UC and PSC at 14.9 years of age. One patient died post-operatively, 2 days after a right hemi-colectomy for CD. One patient died of multi organ failure complicating total parental nutrition. An additional 2 patients developed encephalopathy, but an infectious origin was not proven in either case.

Table 5. Medication exposure of paediatric-onset IBD patients who developed a fatal outcome.

Cause of mortality	Total (n=26)	Sex (M/F)	IBD type	Age at IBD diagnosis, y	Age at death, y	Current exposure			Previous exposure		
						Thiopurines	*Biologics*	*Steroids*	*Thiopurines*	*Biologics*	*Steroids*
Fatal cancer, N (%)	**9 (35)**										
CRC		F	CD	10.5	19.9	yes	no	no	yes	yes	yes
CRC		F	CD	6	20	yes	no	yes	yes	no	no
CRC		F	UC	14.1	25.4	yes	no	no	yes	no	no
CCA		M	UC	12.9	26	no	no	yes	no	no	yes
CCA		M	UC	16	24	no	no	no	no	no	no
CCA		M	UC	5	19	no	no	yes	yes	no	no
HSTCL		M	CD	14.8	20	yes	no	no	yes	no	yes
HSTCL		M	UC	12.0	19.0	yes	no	no	yes	no	yes
HSTCL		M	CD	17.7	23.5	yes	no	no	no	no	yes
IBD-related deaths: infectious causes, N (%)	**5 (19)**										
Sepsis due to unknown infectious agent		F	CD	14	21	no	yes	no	yes	yes	yes
Sepsis due to unknown infectious agent		F	CD	13.3	22.6	no	no	no	yes	yes	no
Disseminated tuberculosis on IFX treatment		F	CD	11.8	12.8	no	yes	yes	yes	yes	yes
Central line sepsis while on TPN		F	IBDU	1.9	2.2	yes	no	yes	no	no	yes
Joubert Syndrome with renal dysfunction and sepsis		F	UC	12.4	15.1	yes	no	no	yes	no	yes

Table 5. Medication exposure of paediatric-onset IBD patients who developed a fatal outcome. (*continued*)

Cause of mortality	Total (n=26)	Sex (M/F)	IBD type	Age at IBD diagnosis, y	Age at death, y	Current exposure			Previous exposure		
						Thiopurines	*Biologics*	*Steroids*	*Thiopurines*	*Biologics*	*Steroids*
IBD-related deaths: other causes, N (%)	**5 (19)**										
Post operatively		M	CD	13.5	15.4	yes	no	no	yes	no	no
Liver failure (in patient with concomitant PSC)		F	UC	14.9	16	no	no	yes	yes	no	Yes
Necrotizing encephalitis		M	IBDU	5	7.7	yes	no	no	yes	no	no
Acute necrotizing encephalopathy		F	UC	13	13	no	no	yes	no	no	yes
Multi organ failure while on TPN		F	CD	13.5	20.5	no	no	no	yes	no	yes
Suicide, N (%)	**3 (12)**										
Suicide		M	UC	2	12	no	no	yes	no	no	yes
Suicide		M	CD	7.9	25	no	no	no	yes	yes	yes
Suicide		F	CD	9	15	no	yes	yes	no	yes	yes
Non-IBD related deaths, N (%)	**3 (12)**										
Traffic accident		M	CD	9.1	17	no	yes	no	yes	yes	yes
Traffic accident		M	CD	11.6	13	no	yes	no	no	yes	yes
Cardiac asthma caused by an aortic stenosis		F	IBDU	7.6	15	yes	no	no	yes	no	yes
Unknown, N (%)	**1 (4)**										
Unknown		F	UC	14.3	15.9	yes	no	yes	no	no	yes

CD, Crohn's disease; UC, Ulcerative colitis; IBD-U, IBD unclassified; CRC, colorectal carcinoma; TPN, total parental nutrition; CCA, cholangiocarcinoma; HSTCL, hepatosplenic T-cell lymphoma.

Three patients committed apparent suicide. All 3 patients had severely complicated disease. One patient had PSC and failed liver transplantation. The second had severe perianal disease and enterocutaneous fistulas, and committed suicide after several years of inpatient care for repeated surgeries and severe postoperative complications. The third was a 15-year-old patient who underwent multiple procedures and had been surgically treated for perianal disease. Based on literature from national registries, the European incidence rate of suicide ranges between 10 to 40 per 1,000,000 in people aged 0-26 years.[19, 20] Overall, the suicide incidence among paediatric-onset IBD patients was not found to be significantly different compared to the general population for this age group (RR = 0.45, 95% CI 0.14 – 1.45). Other causes of death were unrelated to disease or treatment (n=3) or unknown (n=1) and are shown in Table 5.

Risk factors and associated therapy for mortality

Four of the 5 (80%) patients who died due to an infectious cause were receiving immune suppression, of whom 2 were on dual immune suppressive agents and the rest on a single drug (Table 5). Only 2 of those 4 patients were exposed to steroids at the moment of death. The remaining patient was not taking any medication. She had been previously exposed to combination therapy but refused all immunomodulatory or biological therapy 1 year before her death.

Risks of malignancy and mortality in subpopulations

The RR of malignancy or mortality was not found to be significantly different between CD and UC patients from this cohort (RR = 0.99; 95% CI 0.40 – 2.46). When comparing patients with concomitant PSC to patients without PSC, a higher relative risk for fatal malignancy was found (RR = 7.08, 95% CI 2.34 – 21.44, *P*= 0.0005).

DISCUSSION

In this first prospective multinational paediatric study to characterize malignancies and mortalities, we report the largest series of paediatric-onset IBD cases with these outcomes to date. Among the 26 identified fatalities over a 3-year period, 9 were due to malignancies, 10 were due to IBD or IBD-therapy related non-malignant causes (including 5 infections), and suicide was the third leading cause. The most common identified risk factor for cancer-associated mortality was presence of PSC (50% of cases).

In our study, the cancer incidence among paediatric-onset IBD patients was not found to be significantly different compared to the general population for this age group. We used the higher estimates for pan-European paediatric-onset IBD prevalence in order to

be conservative with estimates for malignancy and mortality. Despite our conservative approach, incidences among paediatric-onset IBD patients were higher compared to the general population in some countries, including Sweden, Finland and the Netherlands (*P*=0.007, 0.011 and 0.007 respectively, Figure 1). As this study is unlikely to have bias from over-reporting, the data from these countries should raise some concern. When excluding countries with large negative deviation from the expected number of cases (i.e. Poland and France), the cancer incidence in paediatric-onset IBD patients aged 0-26 years increased to 230 per 1,000,000 (95% CI 157 - 326), demonstrating that these countries lowered the total reported incidence.

An increased RR for malignancy in paediatric-onset IBD patients has been established by several previous studies. Peneau *et al.* identified 9 patients with cancer in 698 paediatric-onset IBD patients over a median follow-up period of 15 years, which translated into an increased risk of cancer in paediatric-onset IBD patients when compared to the background population (SIR 3.0 [95%CI 1.3–5.9]; *P*<0.02).[8] More recently, data from a Swedish cohort also demonstrated a significantly increased adjusted hazard ratio for cancer in paediatric-onset IBD patients (2.2; 95% CI 2.0 – 2.5) compared to a matched general population over a 25-year follow up period.[21, 22] Gastrointestinal cancers had the highest RRs, with a hazard ratio of 134 (95% CI 59.6 – 382) for liver cancers and 19.5 (95% CI 14.7 – 26.2) for CRC.

CCA and CRC were the most common type of neoplastic fatalities in our cohort (CCA, n=3, CRC, n=3). This is in line with the results reported in the EPIMAD study, where CRC was the only cause of neoplastic fatality among 698 paediatric-onset IBD patients followed over a course of 15 years.[8] In fact, in our cohort, HTSCL was only the third most common type of neoplastic fatality occurring in only 3 cases over 3 years. Fatal adenocarcinomas, which are highly likely to be associated with disease rather than treatment, were usually detected after >8 years of disease with the earliest occurrence at age 19. This suggests that current guidelines for surveillance in children and adults which recommend surveillance starting from 8 or 10 years of disease based on risk factors for CRC are adequate except in very rare cases.[23] Unfortunately, data on adherence to surveillance guidelines in our current cohort was not available. Paediatric and adult gastroenterologists treating patients with IBD should have increased awareness that these fatal malignant outcomes might occur in the second and third decades of life with early onset disease, and that patients with PSC should be followed closely including screening for CCA. It is interesting to note that all 3 patients with PSC-associated CCA were not receiving thiopurines or biologics. Thiopurines have been associated with a significant decrease in IBD associated CRCs by van Schaik *et al*, while 5-ASA did not lead to a significant protective effect.[4] However, a recent French study found that 5-ASA was

effective but questioned the efficacy of thiopurines.[24] Data regarding chemoprevention in IBD associated PSC is a current research gap, highlighted by the increased risk for CRC and CCA in these patients at an early age.[24-26] In order to identify gaps and guide future research, details on all collected data for individual patients with PSC-related cancer and mortality in this cohort is provided in Table S4.

Despite a large number of patients, previous population-based studies on paediatric-onset IBD patients are underpowered with regard to drug exposure in patients who develop malignancy, and included patients that were older than in our series. A case series like this cannot truly determine causality between drug use and development of malignancy, but several observations from this study are important. Development of HSTCL is still a rare event, documented in only 3 patients over a 3-year period in the numerous countries surveyed. The 3 new cases identified by this prospective study occurred in patients that had been on current thiopurines without current or previous biologic exposure. This could suggest that current thiopurine exposure can be associated with these rare lymphomas in the absence of anti-TNF therapy. Similar to previous reports[6, 27-30], all patients were males. The recently published DEVELOP study did not evaluate the association between current exposure to drugs and cancer[7], though current exposure and not previous exposure to thiopurines seems to be more important for development of lymphomas.[9] However, the DEVELOP study did demonstrate that exposure to combination therapy, but not to thiopurines or infliximab monotherapy, was associated with an increase in risk for malignancy, with an adjusted SIR of 3.06 for developing a cancer if combination therapy of a biologic and a thiopurine was used. Another interesting observation in our study is that the majority of patients who developed a hematopoietic malignancy had been exposed to thiopurines (n=20, 95%). In fact 71% (n=15) were exposed to thiopurines in the last 3 months prior to their diagnosis; which is significantly higher compared to patients who developed adenocarcinomas (*P*=0.041). Altogether this suggests that current exposure and not previous exposure to thiopurines seems to be more important for development of lymphomas in paediatric-onset IBD patients, which is in line with the findings in adults patients by the CESAME study group.

The second leading cause of fatalities in young patients with IBD was likely associated with therapy. Five patients died from presumed or proven infections, and 4 of 5 were receiving concomitant immune suppression. Two patients died from necrotizing encephalopathy of unknown origin, which could have been infectious. In a previous retrospective study by the Porto group, combination therapy with any combination of 2 immune suppressive drugs was associated with infection-associated mortality.[6] In that study 86% of patients developing a fatal infection or sepsis had received 2 or more

immune suppressive agents. The current study identified fewer cases of infectious mortality than the previous study, but also covered a shorter period of time (3 vs 5 years).

Surprisingly, suicides were the third most common reason for fatalities, surpassing procedural complications (n=2), thromboembolic events (n=0) and liver disease (n=1). It is important to be cautious when interpreting suicides because data regarding previous mental health and other comorbidities are not available. The 3 cases reported, all involved patients with a severe complicated course, including patients with repeated liver- and stem cell transplantations for refractory disease. In fact, 1 suicide occurred during a hospital admission. Although suicide incidence was not significantly increased compared to the general population, the suicide cases may be indirectly considered disease-related deaths. This emphasizes the importance of psychological support in addition to medical treatment in paediatric-onset IBD patients.

Our study provides important insight regarding severe outcomes of paediatric-onset IBD but is not without limitations. First, our results suggest underreporting in several countries. To avoid underestimation of incidence rates in a multinational set-up, it is pivotal to obtain registry-based denominator data in future studies. In addition, lower response rates among adult gastroenterologists and differences in practice between the participating countries may have contributed to underreporting of malignancies after transition to adult care and may have added bias to the reported data. Secondly, the use of thiopurines has become increasingly contentious, since the link between thiopurines and lymphomas[9, 31] and skin cancers[32] has become available. It would be very easy to over-interpret data and assign risk to therapy in the cases with hematopoietic malignancies. However, a case series cannot adjust for underlying age-adjusted population risk. With the exception of HSTCL, hematopoietic malignancies do occur in healthy adolescents without underlying disease or exposure to drugs. Since paediatric-onset IBD tends to be aggressive and extensive, thiopurines are used very early in the disease in a large proportion of patients. Thus, clear associations between therapy and malignancies will require analysis adjusted for underlying risk of IBD and cancer in populations being explored. Current studies that have limited analysis to past exposure are insufficient. We therefore need long-term, prospective data on all children and adults via fully consented (international) registers to provide perspective regarding risk from disease and from therapy.

In conclusion, data from this multinational cohort with the largest number of paediatric-onset IBD patients with cancer and/or fatal outcome to date, suggests that fatal outcomes and malignancies are still rare events. However, PSC appears to be a significant risk factor. While current guidelines for surveillance in children appear to be adequate,

our data raises the question whether chemoprevention in IBD patients with concomitant PSC should be instituted. Future analysis of databases in participating countries may allow us to better evaluate the RRs for paediatric-onset IBD patients compared to the background population.

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SUPPLEMENTARY DATA

Table S1. National paediatric and adult gastroenterologists, percentage of active response and number of cases per country.

		PAediatric representatives		adult representatives		
	Country	**Response rate**	**Representative**	**Response rate**	**Representative**	**Reported cases**
1	Australia	UNK	P. Lewindon	UNK	NA	0
2	Austria	>90%	A.C. Hauer	>90%	C. Hoegenauer-Graz	0
3	Belgium	100%	G. Veereman	100%	S. Vermiere	0
4	Canada	UNK	A. Griffiths	UNK	NA	1
5	Croatia	100%	I. Hojsak	80%	B. Mijandrušić Sinčić	2
6	Czech Republic	100%	J. Bronsky	35%	M. Lukas	2
7	Denmark	100%	V. Wewer	UNK	E. Langholz	0
8	Finland	100%	K. Kolho	80%	T. Sipponen	4
9	France	53%	H. Garnier-Lengline	65%	H. Sokol	4
10	Germany	UNK	S. Koletzko	UNK	B. Brokemeyer	5
11	Greece	100%	E. Roma-Giannikou	95%	E. Tsianos	2
12	Hungary	100%	G. Veres	UNK	T. Molnar	1
13	Ireland	100%	S. Hussey	80%	G. Doherty	2
14	Israel	30-100%	R. Shaoul	20%	B. Bassat	2
15	Italy	UNK	P. Lionetti	92%	M. Lia Scribano	5
16	New Zealand	UNK	A. Day	UNK	NA	1
17	Norway	UNK	G. Perminov	UNK	M.L. Høivik	0
18	Poland	100%	M. Sladek	UNK	M. Klopocka	1
19	Portugal	100%	E. Trindade	UNK	F. Magro	0
20	Romania	100%	D. Serban	100%	M. Diculescu	1
21	Spain	UNK	F. Javier Martin Carpi	UNK	V. Garcia-Sanchez	1
22	Sweden	UNK	U. Fagerberg	UNK	S. Almer	6
23	Switzerland	100%	C. Braegger	UNK	G. Rogler	2
24	Netherlands	100%	L. de Ridder	70%	J. van de Woude	8
25	United Kingdom					10
	England (8)	UNK	C. Spray	UNK	A. Hart	
	Scotland (2)	100%	D. Wilson	55%	J. Satsangi	
	Wales (0)	UNK	I. Davies	UNK	NA	
	Total					**60**

UNK, unknown; NA, not applicable.

Table S2. Denominator data for PIBD patients < 26 years in European countries (denominator data)

Country	PAED coverage[‡]	PAED (0-19)[†]	ADULT (20-26)[†]	PAED covered[§]	ADULT covered[§]	Total covered[¶]	Hypothesized PIBD prevalence (0-26)[‡‡]	No. PIBD patients (0-26)	No. PIBD patients years studied DENOMINATOR DATA[§§]
Austria (AT)	100%	1,618,961	772,055	1,618,961	772,055	2,391,016	60/100.000	**1435**	**5,021**
Belgium (BE)	40%	2,431,351	959,118	972,540	959,118	1,931,658	60/100.000	**1159**	**4,056**
Croatia (HR)	100%	778,697	341,688	778,697	341,688	1,120,385	60/100.000	**672**	**2,353**
Czech Republic (CZ)	100%	2,012,817	780,667	2,012,817	780,667	2,793,484	60/100.000	**1676**	**5,866**
Denmark (DK)	100%	1,238,230	541,501	1,238,230	541,501	1,779,731	60/100.000	**1068**	**3,737**
Finland (FI)	100%	1,131,328	466,649	1,131,328	466,649	1,597,977	60/100.000	**959**	**3,356**
France (FR)	100%	15,626,143	5,333,802	15,626,143	5,333,802	20,959,945	60/100.000	**12576**	**44,016**
Greece (EL)	100%	1,985,281	776,569	1,985,281	776,569	2,761,850	60/100.000	**1657**	**5,800**
Ireland (IE)	100%	1,255,079	392,755	1,255,079	392,755	1,647,834	60/100.000	**989**	**3,460**
Italy (IT)	18%	10,489,520	4,223,265	1,888,114	4,223,265	6,111,379	60/100.000	**3667**	**12,834**
Poland (PL)	100%	7,233,823	3,221,678	7,233,823	3,221,678	10,455,501	60/100.000	**6273**	**21,957**
Portugal (PT)	100%	1,890,717	759,111	1,890,717	759,111	2,649,828	60/100.000	**1590**	**5,565**
Romania (RO)	100%	3,918,293	1,477,708	3,918,293	1,477,708	5,396,001	60/100.000	**3238**	**11,332**
Sweden (SE)	100%	2,183,338	893,132	2,183,338	893,132	3,076,470	60/100.000	**1846**	**6,461**
Switzerland (CH)	79%	1,599,086	697,507	1,263,278	697,507	1,960,785	60/100.000	**1176**	**4,118**
Netherlands (NL)	100%	3,611,877	1,493,725	3,611,877	1,493,725	5,105,602	60/100.000	**3063**	**10,722**
UK - England	100%	12,464,034	4,976,080	12,464,034	4,976,080	17,440,114	60/100.000	**10464**	**36,624**
UK - Scotland	100%	1,088,924	500,524	1,088,924	500,524	1,589,448	60/100.000	**954**	**3,338**
UK - Wales	100%	664,388	292,688	664,388	292,688	957,076	60/100.000	**574**	**2,010**
Summary	**-**	**73,221,887**	**28,900,222**	**62,825,862**	**28,900,222**	**91,726,084**	**-**	**55,036**	**192,625**

[‡]Coverage was based on data obtained by surveys that collected region coverage per country. We assumed full coverage for adults (20-26 years). [†]Numbers were retrieved from 2016 Eurostat census data. [§]Covered populations between 0-19 and 20-26 years were calculated by using the coverage per country and population numbers retrieved from 2016 Eurostat census data. [¶]Corresponding populations covered under the age of 26. [‡‡]An IBD prevalence of 60 per 10.000 was assumed (see methods section). [§§]Based on the percentage of population covered, European census data, IBD prevalence under the age of 26 years and the study duration. Abbreviations: PIBD = pediatric-onset IBD, PAED = paediatric, No = number of, UK = United Kingdom.

Table S3. Patient characteristics of PIBD patients who developed hematopoietic cancer, CRC, or CCA.

	Hematopoietic	CRC	CCA
Total patients, N (%)	21 (48.8)	12 (27.9)	3 (7.0)
Gender			
Male, N (%)	10 (47.6)	7 (58.3)	3 (100)
Female, N (%)	11 (52.4)	5 (41.7)	NA
IBD diagnosis			
CD, N (%)	15 (71.4)	4 (33.3)	NA
UC, N (%)	5 (23.8)	6 (50.0)	3 (100)
IBD-U, N (%)	1 (4.8)	2 (16.7)	NA
Age at IBD diagnosis			
Mean (SD)	13.1 (3.8)	12.2 (3.9)	11.3 (5.7)
Median (IQR)	14.1 (11.0-15.6)	12.2 (10.1-14.9)	12.9 (5.0-16.0)
IBD disease duration to cancer, y			
Mean (SD)	4.7 (3.6)	8.2 (4.1)	10.4 (4.1)
Median (IQR)	3.7 (2.0-7.8)	9.3 (4.3-11.8)	11.3 (6.0-14.0)
Age at cancer, y			
Mean (SD)	17.6 (3.5)	20.5 (4.0)	21.7 (2.5)
Median (IQR)	17.0 (14.9-20.5)	20.7 (16.5-24.4)	22.0 (19.0-24.0)
Comorbidities			
PSC, N (%)	2 (9.5)	2 (16.7)	3 (100)
Perianal disease, N (%)	6 (30.0)	2 (18.2)*	0 (0)*
Mortality, N (%)	3 (14.3)	3 (25.0)	3 (100)

*One missing value; CRC, colorectal carcinoma; CCA, cholangiocarcinoma; NA, not applicable; CD, Crohn's disease; UC, Ulcerative colitis; IBD-U, IBD unclassified; IQR, interquartile range; SD, standard deviation; N, number; y, year.

Table S4. Patient characteristics of PSC patients with concominant IBD who developed malignancy or a fatal outcome..

Outcome	Sex	IBD type	Paris	Age at IBD diagnosis, y	Age at PSC diagnosis, y	Age at cancer, y	Type of cancer	Age at death, y	Cause of death	Treatment
Fatal cancer										
	M	UC	UNK	13	14	14	Biliary cancer	6 months after cancer diagnosis	Cancer	14 months steroids
	M	UC	UNK	16	17	22	Biliary cancer	2 years after cancer diagnosis	Cancer	No medication
	M	UC	E4	5	8	19	Biliary cancer	same year as cancer diagnosis	Cancer	No medication
	F	UC	UNK	14	23	24	CRC	same year as cancer diagnosis	Cancer	thiopurines, duration unknown
	M	UC	UNK	12	13	18	HSTCL	8 months after cancer diagnosis	Cancer	5 years steroids 6 years thiopurines
Non-fatal cancer										
	M	IBDU	UNK	19	17	24	CRC	NR	NR	6.5 years tacrolimus
	F	UC	E4	7	15	16	MDS with secondary AML	NR	NR	0,5 years steroids 4.5 years thiopurines
Non-malignant deaths										
	M	UC	UNK	4	14	NR	NR	25	Suicide	steroids, duration unknown 5 years tacrolimus
	F	UC	UNK	UNK	UNK	16	Liver failure	NR	NR	5 months steroids 3 months thiopurines

04

The incidence and characteristics of venous thromboembolisms in pediatric-onset inflammatory bowel disease; a prospective international cohort study based on the PIBDSETQuality Safety Registry

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ABSTRACT

Background and aims: Guidelines regarding thromboprophylaxis for venous thromboembolisms (VTEs) in children with inflammatory bowel disease (IBD) are based on limited paediatric evidence. We aimed to prospectively assess the incidence of VTEs in paediatric-onset IBD (PIBD), characterize PIBD patients with VTE, and identify potential IBD-related risk factors.

Methods: From October 2016 till September 2020, paediatric gastroenterologists prospectively replied to the international Safety Registry, monthly indicating whether they had observed a VTE case in a patient <19 years with IBD. IBD details (type, Paris classification, clinical and biochemical disease activity, treatment) and VTE details (type, location, treatment, outcome) were collected. To estimate the VTE incidence, participants annually reported the number of PIBD patients, data source and catchment area of their center. A systematic literature review and meta-analysis was performed to calculate the VTE incidence in the general paediatric population.

Results: Participation of 129 PIBD centers resulted in coverage of 24,802 PIBD patients. Twenty cases of VTE were identified (30% Crohn's disease). The incidence of VTEs was 3.72 (95% confidence interval [CI] 2.27 – 5.74) per 10,000 person-years, 14-fold higher than in the general paediatric population (0.27 (95%CI 0.18-0.38), p<0.001). Cerebral sinus venous thrombosis was most frequently reported (50%). All but one patient had active IBD, 45% were using steroids and 45% were hospitalized. No patient received thromboprophylaxis, whereas according to current PIBD guidelines, this was recommended in 4/20 patients.

Conclusion: There is an increased risk of VTEs in the PIBD population compared to the general paediatric population. Awareness of VTE occurrence and prevention should be extended to all PIBD patients with active disease, especially those hospitalized.

INTRODUCTION

A venous thromboembolic event (VTE) is a severe complication that may occur in paediatric patients with inflammatory bowel disease (IBD). It includes deep venous thrombosis (DVT) of the upper and lower extremity or central vasculature, pulmonary embolism (PE), cerebral sinus venous thrombosis (CSVT) and renal vein thrombosis. Population-based studies in the general paediatric population have reported annual incidences of 0.07 to 0.49 per 10,000 children, with higher incidences in neonates and adolescents[1-6]. In hospitalized children this incidence may be increased, with reported incidences of 19 to 58 per 10,000 admissions[5,7-10]. VTE in children is associated with high mortality[2,5,6] and may result in significant morbidity, such as persistent or recurrent thrombosis, post-thrombotic syndrome or persistent neurologic deficits due to CSVT[11]. In addition, VTE in hospitalized children with IBD is associated with increased likelihood of intensive care unit stay and accompanied with increased adjusted total costs[12].

Population-based studies have shown adults with IBD are at increased risk of developing VTEs[13-16]. Few studies reported an increased risk for development of VTE in children with IBD, especially in those hospitalized[15,17-21]. However, most studies are based on retrospective studies involving billing or hospital databases, or report limited paediatric data.

Risk factors are present in over 90% of paediatric VTE cases, including central venous catheter (CVC), surgery, immobility and infection[5,22-25]. In adult patients with IBD, active disease, fistulising or stenosing disease behaviour, extensive colonic involvement, *Clostridium difficile* infection, corticosteroid use, surgery and recent hospitalization are associated with increased VTE risk[14-16,26-30]. Interestingly, hospitalized adult patients with IBD have a 1.5 to 2-fold higher VTE risk than hospitalized adult patients without IBD[14,27]. However, little is known about the IBD-related risk factors associated with VTEs in paediatric IBD (PIBD) patients.

There are conflicting recommendations regarding thromboprophylaxis in current guidelines for adults and children with IBD, as summarized in Supplementary Table 1[31-33]. The ESPGHAN guideline only recommends thromboprophylaxis for hospitalized children with acute severe colitis (ASC), with at least one additional VTE risk factor[31]. By contrast, this is not supported by the consensus statements of the Canadian Association of Gastroenterology, which recommends against VTE prophylaxis in hospitalized children with IBD, even if hospitalizations are related to severe IBD flares[34]. No recommendations exist for children with Crohn's disease (CD). For adults with IBD, VTE prophylaxis is recommended during all hospitalizations according to some guidelines[34,35], whereas ac-

cording to other guidelines only in hospitalized patients with ASC[36-38]. These conflicting recommendations demonstrate that convincing evidence regarding incidence and risk factors of VTEs and safety and efficacy of thromboprophylaxis in paediatric IBD patients is lacking.

We aimed to establish the first international prospective cohort study of VTEs in paediatric IBD patients, allowing us to examine and quantify the incidence of VTEs in this population, for comparison with the general paediatric population. We aimed to examine the clinical phenotype and risk factors in cases reported. We hypothesized there would be an increased incidence of VTEs in PIBD with active disease as the most likely risk factor.

METHODS

PIBD-SETQuality Safety Registry

The PIBD-SETQuality Safety Registry is an international, prospective, electronic registry of rare and severe complications in children and adolescents with IBD, established by PIBD-NET. A list of ten rare but severe complications, including VTE, was established based on current literature and clinical expertise by a team of PIBD experts (Supplementary Table 2). In October 2016, the registry was initiated in the Netherlands and the UK and in following years extended to other countries. Every month, participating physicians are requested via an electronic invite (E-card) to report whether any of the listed complications occurred in a PIBD patient under their care in the last month. Participants were asked to actively report the absence of a complication. To minimize the risk of selection bias, participants who did not respond to the survey received a maximum of nine reminders in 3 months. In addition to the monthly E-card, participants annually received a survey to collect information including; the number of PIBD patients under their care, whether this number was based on a local database or estimated, and at what age children with IBD were transferred to adult care. In this annual survey, participants also reported the catchment area for referrals, based on well-defined geographical regions (Supplementary Methods)[39]. Based on these defined geographical regions, overlap in claimed areas could be examined.

For each complication a follow-up form was designed and sent out automatically following the report of a complication to collect information on the IBD and the complication. IBD characteristics collected included year of diagnosis, IBD type (CD, ulcerative colitis (UC) or IBD unclassified (IBD-U)), Paris classification, clinical and biochemical disease activity, and treatment (details in Supplementary Methods).

Venous thromboembolisms

For VTEs specifically, inclusion criteria were: 1) diagnosis of IBD according to the revised Porto criteria[40], 2) age <19 years at VTE diagnosis, 3) occurrence of a first VTE between September 2016 and August 2020. A VTE was defined as a radiologically confirmed thromboembolism and categorized as extremity DVT (upper or lower), CSVT, renal vein thrombosis or right intra-cardiac thrombosis. For each case the following additional information was collected: VTE type and location, presenting symptoms, history of VTEs, presence of thrombophilia and VTE risk factors, antithrombotic treatment and prophylaxis and outcome (details in Supplementary Methods).

Data extraction

Data were extracted from the online registry on September 30, 2020. Duplicates were excluded by checking responder, centre, sex, year and month of birth, and date of VTE diagnosis. All data were anonymously collected using unique electronic links for each participant. The data was submitted by the participants using REDCap electronic data capture system and stored on secured Queen Mary University of London servers.

Incidence data

The incidence was calculated by the total number of IBD patients who developed a VTE divided by the number of PIBD patient-years in the registry (Supplementary Methods). If participants did not respond to the E-card three consecutive months, they were considered inactive during that time period and this period was thus not included in the calculation of patient-years. To account for possible inaccuracies in reporting of the PIBD population, we performed a sensitivity analysis including only those centers using robust local databases. We also performed a sensitivity analysis where we included the inactive months of participants. Since some centers had more than one reporting physician, the incidence calculations were done on a center level.

Meta-analysis on the incidence of VTEs in the general paediatric population

A systematic literature review was performed to identify studies examining the incidence rate of VTE in the general paediatric population. Databases searched were Ovid Medline and Embase. A detailed search strategy and inclusion criteria are provided in the Supplementary Methods. Titles and abstracts were screened by two independent reviewers (MA and RK) and inconsistencies on inclusion were resolved by consensus. Extracted data included VTE incidence rate, sample size, total VTE number, duration of follow-up and number of patient-years. Studies were included in the meta-analysis if the number of patient-years was reported or could be calculated based on sample size and

duration of follow-up. A random effects model was used to compensate for heterogeneity (I^2) across studies[41].

Statistical analysis

Continuous variables are presented as median (interquartile range [IQR]), rates as percentages (95% confidence interval [CI]). Proportions were compared using Chi square tests or Fisher's exact tests for smaller samples. Medians between groups were compared with the Mann-Whitney U test. For the meta-analysis, the heterogeneity between studies was assessed with the I^2 statistic. The incidence and 95% CIs were calculated based on the total number of VTE cases and patient-years using the normal approximation to the binomial distribution.

To estimate the relative risk of VTE development in the hospitalized compared to the non-hospitalized PIBD patients, we calculated the rate of VTE events in the two groups individually. The denominator for the hospitalized group is the number of inpatient days while for the non-hospitalized group it is the number of outpatient days. The expected number of inpatient days for the PIBD population in our study is a product of the total study population (in patient-days) and the inpatient days rate. This inpatient days rate was calculated using the PIBD population in the USA as a reference. The reported prevalence rates of PIBD by Ye *et al*.[42] and the total number of children (3-17 years) registered in the USA in 2020[43] were used to estimate that the total PIBD population in the USA is 47,319 patients. This corresponds to 17,283,113 patient-days annually. Based on the length of stay and number of PIBD admissions in the USA[44], the total annual inpatient PIBD days in the USA is 25,281. Therefore, according to the US literature, a PIBD patient is expected to spend 1.46 in every 1000 days in the hospital (0.146%).

The proportions of UC/IBD-U and CD patients within the VTE cohort were compared to the proportions of UC/IBD-U and CD patients in the general PIBD population with a one-sample proportion test, using the EUROKIDS cohort, a representative large international cohort study, as a reference[45]. All test statistics were two-sided and a p-value <0.05 was considered statistically significant. Data analyses were performed with IBM SPSS version 25 (Armonk, NY, USA) or R version 4.0.2.

Ethical statement

This study was first approved by the ethics committee of Erasmus Medical Centre in the Netherlands and then conducted as required by local ethics committees. Data security agreements were signed with participating centers if required by national legislation.

RESULTS

Cohort description and denominator data

The PIBD-SETQuality Safety Registry currently has active participation of 149 PIBD specialists from 129 centres in 30 different countries (Supplementary Table 3).The PIBD population under their care is 24,802 patients. The median duration of active participation in the Safety Registry was 2.2 years per participating center (IQR 0.92-3.70). The continuously increasing covered population in combination with the duration of each center's participation, resulted in 53,762 PIBD patient-years of follow-up.

Systematic review and meta-analysis of VTE incidence in children

Electronic search results are presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) diagram (Figure 1). Study characteristics of 14 included studies are presented in Supplementary Table 4. Meta-analysis of ten studies including VTEs in general resulted in a pooled incidence rate of 0.27 (95%CI 0.18 – 0.38,

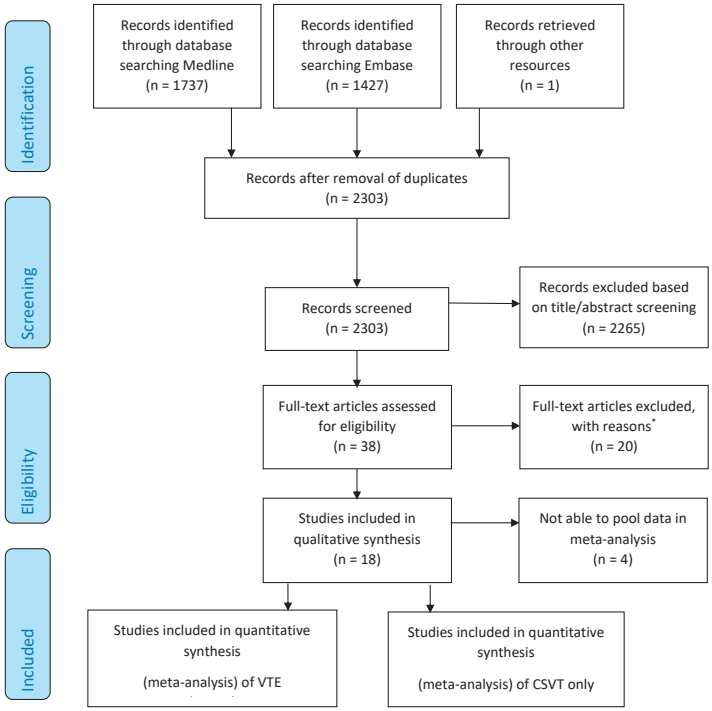

Figure 1. PRISM flow chart. Flow diagram of the systematic literature search on the incidence of venous thromboembolism in the general paediatric population. *Reasons for exclusion included: did not report on a pediatric population (n = 4); did not provide data to calculate incidence rates (n = 5); no population-based study (e.g. only hospital-associated VTE) (n = 2); incidence rates reported per number of hospital admissions (n = 3); no original article (n = 4); not available in full-text (n = 2).

I^2 99.7%) per 10,000 person-years in the general paediatric population (Figure 2). Data of six studies specifically describing CSVT resulted in a pooled incidence rate for CSVT of 0.045 (95%CI 0.025 – 0.070, I^2 94.1%) per 10,000 person-years in the general paediatric population (Figure 3).

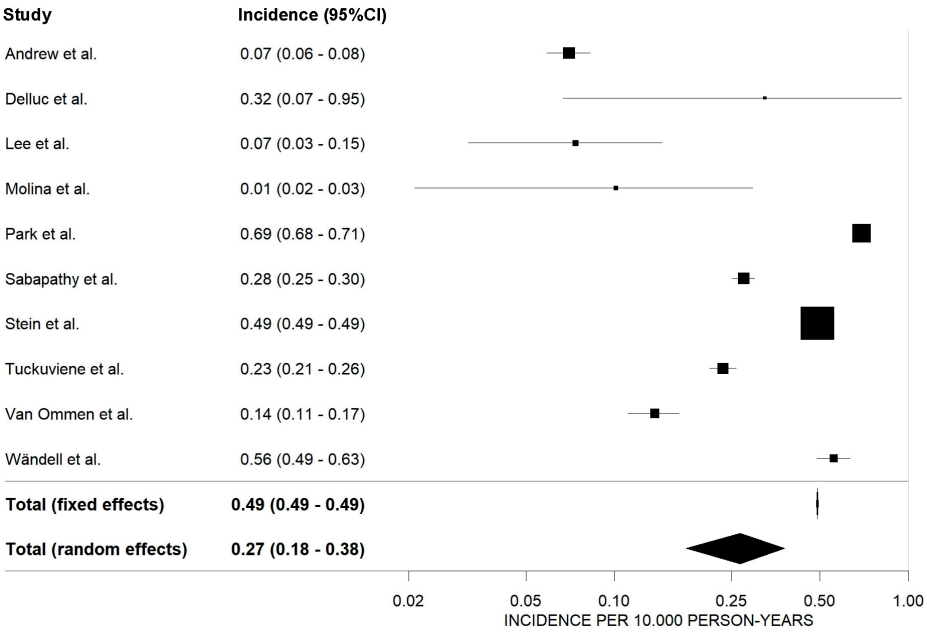

Figure 2. Meta-analysis incidence of VTEs in general paediatric population
Findings of the meta-analysis data regarding the incidence of VTE in the general paediatric population. VTE: venous thromboembolism.

Incidence of VTEs in PIBD patients

During the period of follow-up, 21 cases of first VTE diagnosis in PIBD patients were reported. One case of a CSVT was excluded, because there was too little information to exclude duplicate reporting. We identified no other duplicates. The 20 remaining cases resulted in an incidence of 3.72 per 10,000 patient-years (95% CI 2.27 – 5.74). The VTE incidence in the PIBD population included in this study is thus 13.8 times higher (95%CI 8.8 – 21.7) than the pooled incidence rate in the general paediatric population (3.72 vs 0.27; p<0.001). Ten cases were CSVTs, resulting in an incidence of 1.86 per 10,000 patient-years (95%CI 0.71 – 3.01), 41.3 times higher (95% CI 20.8 – 82.0) than the pooled incidence rate of CSVT in the general paediatric population (1.86 vs 0.045; p<0.001).

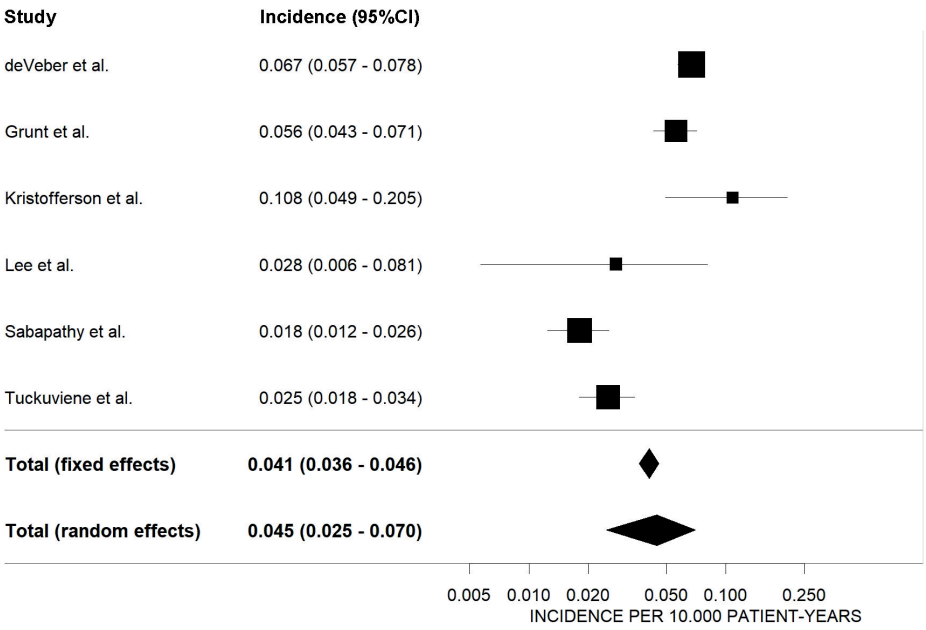

Figure 3. Meta-analysis incidence of CSVT in general paediatric population
Findings of the meta-analysis data regarding the incidence of CSVT in the general paediatric population. CSVT: cerebral sinus venous thrombosis.

Sensitivity analysis

Sensitivity analysis only using cases (n=13) and denominator data (n=26,611) from centers that reported the total number of PIBD patients under their care based on robust local databases, resulted in an estimated incidence of 4.89 per 10,000 patient-years (95% CI 2.60 – 8.35). When calculating the patient-years without excluding the inactive period of at least three consecutive months, the number of patient-years was 55,001. Using this denominator data, the estimated VTE incidence is 3.6 per 10,000 patient-years (95% CI 2.22 – 5.62) and the estimated CSVT incidence is 1.82 per 10,000 patient-years (95% CI 0.87 – 3.34).

VTE risk ratio in outpatient vs hospitalized patients

After applying the expected inpatient days rate (0.146%), on our study population of 53,762 patient-years, we estimated that the Safety Registry patients would have spent 28,723 out of the 19,636,571 patient-days in the hospital. Given that nine VTE events occurred during admission and 11 outside the hospital, the estimated VTE incidence for hospitalized PIBD patients is 1144 (95% CI 523 - 2173) per 10,000 patient-years while the estimated VTE incidence for outpatient PIBD patients is 2.05 (95% CI 1.02 – 3.66) per 10,000 patient-years. Therefore, the estimated relative risk of developing a VTE in inpatients compared to outpatients is 559 (231 – 1348).

Patient Characteristics

In all cases, detailed patient characteristics and disease specifics were available. The median age at VTE occurrence was 13.6 years (IQR 9.6-16.1) of which eight children (40%) were diagnosed <12 years of age. The median IBD duration was 7.9 months (IQR 0.3-20.5) (Table 1). Eight VTEs (38%) presented within 2 months of IBD diagnosis of which six (30%) were at the time of first diagnosis. Fourteen out of 20 cases occurred in children with UC/IBD-U, all with pancolitis. All CD patients had colonic or ileocolonic disease. There were no statistically significant differences between patients with CD and UC/IBD-U concerning age at IBD diagnosis, age at VTE diagnosis or IBD duration prior to VTE diagnosis. Compared to the percentage of UC patients in a large European cohort characterizing PIBD patients (EUROKIDS study) (32%), the percentage of UC patients within the VTE cohort (55%) was significantly higher (p=0.03).

Table 1. Patient characteristics depicted per IBD diagnosis. Comparisons between CD and UC/IBDU patients were performed with the Mann-Whitney U test for continuous variables and the Chi-square or Fisher's exact test for categorical variables.

Patient characteristics	CD n=6	UC/IBD-U n=14	Total n=20	*P*-value*
Sex (n, % male)	1 (16.7)	7 (50.0)	8 (40.0)	0.01
Body mass index SDS (median, IQR)	0.38 (-0.85-0.55)	-0.44 (-2.3-0.49)	-0.43 (-1.7-0.53)	0.40
Age at IBD diagnosis, years (median, IQR)	11.6 (8.5-15.1)	12.9 (7.6-14.8)	12.2 (7.8-14.9)	0.90
Age at VTE diagnosis, years (median, IQR)	13.5 (9.1-16.1)	13.7 (9.3-16.3)	13.7 (9.6-16.1)	1.00
IBD disease duration prior to VTE diagnosis, months (median, IQR)	1.7 (0.2-28.7)	9.6 (1.9-23.8)	8.4 (0.4-20.5)	0.32
Paris classification at latest assessment				
Location/Extent				
	L1: 0	E1: 0		
	L2: 2	E2: 0		
	L3: 4	E3: 0		
	L4a/4b: 2	E4: 14		
Behaviour	B1: 6	n/a		
	B2/B3: 0	n/a		
Perianal disease	0	n/a		

**P*-values are for comparison of CD vs. UC/IBD-U. SDS: standard deviation score; IBD: inflammatory bowel disease; VTE: venous thromboembolism; CD: Crohn's disease; UC: ulcerative colitis; IBD-U: IBD unclassified; n/a: not applicable.

VTE specifics

In 50% of cases (n=10) a CSVT was reported, mostly involving multiple dural venous sinuses (Table 2). Presenting symptoms of CSVT included headache (n=8), seizures (n=3) and hemiparesis (n=2). Extremity DVTs were the second most reported VTE type (n=7). Three patients had a PE (two with a lower extremity DVT). One patient had a simultaneous cerebral arterial thrombosis and DVT.

Risk factors

No patient had a medical or family history of VTEs. Both hereditary and acquired thrombophilia were tested in 70% of cases, but none was identified. In 65% of cases, one or more non-IBD risk factors were identified (Table 2). These included: steroids (45%, n=9), immobility (15%, n=20), central venous catheter (15%, n=3), parenteral nutrition (10%, n=2) and surgery (10%, n=2). Nine out of 20 patients (45%) were diagnosed with the VTE during hospital admission, including eight IBD-related hospitalizations.

IBD characteristics

Most VTEs (90%) occurred during active disease. Of these 15/17 had moderate (n=7) or severe (n=8) disease activity (Table 3). Only two VTEs occurred while the patient's disease was in clinical remission; one was receiving a steroid course and had a faecal calprotectin level of >6000 µg/g 2 months prior to the VTE, the other had a faecal calprotectin level of 194 and presented with a CVC-related upper extremity DVT (Supplementary Table 5). In all other patients, faecal calprotectin levels around VTE diagnosis were >500 µg/g (median 2100 µg/g, IQR 995 – 5615). Blood results around VTE diagnosis show active inflammation in most patients: 12/17 patients had an erythrocyte sedimentation rate (ESR) >20 mm/hour or a CRP level >5 mg/L. Median platelet count was 458 x 10^9/L (IQR 268 – 637).

IBD treatment

Five (25%) patients were not receiving any IBD-related medication at the time VTE of diagnosis. In four of those, the IBD was diagnosed around the time of VTE diagnosis (Table 3). Nine patients (45%) were on steroids, in some cases combined with other IBD-related treatments.

VTE prophylaxis

No patients were using anti-thrombotic prophylaxis prior to the event. In retrospect, based on the most recent ESPGHAN guidelines, only 4/20 cases would have fulfilled the criteria for thromboprophylaxis (Table 2).[31-33]

VTE treatment

The majority of patients (80%) were treated with low molecular weight heparin (LMWH) (Supplementary Table 6). One CSVT patient with a haemorrhagic stroke, received no anti-thrombotic therapy. Anti-thrombotic treatment complications were reported in four patients and were all IBD-related gastrointestinal bleeds; two non-major bleedings and two minor bleedings. Following the VTE event, 8/20 patients received long term antithrombotic prophylaxis after antithrombotic therapy was ceased.

Table 2. Type of venous thromboembolism and presence of risk factors. The column thrombophilia includes hereditary and acquired thrombophilia. [#] Hereditary thrombophilia was not tested.

Case	VTE location	Sex	IBD type	Age at IBD diagnosis, y	Age at VTE, y	Ethnic origin	Thrombophilia
	Intracranial, n=11						
1	*Multiple venous sinuses and left internal jugular vein*	M	UC	7,6	7,6	White	No
2	*Superior sagittal sinus*	F	UC	14,7	14,7	White	No
3	*Multiple venous sinuses*	M	CD	9,3	10,2	White	No
4	*Multiple venous sinuses and proximal internal jugular vein*	F	IBD-U	14,1	15,8	White	Unknown
5	*Multiple venous sinuses*	F	CD	15,0	15,3	White	No
6	*Multiple venous sinuses*	M	UC	2,1	2,3	SEA	No[#]
7	*Dural venous sinus, unspecified*	F	CD	11,6	18,3	White/ SEA	Unknown
8	*Multiple venous sinuses*	M	UC	16,7	16,7	White	No
9	*Superior sagittal sinus and right femoral vein*	F	CD	6,0	5,9	White/ SEA	Unknown
10	*Posterior sagittal sinus*	M	UC	12,7	13,6	Mixed	Unknown
	Lower extremity, n=8[‡]						
11	*Proximal medial gastrocnemius veins*	F	CD	15,4	15,4	White	No
12	*Common femoral vein to popliteal vein*	F	UC	8,4	11,2	White	No
13	*Lower IVC, common iliac, femoral, superficial femoral vein*	M	UC	15,0	16,2	White	No
14	*Femoral and popliteal vein*[*]	F	CD	11,6	11,6	White	Unknown
15	*Left posterior tibial vein*	F	UC	13,3	13,8	Kurdish	No
	Upper extremity, n=1						
16	*Right basilic vein*	F	IBD-U	2,9	13,5	White	No
	Pulmonary, n=3						
17	*Subsegmental pulmonary embolus left lower lobe*	M	UC	13,0	17,0	Black	Unknown
18	*Proximal left pulmonary vein and IVC*	F	UC	8,7	9,4	White	No
19	*(Sub)segmental bilateral lower lobe, left posterior tibial, peroneal and popliteal veins*	M	UC	16,6	17,2	White	No
	Other, n=1						
20	*Right cardiac chamber*	F	IBD-U	7,5	9,2	Hispanic/ Latino	No[¨]

[¨] Acquired thrombophilia was not tested. [‡] Three patients had a lower extremity DVT occurring together with another VTE type. [*] This patient was diagnosed with an arterial thrombosis in the middle cerebral artery branches at the time of VTE diagnosis. [¥] This patient was discharged from an IBD-related hospital admission for two days at the time of VTE diagnosis. VTE: venous thromboembolism; IBD: inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis; IBD-U: IBD unclassified; G6PD: glucose-6-phosphate dehydrogenase; CVC: central venous catheter; PSC: primary sclerosing cholangitis; IVC: inferior vena cava; SEA: South East Asian.

Risk factors	VTE during admission	Comorbidities	Prophylaxis prior to VTE	Considerations regarding prophylaxis according to ECCO/ESPGHAN guidelines
None	No[¥]	None	No	No guidance on prophylaxis in UC that is not ASC
None	No	None	No	Does not fit criteria for consideration of prophylaxis (no additional risk factors)
Steroids	No	None	No	No guidance on prophylaxis in CD
Steroids	No	None	No	No guidance on prophylaxis in UC that is not ASC
Steroids	No	None	No	No guidance on prophylaxis in CD
None	Yes	None	No	Does not fit criteria for consideration of prophylaxis (no additional risk factors)
Steroids	No	None	No	No guidance on prophylaxis in CD
Surgery	Yes	None	No	No guidance on prophylaxis in UC that is not ASC
None	Yes	None	No	No guidance on prophylaxis in CD
Steroids	Yes	None	No	Does not fit criteria for consideration of prophylaxis (no additional risk factors)
None	Yes	None	No	No guidance on prophylaxis in CD
Steroids, immobility	No	Recent severe anaemia	No	Prophylaxis *should be* considered (adolescent girl with 1 risk factor)
None	No	None	No	No guidance on prophylaxis in UC that is not ASC
CVC, steroids, myocarditis	Yes	None	No	No guidance on prophylaxis in CD
None	No	Spherocytosis, chronic haemolysis	No	No additional risk factors, so prophylaxis not recommended
CVC, surgery, parenteral nutrition	Yes	Primary dysmotility	No	No guidance on prophylaxis in UC that is not ASC
Trauma, immobility	No	G6PD deficiency, PSC	No	Prophylaxis *should be* considered (adolescent boy with 1 additional risk factors)
Steroids, sepsis, immobility	Yes	None	No	Prophylaxis *should be* considered (prepubertal girl with 2 additional risk factors)
Obesity, dehydration, hypovolemia	No	None	No	No guidance on prophylaxis in UC that is not ASC
CVC, steroids, immobility, parenteral nutrition	Yes	None	No	Prophylaxis *may be* considered (prepubertal girl with 2 additional risk factors)

Table 3. IBD-related characteristics at time of VTE diagnosis.

	CD n = 6 (30%)	UC/IBD-U n = 14 (70%)	Total n = 20
Physician's global assessment			
None/remission	1	1	2
Mild	1	1	2
Moderate	3	4	7
Severe	1	7	8
Faecal calprotectin, µg/g (median, IQR)	4050 (2100 – 6000)	1637 (985 – 5433)	2100 (995 – 5615)
ESR, mm/hr (median, IQR)	55 (3 – 68.5)	23 (18.5 – 49.5)	27.0 (18.0 – 56.0)
CRP, mg/L (median, IQR)	8.9 (1.8 – 49.0)	27.0 (12.0 – 84.0)	23.0 (3.9 – 60.0)
Haemoglobin, mmol/L (median, IQR)	5.7 (4.5 – 6.7)	5.7 (5.0 – 6.7)	5.7 (4.9 – 6.7)
Platelet count, x 10^9/L (median, IQR)	458 (261 – 468)	436 (268 – 679)	458 (268 – 637)
Leukocyte count, x 10^9/L (median, IQR)	10.2 (7.6 – 13.1)	12.3 (6.0 – 16.8)	11.7 (7.4 – 15.6)
IBD treatment at time of VTE			
Corticosteroid use	4 (67%)	5 (36%)	
Anti-TNF agent use	0	4 (29%)	
Immunomodulator use	3 (50%)	3 (21%)	

Missing values for each variable were: PGA n = 1; Fcal n = 10; ESR n = 7; CRP n = 5; Haemoglobin n = 5; Platelet count n = 4; Leukocyte count n = 4. IBD: inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis; IBD-U: IBD unclassified; PGA: physician's global assessment; ESR; erythrocyte sedimentation rate; CRP: C-reactive protein.

VTE outcome

Sixteen out of 20 patients fully recovered from their VTE. Two CSVT patients died (Supplementary Table 6). One CSVT patient, who needed a craniotomy, experienced mild neurological impairment after recovery. One patient had a post-thrombotic syndrome with persisting leg swelling a few weeks after the VTE, but was lost to follow-up after 2 months. Two patients had recurrent VTEs reported. One patient developed a DVT in the right femoral vein 2 weeks after the CSVT and a third VTE in the right popliteal vein 1 year after the first event, both while on antithrombotic prophylaxis. The other patient had a second and third DVT around 6 and 10 months, respectively, after the first DVT.

DISCUSSION

This is the first prospective, international cohort study reporting data on VTEs in paediatric IBD. With a cohort of almost 25,000 patients, this study covered a larger population

than any previous study. The set-up of this study enabled us to collect data about rare events from multiple countries in a homogeneous manner, resulting in 20 well-described VTE cases.

The results show that PIBD patients have a nearly 14-fold higher VTE risk compared to the general paediatric population. Previously, studies in adults have reported a 1.5 to 3-fold increased incidence in IBD patients[15,46-48], regardless of IBD type[46]. A Danish population based study, showed that the relative risk is higher in children and adolescents and decreases with increasing age[15]. This study found an incidence rate of 8.9 per 10,000 person-years in IBD patients within the age group 0-20 years and a relative risk of 4.5 (1.7-12.0) compared to non-IBD patients. A recently published Canadian population-based study demonstrated that the 5-year incidence of VTE in PIBD patients was 31.2 (23.7 – 41.0) per 10,000 person-years[21]. This is almost ten times higher than in our study. However, the absolute number of VTE cases in their study is not reported and they only included newly-diagnosed IBD patients, who are probably those most at risk, as supported by the fact that the 1-year incidence was 81.2 per 10,000 person-years. Despite these differences in incidence between the studies, all suggest an increased risk of VTEs in PIBD patients.

In another study, Nylund *et al*. used the inpatient billing codes in the USA to assess the risk of developing VTE and reported an absolute risk of 117.9 per 10,000 hospitalizations for children with IBD compared to 50.4 per 10,000 hospitalizations for children without IBD[18]. Similarly, we show that the risk in the hospitalized PIBD population is 559 times higher than in the outpatient PIBD population. It should be taken into consideration that this relative risk was calculated using hospitalization data from the USA, which could be different from hospitalization rates in Europe.

An interesting finding considering the larger proportion of CD patients within the PIBD population is the majority of UC/IBD-U cases in our cohort[45]. A large study in adults with IBD found a 1.32 times greater prevalence among UC patients than CD patients[27]. Saleh *et al*, also found that the relative risk (RR), compared to non-IBD patients, was higher in UC (RR 1.13) than in CD patients (RR 1.08)[47]. By contrast, the Danish population-based study reported a higher risk in patients with CD than those with UC[15]. However, the proportion of UC patients (71%) within their IBD population was remarkably high, which may contribute to their high reported incidence. Disease location in CD was not described in their study, but based on our findings colonic disease may play a role in VTE risk of those patients.

Although thrombophilia may be a risk factor of VTE in adult IBD patients, it does not appear to be an important one in children[49]. None of the patients in our cohort had acquired or hereditary thrombophilia. This is in contrast to a retrospective study in PIBD patients describing thrombophilia in four out of nine (44%) VTE cases[17]. Studies investigating the prevalence of inherited thrombophilia in children with VTE, also reported lower rates (12-15%)[50-52].

In our study all but one patient had active inflammation. Studies in adult IBD patients showed that the risk of VTEs is increased at the time of a disease flare[14,29,53]. Although the aetiology of VTE in patients with IBD is likely to be multifactorial, accumulating evidence exists that the presence of systemic inflammation triggers a hypercoagulable state[54,55]. This is supported by the fact that some other pro-inflammatory conditions are more commonly associated with the development of hospital-acquired VTE in paediatric patients, such as cystic fibrosis, childhood cancer and systemic infection[56-59]. Interestingly, three cases involved VTEs at multiple locations, supporting the theory that systemic in addition to local factors contribute to thrombus formation[60].

In addition to active disease, the most common risk factors in our PIBD cohort were steroid use and presence of a CVC. Nylund et al. performed a multivariate analysis in patients aged 5-20 years and identified older age, CVC, parenteral nutrition and an identified hypercoagulable condition as risk factors, without further defining the term hypercoaguable condition[18]. Notably, steroid use was not included in this analysis. Findings from a meta-analysis showed that systemic corticosteroid use was associated with a 2.2 times higher rate of VTE compared to IBD patients without steroid medication[61].

Remarkably, 50% of VTE cases in our study concerned a CSVT, resulting in a 46-fold higher incidence than in the general paediatric population. This is of particular interest considering the 20% mortality rate in children with CSVT in our cohort and known high rates of persisting neurologic deficits (17-79%) of CSVT in children[62]. In a systematic review by Lazzerini *et al.*, 50/92 cases of arterial and venous thromboembolisms in children with IBD were cerebral[63]. This is higher than the CSVT rate in adult IBD patients (4.5%) or the general paediatric population (10.8%)[6,64]. A possible contributing factor to the large proportion of CSVT in our cohort could be corticosteroid use, as this is also a contributing factor in children with acute lymphatic leukaemia, who have a 2-6% risk of CSVT.[65,66] However, as only 45% of CSVT patients in our cohort were on corticosteroids, the aetiology behind the specific cerebral location remains unexplained.

An important strength of our study is the reporting by the physicians themselves, which led to solid and detailed information about every patient that developed a VTE. Another

strength is the prospective set-up in which physicians report cases within the month of occurrence of the VTE. Physicians need to actively report the absence of a VTE case every month. The risk of selection bias in case reporting is further minimized by actively chasing participants who did not respond to the monthly survey. We are the first to report an incidence of VTEs in children and adolescents with IBD based on a prospective registry. Available studies in children thus far have reported increased incidences based on retrospective billing data bases or ICD-9 and ICD-10 coding, which has limitations[67]. Reporting by the physicians themselves led to solid and detailed information about every patient who developed a VTE. Although the collection of denominator data via the reporting physician could have led to less precise estimates of the denominator, as not in every hospital registries of new and current IBD patients might be up to date, the sensitivity analysis we performed confirmed the higher incidence rate compared to the general paediatric population. Moreover, given the large number of participating centers, we expect any inaccuracies in over- or underreporting to level out, thereby not influencing our findings significantly.

One of the limitations of our study is that our data do not include full coverage of entire countries, but relies on clearly defined geographical catchment areas reported by the local investigators. This could have introduced heterogeneity, as depending on the country or region patients might be referred from other centers to tertiary centers for specialized care and there could be overlap in patients covered by each center. A second limitation is the transition from paediatric to adult care between 14 and 19 years of age in some centers, which could explain the relatively young age of our VTE cohort. This could have resulted in less precise estimates, as we expect the incidence to be higher with increasing age. However, the majority of centers (68%) treat their patients up to the age limit of 18 years. A third limitation of this study is the inability to perform a multivariate analysis on the risk factors of developing a VTE. Despite the large cohort, the small number of patients with a VTE and the lack of a control group prevents such an analysis. Considering this low number of cases was found after 3 years of international case collection, including a large coverage of 24,802 children and adolescents with IBD, this shows that the absolute number of VTE cases in paediatric IBD patients is low.

According to the ECCO guideline, prophylaxis is recommended in adult IBD patients if they are hospitalized, regardless of indication[34]. In our cohort, 11/20 patients developed a VTE while not hospitalized. A survey among 162 paediatric gastroenterologists showed that physicians are hesitant to provide thromboprophylaxis for children with IBD because of lack of clear paediatric guidelines[68]. Safety concerns, specifically the presumed bleeding risk, are the main reason for paediatric and adult gastroenterologists to be cautious about prescribing prophylactic anticoagulation[68,69]. A systematic review assessing

safety and efficacy of thromboprophylaxis in children, showed that major bleeding events occurred in only 0.6% of children (some in neonates)[70]. Studies in children are lacking, but in adults with IBD thromboprophylaxis with LMWH has been shown to be safe, even in patients who initially present with rectal bleeding[71,72]. In future, direct oral anticoagulants may replace the use of LMWH as thromboprophylaxis in children with VTE, because of the advantage of oral over subcutaneous administration and fewer bleeding complications[73].

The current treatment guideline for children with ASC suggests to only administer VTE prophylaxis in pubertal children with at least one other risk factor and in prepubertal children with two other risk factors[31]. This age discrimination is suggested because of limited data on safety and efficacy of thromboprophylaxis in prepubertal children[31], not on differences in VTE risk. In our cohort, 40% of the reported cases occurred in children below 12 years of age, indicating that prepubertal children are at least equally at risk.

Interestingly, findings from a recent British panel of gastroenterologists in the context of the COVID-19 pandemic show that prophylactic anticoagulation was deemed appropriate in all paediatric patients with ASC, thus fitting the guidance of an extra risk factor[74]. We found that four cases should have received prophylaxis if following the recently published paediatric ASC guideline[31]. However, in seven other UC cases, despite the presence of ASC in some, prophylaxis was not suggested because of the absence of extra risk factors.

With this increased risk of VTEs in paediatric IBD patients, especially in those hospitalized, and potentially negative outcomes in paediatric IBD patients, we would advise considering thromboprophylaxis for all hospitalized patients with active UC/IBD-U, regardless of age or presence of additional VTE risk factors, and for all hospitalized children with moderate-to-severe CD with at least one additional VTE risk factor. Further prospective studies are necessary to assess the safety of prophylaxis in paediatric IBD patients, especially in outpatients with active disease.

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SUPPLEMENTARY MATERIAL

SUPPLEMENTAL METHODS

IBD data collection and definition of variables

Data collected included: demographics, sex, ethnicity, co-morbidities, IBD characteristics (year of diagnosis, IBD type, disease location, disease behaviour, disease activity) and previous and current medication. Body mass index (BMI) SDS were calculated for children >5 years old based on the World Health Organization (WHO) growth reference standards.(1)

Disease activity scores

Disease activity was assessed by the PUCAI in those with UC and IBD unclassified (IBD-U), and by the weighted paediatric Crohn's disease activity index (wPCDAI) in those with CD. Disease activity was categorized as remission, mild, moderate or severe according to pre-validated cut-offs.(2, 3) If disease activity scores were unavailable, the physician's global assessment (PGA) was used. Active disease was defined if the PGA was mild, moderate or severe. In case of an absent PGA a faecal calprotectin level of >250 was considered active disease.

Laboratory results

Faecal calprotectin levels and the following biochemical blood tests were obtained: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), haemoglobin, haematocrit, leukocytes, platelet count and albumin. Only faecal calprotectin levels obtained between 1 month prior to the VTE and 1 week after diagnosis of the VTE were included in this study. Blood results were included if obtained within 2 weeks prior to VTE diagnosis and 1 week after.

VTE data collection and definition of variables

Definition of VTE

A VTE was defined as a radiologically confirmed thromboembolism occurring in the veins of the upper limbs or superior vena cava (upper extremity DVT), lower limbs or inferior vena cava (lower extremity DVT), the dural venous sinuses (cerebral venous sinus thrombosis, CSVT), renal vein or right atrium or ventricle (intra-cardiac).

Definition of thrombophilia

Hereditary thrombophilia was defined as a proven protein S, protein C or anti-thrombin deficiency or factor V Leiden mutation. Acquired thrombophilia was defined as proven anti-phospholipid syndrome.

List of VTE risk factors

General VTE-related risk factors that were assessed included: presence of a CVC, hypertension, high dose oestrogen use, recent surgery, chronic heart disease, steroid therapy, malignancy, cigarette smoking, recent trauma, diabetes, pregnancy, sepsis, kidney disease, obesity, immobility, total parenteral nutrition, dehydration, hyperhomocysteinemia, sickle cell anaemia, hypovolemia and congenital disorders of glycosylation.

Definition of antithrombotic therapy complications

Type and duration of antithrombotic treatment and thromboembolic prophylaxis were obtained. Complications of antithrombotic treatment were defined according to a previously published paper by Mitchel et al.(4) Major bleeding was defined as any of the following: 1) fatal bleeding; 2) clinically overt bleeding associated with a decrease in haemoglobin of at least 20 g/L (i.e., 2 g/dL) in a 24-hour period; 3) bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the central nervous system; 4) bleeding that requires surgical intervention in an operating suite. Non-major bleeding was defined as a composite of 1) overt bleeding for which blood product is administered and not directly attributable to the patient's underlying medical condition and 2) bleeding that requires medical or surgical intervention to restore haemostasis, other than in an operating suite. Minor bleeding was defined as any overt or macroscopic evidence of bleeding that does not fulfil the criteria of major or non-major bleeding.

VTE outcome

Additional information on VTE recurrence, recovery status, persisting morbidity and mortality was collected.

Incidence data collection

Each year, active participants received an electronic survey. In this survey they stated how many patients they have under their care at that moment and whether this number of patients was based on an estimate or robust data (e.g. local database or patient notes). They provided additional information about their unit, location and other details regarding the paediatric population they are covering. They report at which age (upper limit) patients are usually transferred to adult care.

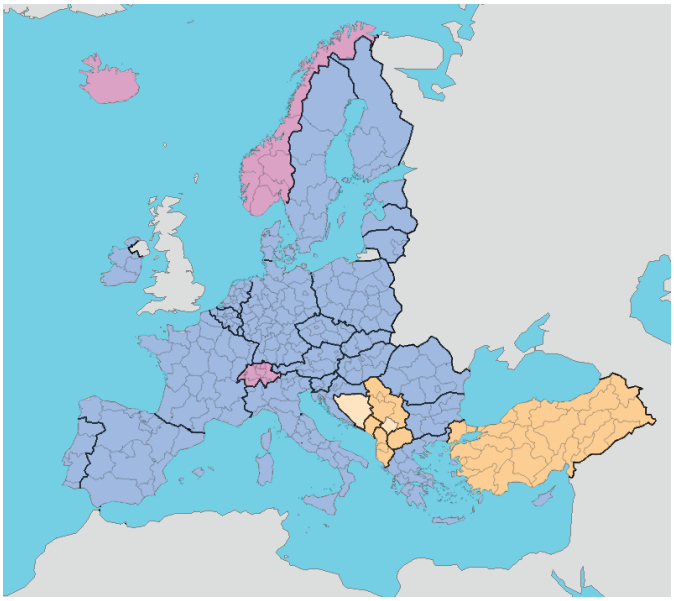
In addition, they report their geographical catchment area by selecting well-defined geographical areas, such as the Nomenclature of Territorial Units for Statistics (NUTS) classification from the Eurostat database, as demonstrated in Supplemental Figure 1.

As reporting centers may join the registry at different time points during the study period, the duration of patients at risk is different for each participating center. Subsequently, instead of counting the total number of patients at the start and end of the study, patient years were first calculated per center by multiplying the number of months a center was participating in the registry by the total number of PIBD patients they have under their care. The sum of patient years for all active centers is used as denominator for the incidence calculation. Since centers might have more than one participating physician, when two responders were reporting from the same centre we selected the report of denominator data that was based on the robust data, or we averaged the estimates.

Search strategy on incidence of VTE in children

The search was conducted according to the search strategy below in Ovid Medline and Embase. Additional relevant publications were retrieved based on review of reference lists of included papers and through discussions with leaders in the field. We included studies if 1) the population included children and adolescents aged 0-20 years, 2) the article was written in English, 3) full text was available, and 4) incidence rates were reported or could be calculated based on

the data provided in the manuscript. Studies focusing on a specific group of children (e.g. children with a malignancy) or neonates only were excluded. Studies merely reporting PE incidence data were excluded.



Supplemental Figure 1.
Map of all Nomenclature of Territorial Units for Statistics (NUTS) regions in Europe.

Embase: 1427 references retrieved

('venous thromboembolism'/mj/exp OR 'vein thrombosis'/mj/exp OR 'leg thrombosis'/mj OR (((venous OR vein OR lung OR pulmonary OR sinus OR cerebrosinal OR sinoven* OR portal* OR leg OR am OR legs OR arms OR extremit* OR limb*) NEAR/3 (thromboembol* OR thrombos* OR thrombus* OR thrombi OR embol*))):ti) AND ('juvenile'/exp OR 'pediatrics'/exp OR (pediatric* OR paediatric* OR child* OR infan* OR adolescen*):Ab,ti) AND ('incidence'/de OR 'epidemiological data'/de OR 'epidemiology'/de OR 'venous thromboembolism'/exp/dm_ep OR 'vein thrombosis'/exp/dm_ep OR (incidence* OR epidemiolog* OR (occurrence* NEAR/3 (rates OR rate))):Ab,ti) NOT ([animals]/lim NOT [humans]/lim) NOT [conference abstract]/lim AND ([english]/lim OR [dutch]/lim)

Medline ALL Ovid: 989 references retrieved

(*Venous Thromboembolism/ OR *Venous Thrombosis/ OR (((venous OR vein OR lung OR pulmonary OR sinus OR cerebrosinal OR sinoven* OR portal* OR leg OR am OR legs OR arms OR extremit* OR limb*) ADJ3 (thromboembol* OR thrombos* OR thrombus* OR thrombi OR embol*))).ti.) AND (exp infant/ OR exp child/ OR adolescent/ OR pediatrics/ OR (pediatric* OR paediatric* OR child* OR infan* OR adolescen*).ab,ti.) AND (Incidence/ OR Epidemiology/ OR *Venous Thromboembolism/ep OR *Venous Thrombosis/ep OR (incidence* OR epidemiolog* OR (occurrence* ADJ3 (rates OR rate))).ab,ti.) NOT (exp animals/ NOT humans/) AND (english.la. OR dutch.la.)

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Supplemental Table 1. Overview of international adult and paediatric inflammatory bowel disease guidelines and the reported recommendations regarding thromboembolic prophylaxis.

Guideline and/or consensus statements	Recommendations
Lichtenstein, American Journal of Gastroenterology, 2018 ACG Guideline for adult CD patients	No recommendations
Rubin, American Journal of Gastroenterology, 2019 ACG Guideline for adult UC patients	VTE prophylaxis with LMWH for hospitalized patients with acute severe colitis
Lamb, Gut, 2019 BSG Guideline for IBD patients	VTE prophylaxis with LMWH for hospitalized patients with acute severe colitis
Harbord, JCC, 2016 ECCO Guideline for extra-intestinal manifestations in adult IBD patients	VTE prophylaxis is recommended for all hospitalized IBD patients and should be considered following discharge from hospital and after recent surgery, and in outpatients with active disease
Van Rheenen, JCC, 2020 ESPGHAN/ECCO Guideline for pediatric CD patients (update)	No recommendations
Turner, JPGN, 2018 ESPGHAN/ECCO Guideline for pediatric UC patients (part 1) – ambulatory care	No recommendations
Turner, JPGN, 2018 ESPGHAN/ECCO Guideline for pediatric UC patients (part 2) – Acute Severe Colitis	VTE prophylaxis with LMWH for pediatric patients with acute severe colitis when 1 or more risk factors are present. Risk factors include: smoking, oral contraceptives, complete immobilization, CVCs (including PICC line), obesity, concurrent significant infection, known thrombotic disorder, previous VTE and family history of VTE.
Nguyen, Gastroenterology, 2014 CAG Consensus statements for VTE prevention in IBD patients	1) VTE prophylaxis with LMWH, low-dose UH or fondaparinux for all hospitalized adult IBD patients. 2) No VTE prophylaxis for children with IBD-related hospitalization without a previous VTE

ACG, American College of Gastroenterology; BSG, British Society of Gastroenterology; CAG, Canadian Association of Gastroenterology; JCC, Journal of Crohn's and Colitis; JPGN, Journal of Paediatric Gastroenterology and Nutrition; CD, Crohn's disease; CVC, central venous catheter; ECCO, European Crohn's and Colitis Organisation; ESPGHAN, European Society for Paediatric Gastroenterology Hepatology and Nutrition; IBD, inflammatory bowel disease; LMWH, low molecular weight heparin; PICC, peripherally inserted central catheter; UC, ulcerative colitis; UH, unfractionated heparin; VTE, venous thromboembolism.

Supplemental Table 2. List of complications that are monthly being registered in the PIBD-SETQuality Safety Registry.

List of rare but severe complications	
1	Death
2	Cancer
3	Severe neurological disease
4	Renal failure
5	Venous thromboembolism
6	Liver failure
7	Severe sepsis
8	Opportunistic infection
9	Bone marrow failure
10	Haemophagocytic lymphohistiocytosis
11	Other rare AND serious event related to IBD

Supplemental Table 4. Overview of population-based cohort studies providing incidence data on venous thromboembolisms and cerebral sinus venous thrombosis in the general paediatric population. Studies that included children and young adults up to the age of 20 years old were included.

Study	Country, Period	Study Design	Included types of VTEs	Total number of cases	Age	Reported or calculated incidence of VTE events in children /10.000/ year	Study specific comments
Andrew et al. * Blood 1994	Canada, 1990-1992	Prospective registry in 15 tertiary care pediatric centers.	DVT, PE (no CSVT, PVT, RVT or other non-extremity VTE)	137 DVT + PE	**1m-18y**	**0.07**	This study reported an incidence of 5.3/10.000 hospital admissions.
Cheuck et al. Br J Surg 2004	Hong Kong, 2000-2001	Retrospective review Hong Kong CDARS using ICD-9-CM codes	DVT, PE	Unknown	**5-14y**	0.08 DVT 0.01 PE	This study did not report number of events, sample size or patient years.
Delluc et al.* Thromb Haemost 2016	France, 2013-2014	Prospective registry in Western France	Lower extremity DVT, PE (excluded other VTE types)	3 VTE	**0-19y**	**0.32**	Incidence calculated based on data provided in paper.
Heit et al. Mayo Clin Proc 2001	Minnesota (USA), 1980-1990	Retrospective review of medical records	DVT, PE	7 VTE	**1-19y**	0.1 male 0.4 female	This study only reported incidences for males/females separately. Did not report sample size.
Hong et al. PLoS ONE 2018	Korea, 2009-2013	Retrospective review of Korean HIRA databases	Lower extremity DVT, PE (excluded other VTE types)	Unknown	**0-19y**	0.035 (0-9y) 0.078 (10-19y)	This study reported incidence numbers for two age categories, but did not report number of events or sample size.
Kevane et al. BMJ open 2019	Ireland, 2016-2017	Retrospective review HIPE records (hospital discharges using ICD-10-CM codes)	VTE	4 VTE	**0-17y**	**0.00**	This study reported incidence and number of events. Not able to calculate sample size with provided data.

Supplemental Table 4. Overview of population-based cohort studies providing incidence data on venous thromboembolisms and cerebral sinus venous thrombosis in the general paediatric population. Studies that included children and young adults up to the age of 20 years old were included.

Study	Country, Period	Study Design	Included types of VTEs	Total number of cases	Age	Reported or calculated incidence of VTE events in children /10.000/ year	Study specific comments
Lee et al.* Hong Kong Med J 2003	Hong Kong, 1995-2000	Retrospective review of hospital discharge records	DVT, PE, CSVT	8 VTE	**1y-14y**	**0.074**	Incidence calculated based on data provided in paper.
Molina et al.* Ann Acad Med Singapore 2009	Singapore, 2006	Retrospective review of ODS database based on hospital discharges	VTE	3 VTE	**0-14y**	**0.101**	Incidence calculated based on data provided in paper.
Park et al.* Korean Med Sci 2019	Korea, 2008-2016	Retrospective Korean Health Insurance Review and Assessment Service database	DVT, PE, CSVT, phlebitis and thrombophlebitis, RVT, PVT, thrombosis of vena cava	9,085 VTE	**0-20y** 0-1y 1y-5y 6y-10y 11y-15y 16y-20y	**0.69** 2.02 0.20 0.23 0.52 1.55	This study included patients aged 0-30y. Incidence was calculated for age group 0-20y based on data provided in paper.
Sabapathy et al.* J Pediatr 2016	Quebec (Canada), 1994-2004	Retrospective MED-ECHO & RAMQ database (hospital discharges using ICD-9-CM codes)	DVT, PE, CSVT, RVT	487 VTE 319 DVT 80 PE	**1y-17y** 1y-5y 6y-10y 11y-14y 15y-17y	**0.29** 0.04 0.03 0.06 0.16	Some patients had combination of VTEs.
Stein et al.* J Pediatr 2004	United States, 1979-2001	Retrospective NHDS database (hospital discharges using ICD-9-CM codes)	DVT, PE	64,000 DVT 13,000 PE	**0-17y** 0-1y 2y-14y 15y-17y	**0.49** 1.05 0.24 1.14	

Supplemental Table 4. Overview of population-based cohort studies providing incidence data on venous thromboembolisms and cerebral sinus venous thrombosis in the general paediatric population. Studies that included children and young adults up to the age of 20 years old were included.

Study	Country, Period	Study Design	Included types of VTEs	Total number of cases	Age	Reported or calculated incidence of VTE events in children /10.000/ year	Study specific comments
Tuckuviene et al.* J Pediatr 2011	Denmark, 1994-2006	Retrospective; Danish National Patient Registry (ICD-10 code for VTE and/or arterial TE)	PE, DVT	331 VTE	**0-18y** 1-4y 5y-9y 10y-14y 15y-18y	**0.21** 0.38 0.020 0.019 0.050 0.85	A separate study was published by this author reporting the number of CSVT in the same study population.
Van Ommen et al.* J Pediatr 2001	The Netherlands, 1997-1999	Prospective registry of the Dutch Paediatric Surveillance Unit in primary, secondary and tertiary centers	VTE	99 VTE	**0-18y** 28d-1y 1y-4y 5y-9y 10y-14y 15y-18y	**0.14** 0.25 0.08 0.1 0.18 0.05	
Wändell et al.* J Thrombolysis 2019	Stockholm (Sweden), 2011-2018	Retrospective review using health data register (using ICD-10 codes)	VTE	233 VTE	**0-18y**	**0.56**	Incidence calculated based on data provided in paper.
CSVT only							
DeVeber et al. New Engl J Med 2001	Canada, 1992 - 1997	Registry based on ICD-9 coding	CSVT	160	**0-18y**	**0.067**	This study included neonates, but did not report raw data that could be separately analysed.
Grunt et al. Dev Med Child Neurol 2010	Switzerland, 2000-2008	Prospective registry	CSVT	65	**0-16y**	**0.056**	This study included neonates, but did not report raw data that could be separately analysed.

Supplemental Table 4. Overview of population-based cohort studies providing incidence data on venous thromboembolisms and cerebral sinus venous thrombosis in the general paediatric population. Studies that included children and young adults up to the age of 20 years old were included.

Study	Country, Period	Study Design	Included types of VTEs	Total number of cases	Age	Reported or calculated incidence of VTE events in children /10.000/ year	Study specific comments
Kristofferson et al. Stroke 2020	Oslo (Norway), 2011 – 2017	Retrospective cross-sectional hospital population-based study	CSVT	9	**0-18y**	**0.11**	
Lee et al. Hong Kong Med J 2003	Hong Kong, 1995-2000	Retrospective review of hospital discharge records	CSVT	3	**1-14y**	**0.03**	
Sabapathy et al. J Pediatr 2016	Quebec (Canada), 1994-2004	Retrospective MED-ECHO & RAMQ database (hospital discharges using ICD-9-CM codes)	CSVT	32	**1-17y**	**0.02**	
Tuckuviene et al. Acta Paediatr Int J Paediatr 2011	Denmark, 1994-2006	Retrospective; Danish National Patient Registry (ICD-10 code for VTE and/or arterial TE)	CSVT	40	**1-18y**	**0.03**	

DVT: deep venous thrombosis; PE: pulmonary embolism; VTE: venous thromboembolism; PVT: portal vein thrombosis; RVT: renal vein thrombosis; CSVT: cerebral sinus venous thrombosis.
*These studies were included in the quantitative analysis (meta-analysis) of the VTE incidence in the general paediatric population.

Supplemental Table 5. Individual IBD related characteristics at time of VTE diagnosis.

Case	VTE Type	IBD disease duration until VTE, m	Disease location	IBD in remission during VTE	PGA	Fcal (µg/g)	ESR (mm/ hour)	CRP (mg/L)	Hb (mmol/L)	Platelet count (*10^9/L)	IBD treatment at time of VTE
ULCERATIVE COLITIS (n=11, 55%)											
13	*Lower extremity DVT*	33,5	E4	No	Severe	N/A	19	50	6.3	690	5-ASA, CS
14	*IVC + lower extremity DVT*	14,7	E4	Unknown	N/A	980	N/A	N/A	N/A	N/A	5-ASA
1	*CSVT*	0,2	E4	No	Moderate	5268	14	N/A	4.0	392	None
2	*CSVT*	0,1	E4	No	Severe	6000	N/A	187	5.5	667	None
6	*CSVT*	2,4	E4	No	Severe	1000	17	109	5.7	109	5-ASA, AZA, cyclosporine, IFX, MTX
10	*CSVT*	10,3	E4	No	Severe	N/A	N/A	N/A	N/A	N/A	Antibiotics, CS
18	*Pulmonary embolus*	48,1	E4	No	Severe	N/A	120	17	6.7	362	5-ASA
19	*Pulmonary embolus + IVC*	8,8	E4	No	Severe	N/A	N/A	12	N/A	253	5-ASA, ADA, CS
16	*Lower extremity DVT*	6,3	E4	No	Mild	5487	19	4	7.4	480	None
20	*Lower extremity DVT*	7,9	E4	No	Moderate	N/A	34	29	4.6	260	None
8	*CSVT*	0,3	E4	No	Moderate	2100	27	2	7.2	703	5-ASA, CS
IBD-unclassified (n=3, 15%)											
17	*Upper extremity DVT*	127,7	E4	Yes	None	194	57	27	6.0	548	5-ASA
4	*CSVT*	20,5	E4	No	Moderate	N/A	47	84	5.5	683	5-ASA, AZA, IFX
21	*Other - right cardiac ventricle*	20,5	E4	No	Severe	1174	19	23	5.0	292	6MP, CS, IFX
CROHN'S DISEASE (n=6, 30%)											
12	*Lower extremity DVT*	0,5	L3+L4	No	Moderate	2100	55	60	6.5	455	None

Supplemental Table 5. Individual IBD related characteristics at time of VTE diagnosis.

Case	VTE Type	IBD disease duration until VTE, m	Disease location	IBD in remission during VTE	PGA	Fcal (µg/g)	ESR (mm/hour)	CRP (mg/L)	Hb (mmol/L)	Platelet count (*10^9/L)	IBD treatment at time of VTE
3	*CSVT*	11,7	L2	No	Mild	N/A	N/A	N/A	N/A	N/A	AZA, CS
5	*CSVT*	2,8	L3	Yes	None	6000	N/A	2	4.9	460	AZA, CS
7	*CSVT*	79,6	L3	No	Moderate	N/A	N/A	N/A	N/A	N/A	5-ASA, AZA, CS
9	*CSVT + lower extremity DVT*	0,2	L2	No	Severe	N/A	3	16	4.4	196	None
15	*Lower extremity DVT*	0,1	L3+L4	No	Moderate	N/A	82	2	6.8	470	CS

VTE: venous thromboembolism; IBD: inflammatory bowel disease; PGA: physician's global assessment; Fcal: faecal calprotectin level; ESR; erythrocyte sedimentation rate; CRP: C-reactive protein; Hb: haemoglobin; DVT: deep venous thrombosis; SVC: superior vena cava; IVC: inferior vena cava; CSVT: cerebral sinus venous thrombosis; N/A: not available; 5-ASA: 5-aminosalicylate acid; CS: corticosteroid; AZA: azathioprine; ADA: adalimumab, 6MP: 6-mercaptopurine; IFX: infliximab; MTX: methotrexate.

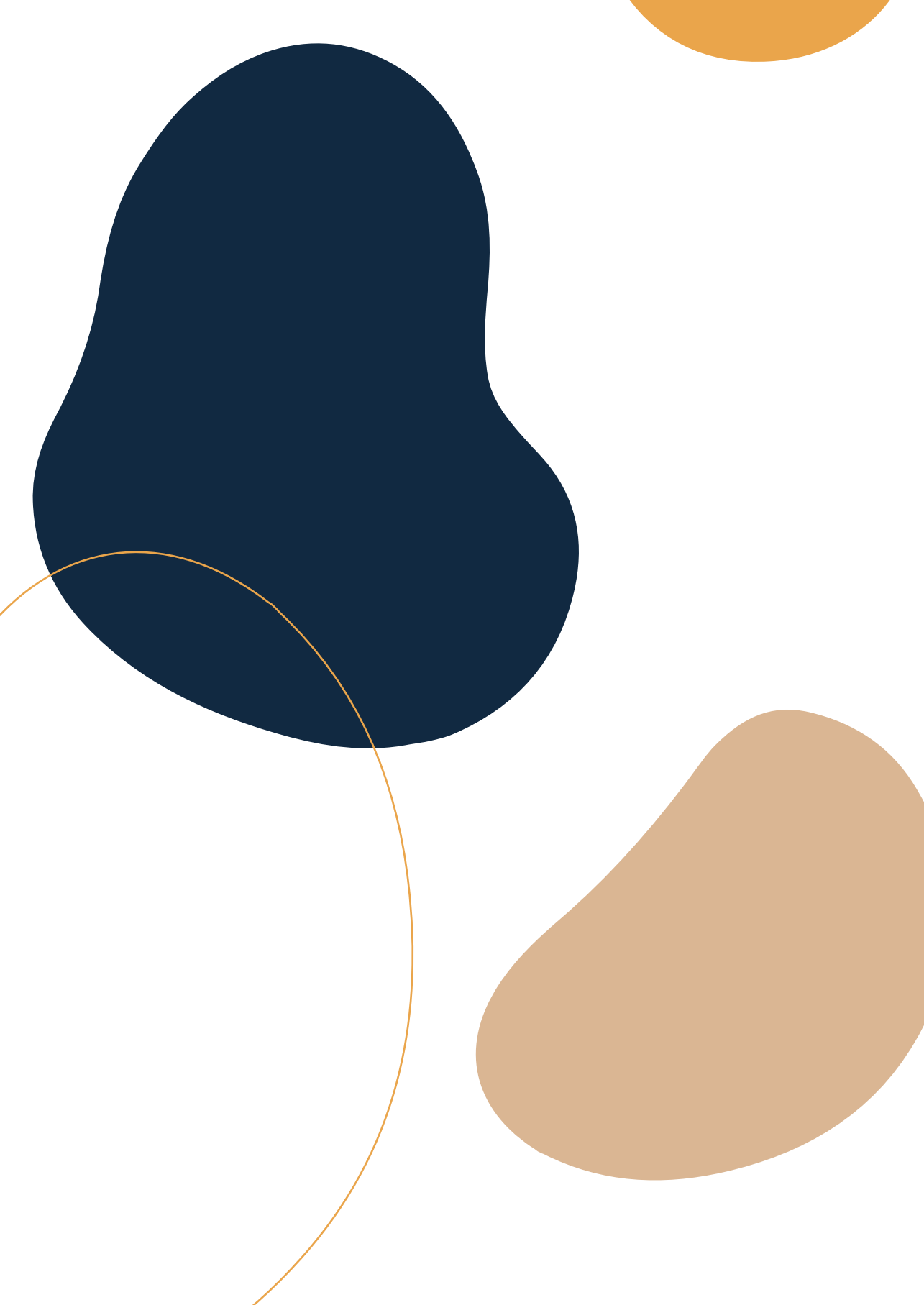
Supplemental Table 6. VTE treatment and outcome.

Case	VTE location	Anti-thrombotic therapy	Treatment duration, m	Anti-thrombotic therapy complication	>1 TE (recurrent / concurrent)	VTE recovery status	Consequences / disabilities
	Intracranial, n=10						
1	*Multiple venous sinuses and left internal jugular vein*	LMWH, vit K-A	6	No	No	Fully recovered	
2	*Superior sagittal sinus*	LMWH	6	No	No	Fully recovered	Venous infarction with secondary haemorrhage
3	*Multiple venous sinuses*	Enoxaparin, heparin	>6	No	Yes, recurrent	Partially recovered	Venous infarction with secondary haemorrhage, craniotomy, neurological impairment
4	*Multiple venous sinuses and proximal internal jugular vein*	LMWH	3	No	No	Fully recovered	
5	*Multiple venous sinuses*	LMWH	6	No	No	Fully recovered	
6	*Multiple venous sinuses*	-	-	-	-	Fully recovered	Venous infarction with secondary haemorrhage
7	*Dural venous sinus, unspecified*	-	-	-	-	Death	
8	*Multiple venous sinuses*	Heparin, LMWH, vit K-A	6	Yes, non-major[x]	No	Fully recovered	
9	*Superior sagittal sinus and right femoral vein*	LMWH	3	No	Yes, concurrent	Fully recovered	
10	*Posterior sagittal sinus*	LMWH	-	No	No	Death	
	Lower extremity, n=8[‡]						
11	*Proximal medial gastrocnemius veins*	LMWH	6	No	No	Fully recovered	
12	*Common femoral vein to popliteal vein*	LMWH	3	No	No	Partially recovered	Post thrombotic syndrome (persisting leg swelling). Lost to follow-up 2 months after VTE.
13	*Lower IVC, common iliac, femoral, superficial femoral vein*	LMWH	6	Yes, minor[#]	No	Fully recovered	

Supplemental Table 6. VTE treatment and outcome.

Case	VTE location	Anti-thrombotic therapy	Treatment duration, m	Anti-thrombotic therapy complication	>1 TE (recurrent / concurrent)	VTE recovery status	Consequences / disabilities
14	*Femoral and popliteal vein**	Heparin, LMWH	3 days, 1	No	Yes*, arterial, concurrent	Fully recovered*	Persisting mild right hemiparesis, gait asymmetry and mild cognitive impairments due to arterial TE.
15	*Left posterior tibial vein*	LMWH, vitKA	3, 12	No	No	Fully recovered	
	Upper extremity, n=1						
16	*Right basilic vein*	LMWH	3	No	No	Fully recovered	
	Pulmonary, n=3						
17	*Subsegmental pulmonary embolus left lower lobe*	LMWH	3	No		Fully recovered	
18	*Proximal left pulmonary vein and IVC*	LMWH, vit K-A	3, ?	Yes, minor[#]	Yes, concurrent[¥]	Fully recovered	
19	*(Sub)segmental bilateral lower lobe, left posterior tibial, peroneal and popliteal veins*	Heparin, DOAC	1,5 day, >6	Yes, minor[°]	Yes, both[‡]	Fully recovered	
	Other, n=1						
20	*Right cardiac chamber*	LMWH	3	No	No	Fully recovered	

[‡] Three patients had a lower extremity DVT occurring together with another VTE type. *This patient was diagnosed with an arterial thrombosis in the middle cerebral artery branches at the time of VTE diagnosis. [¥] PE and concurrent thromboembolism in the IVC, diagnosed following an incidental finding on abdominal CT-scan. [×]Clinically overt gastrointestinal bleeding with a decrease in haemoglobin of at least 20 g/L in a 48-hour period, requiring modulation of antithrombotic therapy and transfusion of blood products. [#]Worsening of rectal bleeding, continuation of antithrombotic despite the complication. [°]Severe rectal bleeding requiring several blood transfusions in a patient with a concurrent C. difficile infection. [‡]DVT and concurrent PE (incidental finding on CPTA). Patient suffered from two episodes of recurrent DVT in left popliteal veins, both with complete resolution. VTE: venous thromboembolism; IBD: inflammatory bowel disease; IVC: inferior vena cava; CD: Crohn's disease; UC: ulcerative colitis; IBD-U; IBD-unclassified; LMWH: low molecular weight heparin; vit K-A: vitamin K antagonist; N/A: not available



05

First-line treatment with infliximab versus conventional treatment in children with newly diagnosed moderate-to-severe Crohn's disease: an open-label multicentre randomized controlled trial

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ABSTRACT

Objective: In newly diagnosed paediatric patients with moderate-to-severe Crohn's disease (CD), infliximab (IFX) is initiated once exclusive enteral nutrition (EEN), corticosteroid, and immunomodulator therapies have failed. We aimed to investigate whether starting first-line infliximab IFX (FL-IFX), is more effective to achieve and maintain remission than conventional treatment.

Design: In this multicentre open-label randomised controlled trial, untreated patients with a new diagnosis of CD (3–17 years old, weighted Paediatric CD Activity Index score (wPCDAI) >40) were assigned to groups that received 5 infusions of 5 mg/kg IFX at weeks 0, 2, 6, 14, and 22 (FL-IFX), or EEN or oral prednisolone (1 mg/kg, maximum 40 mg) (conventional). The primary outcome was clinical remission on azathioprine, defined as a wPCDAI <12.5 at week 52, without need for treatment escalation, using intention-to-treat analysis.

Results: 100 patients were included, 50 in the FL-IFX group and 50 in the conventional group. Four patients did not receive treatment as per protocol. At week 10, a higher proportion of patients in the FL-IFX group than in the conventional group achieved clinical (59% vs 34%, respectively, p=0.021) and endoscopic remission (59% vs 17%, respectively, p=0.001). At week 52, the proportion of patients in clinical remission was not significantly different (p=0.421). However, 19/46 (41%) patients in the FL-IFX group were in clinical remission on azathioprine monotherapy without need for treatment escalation vs 7/48 (15%) in the conventional group (p=0.004).

Conclusions: FL-IFX was superior to conventional treatment in achieving short-term clinical and endoscopic remission, and had greater likelihood of maintaining clinical remission at week 52 on azathioprine monotherapy.

Trial registration number: ClinicalTrials.gov Registry (NCT02517684).

INTRODUCTION

In newly diagnosed paediatric patients with Crohn's disease (CD), rapid disease control is desirable, but this outcome is not always achieved with current treatment strategies. The European Society of Paediatric Gastroenterology, Hepatology and Nutrition consensus guideline recommends starting with exclusive enteral nutrition (EEN) or oral corticosteroids for induction of remission in conjunction with immunomodulator maintenance treatment. Infliximab (IFX), an anti-tumour necrosis factor alpha (TNF-α) agent, is increasingly being used in paediatric patients with CD refractory to steroids and/or immunomodulators and results in high sustained remission rates.[1] IFX is started if response to the conventional treatment strategy case is inadequate.[2]

In many paediatric patients with CD, however, particularly in those with moderate-to-severe CD, mucosal healing and sustained clinical remission are not achieved with conventional treatment. [3] First-line IFX (FL-IFX) is mentioned in the current paediatric CD treatment guidelines as the preferred strategy only for patients with CD with active perianal fistulising disease and those at risk of disabling disease.[2,4] It has already been suggested by several observational studies, however, that primary IFX therapy may be very effective in inducing and maintaining clinical remission in paediatric patients with luminal CD.[5-7] A randomised controlled trial (RCT) in adult patients with CD who had recently been diagnosed showed that early treatment with IFX in combination with immunomodulators was more effective than conventional treatment with corticosteroids, but an RCT in therapy-naïve patients has not been performed.[8] As paediatric-onset CD often presents with a more severe phenotype of disease than adult-onset CD,[9] this suggests that paediatric patients with CD may benefit even more from a FL-IFX strategy by preventing accumulating damage due to chronic uncontrolled inflammation.[10] If mucosal healing can be achieved by establishing early control of inflammation, sustained clinical remission will be attained and development of complications such as strictures and perforations may be prevented in these paediatric patients.

We hypothesise that induction of remission with FL-IFX in moderate-to-severe paediatric patients with CD results in higher early clinical and endoscopic remission rates, and superior rate of clinical remission maintenance on azathioprine (AZA) monotherapy compared to conventional treatment. Therefore, we aim to compare the efficacy of FL-IFX treatment with conventional treatment in newly diagnosed patients with moderate-to-severe paediatric CD.

METHODS

Study design and participants

We designed an investigator-initiated international open-label RCT in adherence to the Consolidated Standards of Reporting Trials statement. The trial was performed in 12 hospitals in three European countries (the Netherlands, Croatia, and Finland). The study protocol was published.[11] Inclusion and exclusion criteria are defined in Table 1. It was aspired to enroll patients as soon as possible following diagnostic endoscopy. After CD diagnosis had been established and eligibility criteria had been met, written informed consent was obtained from the patient (if ≥12 years) and both parents and/or guardians.

Table 1: Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Patient is 3-17 years of age	Indication for primary surgery
Patient presents with new-onset untreated CD according to the revised Porto criteria[34]	Symptomatic stenosis or stricture in the bowel due to scarring
wPCDAI >40 at baseline	Active perianal fistulas
Body weight >10 kg at baseline	Presence of a serious comorbidity, such as infection, sepsis, opportunistic infection, positive stool culture (*Salmonella enterica, Shigella spp., Yersinia enterocolitica,* or *Campylobacter spp.*), positive *Clostridium difficile* toxin assay, or positive tuberculosis screening
	Presentation with suspected or definite pregnancy
	Already using CD-specific therapy

CD=Crohn's disease; wPCDAI=weighted pediatric Crohn's disease activity index (range 0-125).

Randomisation and masking

Included patients were stratified by centre and equally randomised into two treatment groups with a validated variable block randomisation model, incorporated in the web-based database used for this trial (Castor Electronic Data Capture).[12] Allocation was concealed for all participants and healthcare providers. Participants were randomly assigned to the experimental FL-IFX group or to the control group, referred to as the conventional treatment group. Participants, investigators and healthcare providers were not masked to treatment allocation.

Procedures

The FL-IFX group received five intravenous IFX (Inflectra, CT-P13) infusions of 5 mg/kg induction at weeks 0, 2, and 6, followed by two maintenance infusions every 8 weeks. This was combined with oral AZA as maintenance treatment (once daily, dosed 2–3 mg/kg), which was initiated on the day induction treatment was started (Figure 1). Conventional

treatment consisted of standard induction treatment with either EEN (polymeric feeding for 6–8 weeks, after which normal diet was gradually reintroduced within 2–3 weeks) or oral prednisolone (for 4 weeks 1 mg/kg daily with a maximum of 40 mg, followed by tapering down to 5 mg per week until stop). [2] Whether patients received induction treatment with EEN or prednisolone was based on patient preference, in accordance with the treating physician. Patients and parents were informed about all treatment options prior to randomisation. The choice between EEN and prednisolone was made after being assigned to the conventional treatment group. Similar to the FL-IFX group, both EEN and prednisolone were combined with oral AZA as maintenance treatment (2–3 mg/kg, once daily) in the conventional treatment group. AZA dosing was halved in case of thiopurine methyl transferase (TPMT) heterozygosity. As part of clinical care, AZA metabolites (6-thioguanine nucleotides and 6-methylmercaptopurine) were measured around the time of induction treatment cessation, and complete blood counts were performed weekly in the first month, monthly in the second and third months, and thereafter once every 3 months (Online Supplemental Table 1). In both groups, methotrexate was the second choice immunomodulator, only prescribed in the event of low or absent TPMT activity or side effects of AZA.

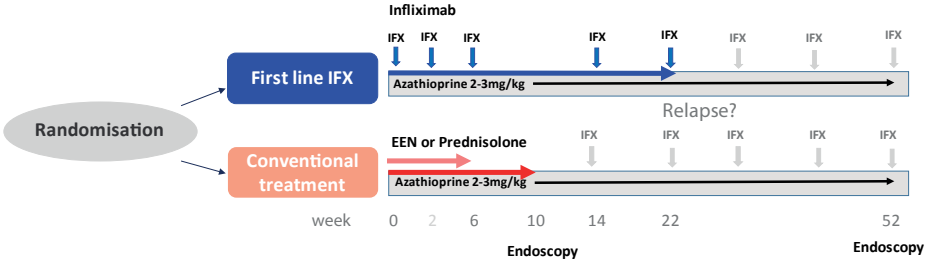

Figure 1: Trial design. Illustration of treatment procedures in this trial. EEN=exclusive enteral nutrition; IFX=infliximab.

In both groups, data were collected prior to start of induction therapy, at weeks 6, 10, 14, 22 and 52. At each visit, weighted Paediatric Crohn's Disease Activity Index (wPCDAI) was determined,[13] blood was obtained for routine laboratory analysis, and serum samples were collected (in conventionally treated patients at start, week 10, and week 52). SD scores (SDS) adjusted for sex and age were used to evaluate linear growth. The height-for-age SDS were calculated with the Growth Analyser Research Calculation Tool, based on the Dutch national reference standards for all patients included in the Netherlands and the WHO growth reference standards for all patients included in other countries.[14] Target height and target height SDS were calculated.[15] Endoscopy (ileocolonoscopy) was performed prior to start of treatment, at week 10, and optionally at week 52. During endoscopy, the Simple Endoscopic Score for Crohn's Disease (SES-CD) was used

to evaluate endoscopic remission,[16] which was defined as a SES-CD score <3. A single reader, blinded for both assigned treatment and time point, evaluated and rescored all endoscopic still images available by using the physician global assessment endoscopy score,[17] to check interobserver variability between paediatric gastroenterologists (r=0.661, p>0.001). The SES-CD score was used for analyses regarding endoscopic findings. Faecal samples were collected for faecal calprotectin level measurement prior to start of treatment, at week 10, and at week 52. Faecal calprotectin levels were assessed in the Erasmus Medical Centre with ELISA (CALPRO assay). When faecal samples were missing, faecal calprotectin levels determined in the local hospital at this time point were used, which accounted for 15% of all samples. A faecal calprotectin level <100 µg/g was defined as biochemical remission.[18] In patients ≥9 years old quality of life (QOL) was assessed with the validated IMPACT III questionnaire. Scores range from 0 to 100, with a higher score indicating a better QOL.[19]

In case of non-response or absence of response (response being a decrease in wPCDAI of >17.5 points), the treatment advice for FL-IFX treated patients was to shorten the IFX dosing interval to 6 weeks and/or to double the dose to 10 mg/kg. In accordance with clinical practice clinicians could perform reactive therapeutic drug monitoring (TDM) to guide this decision. Initiation of IFX treatment was advised for conventionally treated patients. To guide clinical decision-making for treatment escalation, secondary loss of response was defined either by an increase of the wPCDAI with >17.5 points or by a total wPCDAI score >40 after response had been achieved. If FL-IFX-treated patients were not in clinical remission at week 22, it was recommended to continue the IFX infusions as standard care, instead of stopping after five infusions. Patients requiring such extended IFX therapy were considered treatment failures in intent-to-treat analysis of outcomes following five doses of FL-IFX. If FL-IFX-treated patients had loss of response during AZA monotherapy, it was advised to check AZA metabolite levels to assess optimal treatment. Contingent upon optimal AZA metabolite levels, it was advised to restart IFX maintenance therapy every 8 weeks, also meaning treatment failure. Conventionally treated patients with loss of response during AZA monotherapy were advised to step up to IFX therapy after checking AZA metabolites and optimising its dosing in case of suboptimal levels. In addition to these guidelines, in patients without response, loss of response or intolerance to treatment, changes in treatment could be made according to the physician's discretion.

Outcomes

Primary outcome

The primary outcome of this study was clinical remission, defined as wPCDAI <12.5 at week 52, without need for treatment escalation. Any additional CD-related therapy or surgery during the 52 weeks was considered treatment escalation.

Definition of treatment escalation

Additional CD-related therapy in the FL-IFX group included (1) any course of corticosteroids, (2) increase of the IFX dose, (3) shortening of the IFX treatment interval, (4) continuation or restart of IFX after the standard five infusions, or (5) start of another biological agent. Additional CD-related therapy in the conventional treatment group included initiation of IFX and any course of corticosteroids that was additional to the standard treatment described in the previous section.

Secondary outcomes

Secondary outcomes included time-to-treatment escalation from start of induction and clinical disease activity scores over time. At week 10, clinical remission rate, endoscopic remission rate and faecal calprotectin level were assessed. QOL was evaluated at week 14. At week 52, the following outcomes were assessed: (1) additional corticosteroid use, (2) need for treatment escalation, (3) linear growth, (4) clinical remission rate, (5) endoscopic remission rate, (6) faecal calprotectin level, (7) QOL and (8) rate of adverse events. An adverse event was defined as any undesirable experience occurring to a subject during the study, whether or not it was considered to be related to the investigational product or the experimental treatment.

Statistical analysis

Based on published studies reporting effectiveness of FL-IFX treatment and early IFX use [6] in paediatric patients with CD, a power calculation was performed.[7,20] Based on these studies a clinical remission rate of 60% in conventionally treated patients and 85% in FL-IFX-treated patients was expected. One-hundred patients (50 in each arm, considering a drop-out rate of 2%) were required to find this 25% difference in clinical remission at week 52 with a power of 80% (two-sided α 0.05).[11] Data were analysed on an intention-to-treat basis. Safety analyses were based on the actual treatment patients received (i.e. per protocol). Continuous variables were presented as medians and IQRs and compared with the Mann-Whitney U-test. Categorical variables were presented as absolute frequencies and percentages and compared by the X^2 test or the Fisher exact test. The Wilcoxon signed rank test was used to compare height-for-age SDS at different time points within one treatment group. SES-CD scores with a missing ileum subscore due to the endoscopist's failure to intubate the terminal ileum were included in the

analysis to evaluate endoscopic remission. The median faecal calprotectin levels and SES-CD scores were subject to right censoring. To correct for this, medians of faecal calprotectin levels and SES-CD scores were calculated using the Kaplan-Meier method, and treatment groups for these outcomes were compared using the log rank test. The multiple imputation method was used for missing erythrocyte sedimentation rate (ESR) levels (14.8%), missing albumin levels (10.5%), and missing faecal calprotectin levels (10.9%) in order to calculate biochemical remission rate. Twenty complete datasets were created for multiple imputation. For the primary outcome, no imputation was performed as <5% of data were missing. The time–to-treatment escalation outcomes were analysed using the Kaplan-Meier method. A paired analysis was performed for the linear growth. The mean clinical disease activity score over time was calculated with a linear mixed model, including the assigned treatment as a fixed effect and intercept as random effect. Random slopes were tested but not included.

All analyses were performed based on a significance level of 0.05. Calculations were performed using IBM SPSS Statistics V.24.0.

RESULTS

Patients were recruited between 7 April 2015, and 19 November 2018. A total of 195 patients were screened for eligibility in this trial. One hundred patients were randomly assigned to FL-IFX (n=50) or conventional treatment (n=50) (Figure 2). One patient in the conventional treatment group did not receive the study treatment she had been assigned to. Based on ethical considerations, she received the same (FL-IFX) treatment as her monozygotic twin sister, who had been included in this study previously. Two patients declined participation after randomisation, prior to the start of treatment. In the FL-IFX group, one patient was initially misclassified as CD, and this diagnosis was adjusted to ulcerative colitis a later stage of the study. This patient, therefore, was excluded from all analyses. Patient and disease characteristics at baseline were similar between treatment groups (Table 2).

The median time between diagnostic endoscopy and start of treatment for all included patients was 8 days (IQR 4-14). Twenty-seven patients (56%) in the conventional treatment group received EEN as primary induction therapy, while 20 patients (42%) received prednisolone (Online Supplemental Table 2A).

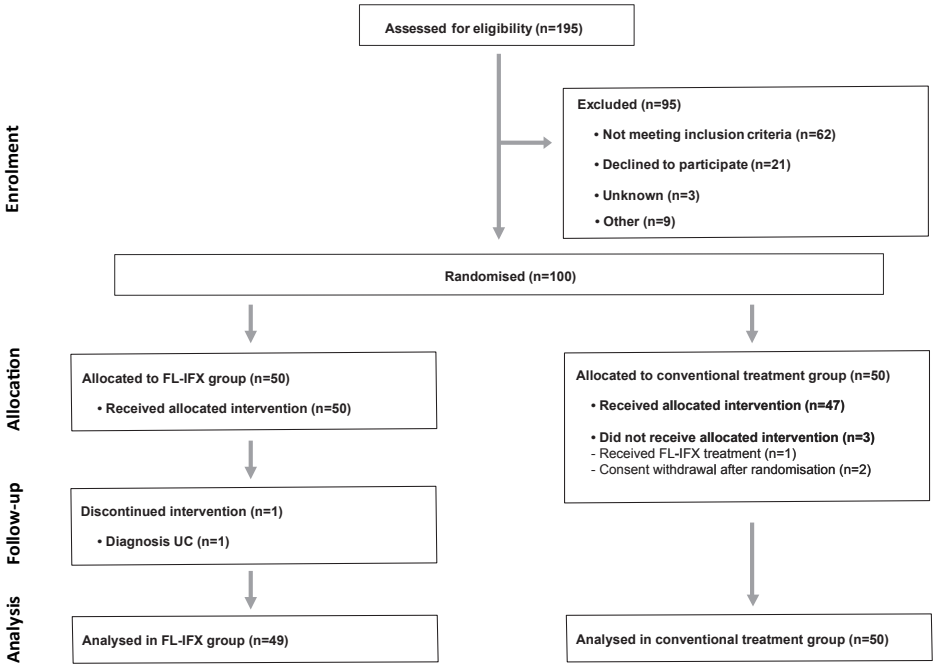

Figure 2: Trial profile. Flow chart of screened, randomised, and treated patients. FL-IFX=first-line IFX treatment; UC=ulcerative colitis.

Table 2: Baseline characteristics per treatment group. Data are presented as n (%) or median (IQR). Baseline characteristics were not significantly different between treatment groups.

	FL-IFX n=49	Conventional n=50
Age at diagnosis, years	15.1 (11.9-16.6)	14.1 (11.3-16.1)
Male sex, n	24 (49.0%)	27 (54.0%)
Height, cm	166 (154-175)	161 (143-170)
Height-for-age, SDS	-0.07 (-0.84-0.76)	-0.53 (-1.06-0.26)
Weight, kg	47.3 (36.8-57.1)	44.7 (30.3-55.0)
Tanner stage	4 (2-5)**	3 (1-4)**
wPCDAI	57.5 (47.5-67.5)	57.5 (47.5-73.8)
CRP, mg/L	32.0 (11.5-46.5)	38.0 (22.0-65.9)
ESR, mm/hour	35.0 (26.0-47.5)	32.0 (21.5-52.0)*
SES-CD	18.0 (11-26)*	18.0 (9-23)
Leukocytes, 10^9/L	8.2 (7.3-10.7)	9.1 (6.8-11.9)
Faecal calprotectin, µg/g	1114 (763-1869)	1086 (592-1661)
Perianal disease†	5 (10%)	9 (18%)

Table 2: Baseline characteristics per treatment group. Data are presented as n (%) or median (IQR). Baseline characteristics were not significantly different between treatment groups. (*continued*)

		FL-IFX n=49	Conventional n=50
Paris classification			
Age at diagnosis	<10 years	4 (8%)	9 (18%)
	10-17 years	39 (80%)	37 (74%)
	17-40 years	6 (12%)	4 (8%)
Disease location	L1	12 (25%)	11 (22%)
	L2	11 (22%)	12 (24%)
	L3	25 (51%)	27 (54%)
	Isolated L4	1 (2%)	-
Upper disease location	No upper GI	29 (59%)	25 (50%)
	L4a	19 (39%)	21 (42%)
	L4b	1 (2%)	4 (8%)
Disease behaviour	B1	46 (94%)	43 (86%)
	B2	3 (6%)	7 (14%)
	B3	-	-
	B2B3	-	-
Growth delay		0 (0%)*	2 (4%)
Time between diagnostic endoscopy and start of treatment, days		9 (5-14)	7 (2-14)

*1 missing data point. **>1 missing data point. †perianal disease comprised inactive fistula, skin tags, or anal fissures. CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; FL-IFX=first-line Infliximab; SDS= SDscore; SES-CD=Simple Endoscopic Score for Crohn's Disease (range 0-60); wPCDAI=weighted pediatric Crohn's disease activity index (range 0-125).

Efficacy of induction therapy

Ten weeks after start of induction therapy, significantly more FL-IFX-treated patients than conventionally treated patients were in clinical remission (59% [24/41] vs 34% [15/44], p=0.021). Fifty-seven patients (27 FL-IFX and 30 conventional), with similar baseline characteristics (Online Supplemental Table 2B), underwent endoscopy at week 10. A higher proportion of patients in the FL-IFX group achieved endoscopic remission (16/27 [59%] vs 5/30 [17%], p=0.001, Table 3) and median SES-CD scores were lower in the FL-IFX group (3 [IQR 0-5] vs 9 [IQR 3-19], p=0.005). In addition, the proportion of patients with a faecal calprotectin level <100 µg/g was higher in the FL-IFX group and C reactive protein, ESR and leukocyte levels were lower (Table 3).

Table 3: Findings at 10 weeks after start of induction therapy in the first-line IFX group versus the conventional treatment group.

	First-line IFX	Conventional	*P*-value
Fcal, µg/g, median (IQR)	286 (62-596)	545 (279-1108)	0.004
Patients with Fcal <100 µg/g, n (%)	13/39 (33%)	5/38 (13%)	0.036
CRP, mg/L, median (IQR)	2.0 (0.8-3.2)	8.4 (2.0-23.8)	<0.001
ESR, mm/hour, median (IQR)	6.5 (3.0-17.3)	17 (8.0-33.0)	0.003
Total leukocyte count, 10^9/L, median (IQR)	5.5 (4.8-7.1)	7.3 (5.9-9.3)	0.001

CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; Fcal=faecal calprotectin level; IFX=infliximab.

Treatment course

The mean wPCDAI score at all time points, corrected for repeated measurements, was lower in the FL-IFX group than in the conventional treatment group, although not significantly different (9.8 vs. 14.2, respectively, p=0.07) (Online Supplemental Figure 1). During the 52 weeks of follow-up, 43% of patients (95%CI 30-57) in the FL-IFX group and 75% of patients (95%CI 60-86) in the conventional treatment group needed treatment escalation (p=0.001, Figure 3A). Disease activity scores and level of inflammatory markers at 10 and 14 weeks after induction treatment were higher in those who received treatment escalation than in those who did not (Online Supplemental Table 3).

FL-IFX treatment

Twenty-one patients in the FL-IFX group needed treatment escalation. Twelve (24.5%) continued IFX therapy after the five per-protocol infusions (Table 4A, Figure 3B). Twenty-eight patients did not need treatment escalation.

Based on reactive TDM 2/49 patients received dose escalation within the first 22 weeks. None of the seven patients that restarted IFX experienced side effects or needed to stop within the first year of follow-up.

Conventional treatment

As depicted in Figure 3B, 40% of conventionally treated patients were already escalated to a second course of corticosteroids (19%) or IFX (21%) at week 14. Twenty patients received one or more courses of corticosteroids on top of the per protocol use within the first year (Table 4B). This resulted in extra corticosteroid use for a median duration of 67 days (IQR 53.3-72.3) in these patients. None of the patients received an extra EEN course. Thirty-six patients in the conventional treatment group needed treatment escalation.

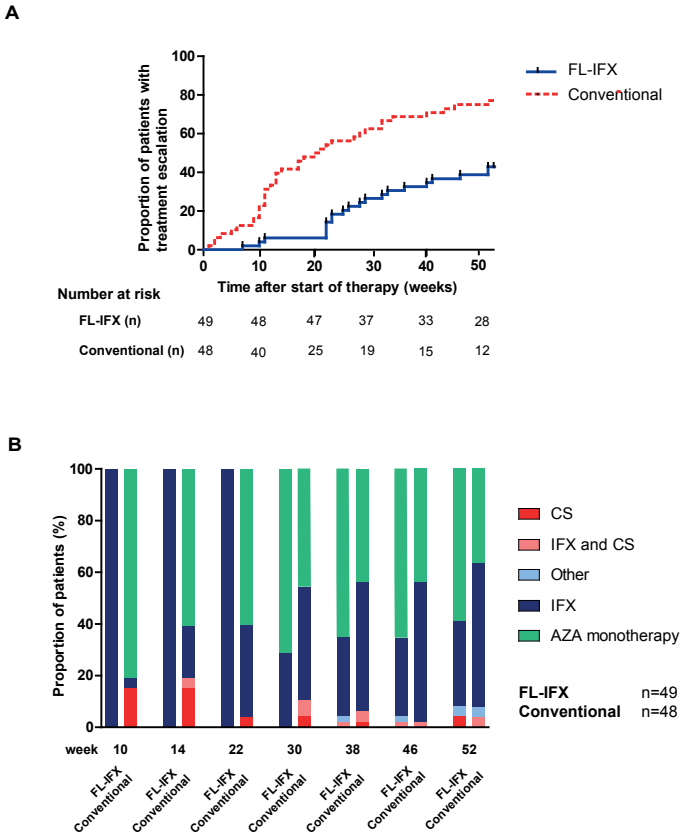

Figure 3: Proportion of patients who needed treatment escalation

A) Kaplan-Meier estimates of the time to treatment escalation after start of therapy. Any additional CD-related therapy or surgery during the 52 weeks was considered treatment escalation. Additional CD-related therapy in the FL-IFX group included: 1) any course of corticosteroids, 2) increase of the infliximab dose, 3) shortening of the infliximab treatment interval, 4) continuation or restart of infliximab after the standard five infusions, or 5) start of another biological agent. In the conventional treatment group, additional CD-related therapy included start of IFX and any course of corticosteroids that was additional to the standard treatment.

B) Proportion of patients receiving each treatment option from 10 weeks onwards, depicted per randomised group.

AZA=azathioprine; CD=Crohn's disease; CS=corticosteroid; FL-IFX=first-line infliximab.

Table 4A: Type of treatment escalation in the FL-IFX treatment group within 52 weeks.

Number of patients needing treatment escalation in the FL-IFX group, per treatment escalation type	
Continuation of IFX after 5 infusions; n (%)	12/49 (24.5)
Restart anti-TNF therapy; n (%)	7/49 (14.5)
Infliximab; n	*6*
Adalimumab; n	*1*
Corticosteroid course; n (%)	2/49 (4)

FL-IFX=first-line infliximab; TNF=tumor necrosis factor.

Table 4B: Type of treatment escalation in the conventional treatment group. IFX=infliximab.

Number of patients needing treatment escalation in the conventional group, per treatment escalation type	
Intensification to IFX; n (%)	16/48 (33)
Additional corticosteroids followed by IFX; n (%)	13/48 (27)
One or more courses of corticosteroids; n (%)	7/48 (15)

IFX=first-line infliximab

Findings after one year follow-up

At week 52, the primary outcome of clinical remission without need for treatment escalation was reached in more FL-IFX-treated patients than in conventionally treated patients. In particular, 19/46 (41%) of the FL-IFX-treated patients were in clinical remission without need for treatment escalation, vs 7/48 (15%) of the conventionally treated patients (Figure 4). This resulted in a 26% absolute difference (95%CI 0.18-0.35, p=0.004). Irrespective of any treatment escalation during the study period, no significant differences were found in clinical, biochemical and endoscopic remission at week 52 (Table 5).

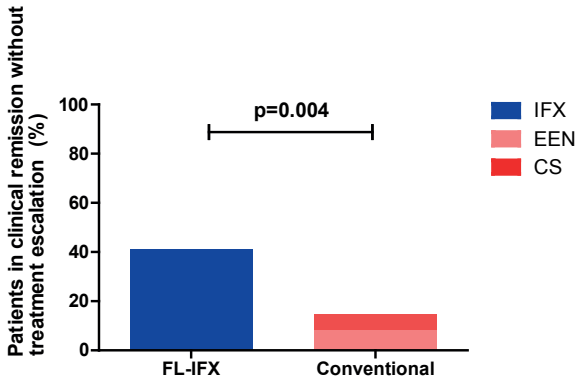

Figure 4: Proportion of patients in clinical remission without treatment escalation. The proportion of patients in clinical remission, defined as a weighted paediatric Crohn's Disease Activity Index <12.5, without treatment escalation at 52 weeks after the start of induction therapy.
CS=corticosteroid; EEN=exclusive enteral nutrition; FL-IFX=first-line infliximab.

In contrast, in the FL-IFX-treated patients median SDS height-for-age significantly improved between baseline and week 52 (median SDS of -0.07 [IQR -0.84 to 0.76] at baseline vs 0.02 [IQR -0.81 to 0.70] at week 52, p=0.045), while it significantly decreased in conventionally treated patients (median SDS of -0.53 [IQR -1.06 to 0.26] at baseline vs -0.66 [IQR -1.13 to 0.11] at week 52, p=0.020) (Table 6).

Table 5: Findings at week 52 per treatment group. Clinical remission is defined as a wPCDAI <12.5. Endoscopic remission was defined as a SES-CD <3. The group of patients on immunomodulator monotherapy comprised patients on azathioprine (n=46) and methotrexate (n=1). Baseline characteristics of these patients are similar (Online Supplemental Table 2C).

	First-line IFX	Conventional	*P*-value
wPCDAI, median (IQR)	7.5 (0-15)	10 (0-17.5)	0.476
Clinical remission, n (%)	33/47 (70)	26/46 (57)	0.420
Clinical remission in patients on immunomodulator monotherapy, n (%)	22/29 (76)	12/18 (67)	0.958
Endoscopic remission, n (%)*	5/18 (28)	5/14 (36)	0.630
SES-CD, median (IQR)	7 (2-7)	6 (0-10)	0.961
Fcal <100 µg/g, n (%)	17/48 (35)	9/47 (19)	0.120

*Eighteen FL-IFX patients and 14 conventional treated patients consented for endoscopy at week 52. Fcal=faecal calprotectin level; IFX=infliximab; SES-CD=Simple Endoscopic Score for Crohn's Disease (range 0-60); wPCDAI=weighted pediatric Crohn's disease activity index (range 0-125).

Table 6: Change in SDS height-for-age between baseline and 52 weeks.

	First-line IFX n=48	Conventional n=47	*P*-value
SDS height for age at baseline, median (IQR)	-0.07 (-0.84-0.76)	-0.53 (-1.06-0.26)	0.069
SDS height for age at week 52, median (IQR)	0.02 (-0.81-0.70)	-0.66 (-1.13-0.11)	**0.021**
Change in SDS height-for-age between baseline and 52 weeks	0.08 (-0.05-0.21)	-0.08 (-0.23-0.04)	**0.002**
Median increase in height (cm) between baseline and 52 weeks	4.0 (1.1-6.2)	2.4 (0.7-5.4)	0.226

IFX=infliximab; SDS=SD score

Quality of life

At week 14 and week 52, the median QOL score in the FL-IFX group and convential group were similar and in both groups significantly higher at both time points than at baseline (Online Supplemental Table 4). The median QOL score in the FL-IFX group increased from 59.3 at baseline (IQR 48.2-71.8) to 79.7 at week 52 (IQR 70.9-88.5, p<0.001) and in the conventional group from 61.2 (IQR 49.8-70.7) to 77.5 (IQR 66.3-85.0, p<0.001).

Safety

There was no significant difference between the proportion of patients with an adverse event in the FL-IFX group (44%) versus the conventional treatment group (60%; absolute difference of 16%; 95%CI: -0.04-0.33, p=0.125). In total, 94 adverse events occurred, 40 of which were reported in FL-IFX-treated patients and 54 in conventionally treated patients. Fiftheen serious adverse events were reported (Table 7).

Table 7: Reported serious adverse events during 52 weeks of follow-up.

	First-line IFX (n=50)	Conventional (n=47)	Total
Ileocecal resection	1[1]	2[1,1]	3
Intra-abdominal abscess	1[1]	1[1]	2
Psychosis	1[1]	0	1
Perianal abscess drainage	0	3[1,3,3]	3
Excision of pilonidal cyst	1[2]	0	1
Hospitalization	2[1,1]	3[1,3,3]	5
Total	**6**	**9**	**15**

[1] One patient treated with IFX and azathioprine; [2] One patient treated with azathioprine; [3] One patient treated with prednisolone and azathioprine.
IFX=infliximab.

DISCUSSION

This is the first RCT to compare the efficacy of IFX directly after diagnosis to conventional treatment with corticosteroids or EEN in newly diagnosed paediatric patients with moderate-to-severe CD. Ten weeks after induction therapy, higher clinical remission rates are found in the FL-IFX group. Of the FL-IFX-treated patients that underwent an endoscopy at week 10, a higher proportion is in endoscopic remission than in the conventional treatment group. Overall, the proportion of patients in clinical and biochemical remission at one year did not significantly differ between the two treatment groups. However, the trajectory towards remission is very different between groups. In particular, FL-IFX treatment is superior to conventional treatment in achieving clinical remission without need for treatment escalation 1 year after the start of therapy. Children with moderate-to-severe CD benefit from an effective therapy from diagnosis onwards. In this young population, delay in achieving remission and frequent flare-ups in the first year after diagnosis may slow their pubertal development and affects their school attendance and general well-being.[21] Moreover, ineffective induction treatment strategies in children and adolescents put them at risk of developing fistulising or stricturing complications.[9] Findings from the GROWTH study show that children with higher inflammatory markers after induction treatment were more at risk of a disease relapse in 18 months and early

surgery.[22,23] Similarly, we found in our cohort that inflammatory markers after induction treatment were higher in patients needing treatment escalation. Frequent or ongoing corticosteroid use, which is needed in 42% of the conventionally treated group in our cohort, has debitilitating side effects and may also affect growth. Our finding, that the SDS height-for-age decreases in significantly more conventionally treated patients than FL-IFX-treated patients during the first year, argues that conventional treatment provides insufficient disease control. In addition, steroid-sparing therapy may also result in a lower chance of developing disease complications.[24] While the efficacy of IFX in refractory paediatric patients with CD is well established,[1, 2] this RCT now proves what was suggested in only a small number of observational cohort studies in children with CD: that FL-IFX therapy results in lower relapse rate and longer duration of remission than induction with EEN or corticosteroids.[5,6,20,25]

In our cohort, endoscopic remission rates in FL-IFX-treated patients were significantly higher at week 10 than those in conventionally treated patients. The endoscopic remission rate of 59% in the FL-IFX group is superior to previously reported endoscopic remission rates in both paediatric and adult studies,[26,27] which may be explained by the primary IFX use in our study versus the secondary use of IFX in other paediatric studies.[28] Clinical and endoscopic remission rates in the conventionally treated group are lower than previously shown by Borrelli *et al*.[3] This difference may be due to the use of a stricter definition of endoscopic remission (SES-CD <3) in our cohort and the 2-4 weeks' longer duration of EEN in the Italian cohort. It could suggest that children with moderate-to-severe CD may benefit from EEN treatment with a duration of more than 6 weeks. The majority of conventionally treated patients in our study did not reach clinical remission without the need for additional therapies. However, if the 15% of patients in the conventional treatment group that did achieve clinical remission without treatment escalation would have received FL-IFX, they might have been overtreated. As we have so far been unable to discriminate these patients on the basis of their clinical profile at diagnosis, studies identifying predictors of disease course and treatment response are essential.

Since the design of this study in 2015, guidelines were updated and the role of therapeutic drug monitoring has increased. In our study, reactive TDM was performed based on clinical practice and thus the clinician's decision. In only a few patients this resulted in treatment optimisation, as only 2 out of 49 patients received interval shortening and/or dose escalation within the first 22 weeks. Thusfar, IFX could be safely restarted in the patients in our cohort. However, the risk of increased immunogenicity and consecutive loss of response after restarting IFX has been demonstrated and longer follow-up of our cohort is needed.[29] Based on progressive understanding in clinical practice since

the design of our study, we do not favor stopping FL-IFX therapy after five infusions. However, in adult patients with IBD, the concept of cycles of biologics treatment and planned de-escalation is currently being investigated. Reenaers *et al*. demonstrated that re-treatment with IFX was effective and well-tolerated in a group of patients that stopped IFX treatment after at least 1 year and 6 additional months of corticosteroid-free remission.[30] In 60% of FL-IFX-treated patients in our cohort, there was no need to continue or restart IFX within 6 months after the fifth infusion; they continued on AZA monotherapy. Concerns have been raised about the use of AZA maintenance therapy, especially due to the associated risk of lymphoproliferative disorders.[31] Although international guidelines and clinical practice differ regarding the use of AZA in CD,[2,4] this may be a reason to continue IFX monotherapy after five infusions instead of continuing AZA monotherapy. We cannot draw firm conclusions which treatment strategy is most effective and safe as our study was not designed to investigate the effectiveness of IFX monotherapy versus AZA monotherapy after five IFX infusions.

Counterarguments for implementation of FL-IFX therapy could be the increased risk of side effects and higher costs.[32] The overall incidence of adverse events within 1 year was similar between both treatment groups, which is in line with findings in adults[7] and indicates that the use of first-line anti-TNF in these patients is safe. The introduction of biosimilars has led to significantly decreased costs of IFX treatment.[33] In cost effectiveness studies patients received the originator IFX, whereas children in our study received the biosimilar CT-P13.[32]

A clear strength and innovative aspect of this study is the inclusion of new-onset and therapy-naïve patients with CD. Performing an RCT in children with CD is rarely done and extremely challenging. Only 21 patients and their parents declined to participate in this trial, which demonstrates the patients' interest in FL-IFX treatment. There are some drawbacks associated with our study. First, treatment assignment and assessments guiding treatment changes were not masked for patients and investigators, which could have created a performance bias. However, this bias is partly mitigated by the evaluation of growth, faecal calprotectin and endoscopic remission as objective outcome measures in this study. Second, while participating in the study not all patients agreed on the endoscopic evaluation scheduled in this study at week 10 and 52. Based on ethical considerations these patients continued to participate in the study, which led to missing endoscopic results. Despite the lower numbers, this did not introduce a bias as patients who underwent endoscopy had comparable disease characteristics at baseline (Online Supplemental Table 2B and 2C). Third, the difference in duration of therapy between FL-IFX (five IFX infusions in 22 weeks) and conventional treatment (6-8 weeks of EEN or 10 weeks of prednisolone) may have influenced the interpretation of our findings.

The duration of conventional treatment, however, was in accordance with paediatric CD guidelines and, as such, reflects current clinical practice.[2] We expect the effect of the difference in therapy duration to be minimal, as both groups had received AZA monotherapy per protocol for at least 6 months at 52 weeks. Although AZA metabolite levels were measured as part of clinical care in 74/97 patients and were therapeutic on average, we did not incorporate these results in our conclusions as data were collected in a non-standardized fasion.

In conclusion, despite the similar clinical remission rates at one year after diagnosis in both treatment groups, we argue that children and adolescents with moderate-to-severe CD would benefit from FL-IFX treatment as an insufficiently effective treatment strategy impacts their growth and development. Ongoing disease activity or corticosteroids use prior to escalation to IFX in the conventional treatment group could have been prevented by starting FL-IFX. This innovative treatment was well accepted by children and their parents, which shows the importance of moving forward with protocols to allow us to learn what is best. Future follow-up and additional research are needed to determine whether IFX can be stopped and for which patients this will be beneficial.

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SUPPLEMENTAL TABLES

Supplemental Table 1.

	First-line IFX n=35	Conventional n=39	P-value
6-MMP levels	1400 (800-2700)	1500 (597-2875)*	0.818
6-TGN levels	567 (438-660)	490 (224-650)	0.258
6-MMP/6-TGN ratio	3.21 (1.57-5.38)	2.91 (1.25-6.35)*	0.881

Azathioprine metabolites measured according to clinical practice. *Three out of 29 6MMP levels were missing. IFX=infliximab; 6 MMP=6-methylmercaptopurine; 6 TGN=6-thioguanine nucleotide.

Supplemental Table 2A: Baseline characteristics of patients treated with exclusive enteral nutrition versus oral prednisolone.

		Exclusive enteral nutrition (n=27)	Oral prednisolone (n=20)	P value
Age at diagnosis, years		14.5 (12.4-16.5)	13.8 (11.6-15.6)	0.282
Male sex		16 (59%)	10 (50%)	0.528
Height, cm		164.3 (149.2-175.0)	157.4 (143.5-16.6)	0.169
Weight, kg		48.5 (33.8- 56.3)	41.8 (31.1-53.9)	0.240
wPCDAI		60.0 (48.8-67.8)	53.8 (45.6-81.3)	0.909
CRP, mg/L		34.5 (24.7-65.9)	39.5 (20.5-69.0)	0.921
ESR, mm/hour		27.0 (17.0-47.5)	34.0 (22.5-71.0)	0.091
SES-CD		15 (6-22)	19 (6-28)	0.275
Leukocytes, 10^9/L		8.9 (6.8-11.7)	9.1 (6.2-11.8)	0.982
Faecal calprotectin, µg/g		1197 (1033-1661)	592 (555-1133)	0.014
Perianal disease†		5 (19%)	4 (20%)	0.898
Paris classification				
Age at diagnosis	<10 years	4 (15%)	3 (15%)	0.757
	10-17 years	20 (74%)	16 (80%)	
	17-40 years	3 (11%)	1 (5%)	
Disease location	L1	6 (22%)	5 (25%)	0.755
	L2	6 (22%)	6 (35%)	
	L3	15 (56%)	9 (45%)	
	Isolated L4	-	-	
Upper disease location	No upper GI	14 (52%)	11 (55%)	0.942
	L4a	12 (44%)	8 (45%)	
	L4b	1 (4%)	1 (5%)	
Disease behavior	B1	25 (93%)	16 (80%)	0.201
	B2	2 (7%)	4 (20%)	
	B3	-	-	
	B2B3	-	-	
Growth delay		1 (4%)	1 (5%)	0.828
Time between diagnostic endoscopy and start of treatment, days		7 (1-13)	8 (3-17)	0.266

Data are presented as n (%) or median (IQR)**.** wPCDAI, weighted paediatric Crohn's disease activity index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SES-CD, Simple Endoscopic Score for Crohn's Disease; †perianal disease comprised inactive fistula, skin tags, or anal fissures**.**

Supplemental Table 2B: Baseline characteristics of patients that underwent an endoscopic evaluation at week 10.

		FL-IFX (n=27)	Conventional (n=30)	P value
Age at diagnosis, years		15.1 (11.9-16.6)	14.1 (11.3-16.1)	0.181
Male sex		15 (49%)	18 (54%)	0.734
Height, cm		168 (151-177)	161 (143-174)	0.136
Weight, kg		52.0 (34.0-63.0)	43.2 (28.8-55.0)	0.248
wPCDAI		57.5 (47.5-65)	50 (45-75.6)	0.937
CRP, mg/L		29.0 (12.0-46.0)	39.5 (22.0-65.9)	0.091
ESR, mm/hour		35.0 (27.0-55.0)	28.0 (18.0-60.0)*	0.795
SES-CD		19 (9-24)	17 (6-19)	0.869
Leukocytes, 10^9/L		8.6 (7.4-10.4)	9.3 (7.4-12.1)	0.895
Faecal calprotectin, µg/g		1045 (684-1228.0)	1078 (617-1661)	0.765
Perianal disease†		2 (7%)	7 (23%)	0.100
Paris classification				
Age at diagnosis	<10 years	2 (7.5%)	5 (17%)	0.568
	10-17 years	23 (75%)	23 (76%)	
	17-40 years	2 (7.5%)	2 (7%)	
Disease location	L1	8 (30%)	5 (17%)	0.392
	L2	5 (18%)	9 (30%)	
	L3	13 (48%)	16 (53%)	
	Isolated L4	1 (4%)	-	
Upper disease location	No upper GI	12 (44%)	16 (53%)	0.252
	L4a	15 (56%)	12 (40%)	
	L4b	-	2 (7%)	
Disease behavior	B1	25 (92%)	26 (87%)	0.467
	B2	2 (8%)	4 (13%)	
	B3	-		
	B2B3	-	-	
Growth delay		0 (0%)	2 (7%)	0.172
Treated with exclusive enteral nutrition			16 (53%)	
Time between diagnostic endoscopy and start of treatment, days		9 (6-13)	8.5 (2-14.5)	0.860

Data are presented as n (%) or median (IQR). FL-IFX, first-line IFX; wPCDAI, weighted paediatric Crohn's disease activity index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SES-CD, Simple Endoscopic Score for Crohn's Disease; EEN, exclusive enteral nutrition. *1 missing data point. †perianal disease comprised inactive fistula, skin tags, or anal fissures.

Supplemental Table 2C: Baseline characteristics of patients that underwent an endoscopic evaluation at week 52.

		FL-IFX (n=18)	Conventional (n=14)	P value
Age at diagnosis, years		15.5 (11.1-16.6)	12.0 (9.4-14.6)	0.168
Male sex		10 (55.6%)	8 (57.1%)	0.928
Height, cm		160.9 (146.4-174.3)	147.9 (135.0-167.6)	0.193
Weight, kg		45.6 (31.3-55.5)	36.3 (24.9-43.0)	0.338
wPCDAI		56.3 (49.4-73.1)	52.5 (45.0-61.9)	0.338
CRP, mg/L		28.5 (7.8-40.3)	27.0 (17.8-46.0)	0.168
ESR, mm/hour		39.0 (30.0-40.0)	29.5 (19.8-62.5)	0.694
SES-CD		16 (10-23)	15 (8-15)	0.346
Leukocytes, 10^9/L		8.6 (7.4-10.4)	7.5 (5.4-11.7)	
Faecal calprotectin, µg/g		1076 (652-1445)	1033 (555-1087)	0.337
Perianal disease†		2 (6%)	7 (23%)	0.109
Paris classification				
Age at diagnosis	<10 years	3 (17%)	5 (36%)	0.250
	10-17 years	13 (72%)	9 (64%)	
	17-40 years	2 (11%)	-	
Disease location	L1	4 (22%)	4 (28.5%)	0.773
	L2	4 (22%)	4 (28.5%)	
	L3	9 (50%)	6 (49%)	
	Isolated L4	1 (6%)	-	
Upper disease location	No upper GI	9 (50%)	11 (78%)	0.073
	L4a	9 (50%)	2 (14%)	
	L4b	-	1 (7%)	
Disease behavior	B1	17 (94%)	10 (71%)	0.075
	B2	1 (6%)	4 (29%)	
	B3	-	-	
	B2B3	-	-	
Growth delay		0 (0%)	1 (7%)	0.249
Treated with exclusive enteral nutrition			7 (50%)	
Time between diagnostic endoscopy and start of treatment, days		10 (4-13.3)	9 (4-18)	0.837

Data are presented as n (%) or median (IQR). FL-IFX, first-line IFX; wPCDAI, weighted paediatric Crohn's disease activity index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SES-CD, Simple Endoscopic Score for Crohn's Disease; EEN, exclusive enteral nutrition. †perianal disease comprised inactive fistula, skin tags, or anal fissures.

Supplemental Table 3: Levels of inflammatory markers after induction treatment in patients that received and did not receive treatment escalation.

	First-line IFX		p-value	Conventional		P-value
Received treatment escalation	**Yes**	**No**		**Yes**	**No**	
wPCDAI, median (IQR)	17.5 (0.0-35.0)	0.0 (0.0-22.5)	0.109	21.3 (8.1-31.9)	10 (0.0-20.0)	**0.020**
Fcal, µg/g, median (IQR)	312 (193-896)	89 (34-496)	**0.027**	572 (403-219)	139 (93-806)	**0.023**
CRP, mg/L, median (IQR)	2.0 (1.1-4.6)	0.7 (0.0-2.6)	**0.003**	10.0 (0.9-26.5)	4.8 (0.9-8.7)	0.277
ESR, mm/hour, median (IQR)	12.0 (5.5-24.5)	3.0 (1.0-6.3)	**0.023**	17.0 (2.8-33.8)	10.0 (3.0-17.0)	0.176

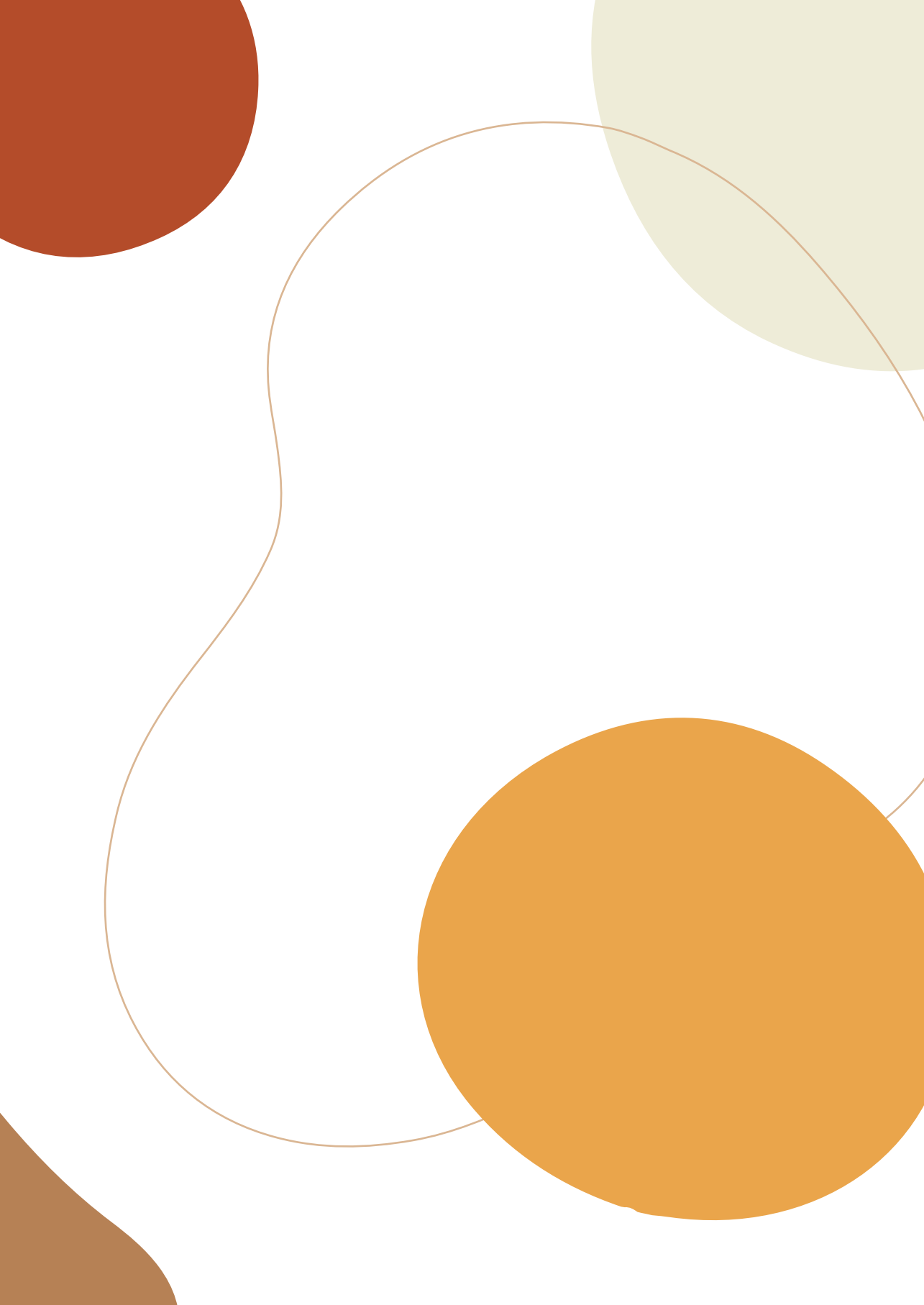
Levels are depicted per treatment group. wPCDAI scores, CRP levels and ESR levels are obtained 14 weeks after start of induction treatment. Fcal levels were obtained 10 weeks after start of induction treatment. IFX=infliximab; wPCDAI= weighted paediatric Crohn's disease activity index; Fcal=faecal calprotectin level; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate.

Supplemental Table 4: Quality of life assessment based on the IMPACT III questionnaire.

	First-line IFX (n=47)	Conventional (n=42)	P-value
Baseline QOL score, median (IQR)	59.6 (49.5-72.0) *[n=36]*	61.1 (49.5-70.9) *[n=28]*	0.660
Week 14 QOL score , median (IQR)	81.8 (70.7-86.8)* *[n=36]*	77.1 (68.6-85.7)* *[n=27]*	0.297
Week 52 QOL score, median (IQR)	80.0 (71.4-88.6)* *[n=31]*	77.5 (66.6-85.5)* *[n=28]*	0.261

The total IMPACT III score ranges from 0 to 100 with a higher score indicating a better quality of life. IFX=infliximab; QOL=quality of life.

*significantly higher compared to the score at baseline (p<0.001)



06

Vedolizumab trough levels in children with anti-tumor necrosis factor refractory inflammatory bowel disease

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ABSTRACT

Objectives: Inflammatory bowel disease (IBD) can be successfully treated with vedolizumab. Studies in adult IBD patients have shown that differences in response to vedolizumab may be related to variability in vedolizumab trough levels, but in children with pediatric-onset IBD data regarding vedolizumab trough levels are not available. Thus far, the role of trough levels in pediatric-onset IBD treatment remains unclear. We aimed to investigate predictors of vedolizumab trough levels in pediatric-onset IBD patients.

Methods: Data from anti-tumor necrosis factor refractory pediatric-onset IBD patients who received vedolizumab were collected retrospectively. Vedolizumab trough levels were measured in serum samples collected before each infusion. A linear mixed model was conducted to analyze factors that influence trough levels.

Results: Twenty-six pediatric-onset IBD patients (14 ulcerative colitis [UC], 9 Crohn's disease [CD], 3 IBD-unclassified [IBD-U]) received 258 vedolizumab infusions. Mean vedolizumab trough level at week 6 was 29.9 µg/ml (SD 17.8), and 11.5 µg/ml (SD 4.9) during maintenance therapy. CD patients had significantly lower trough levels than UC/IBD-U patients (β 15.2; 95% confidence interval [CI] –1.1 to 29.2; *P*=0.036). Higher fecal calprotectin (β -0.009; 95% CI –0.02 to –0.003; *P*=0.007) and C-reactive protein levels (β –0.4; 95% CI –0.72 to –0.04; *P*=0.027) were associated with lower trough levels, whereas shortening of time between infusions led to higher trough levels (β -0.77; 95% CI –0.9 to 0.64; *P*<0.001).

Conclusions: In this group of pediatric-onset IBD patients, trough levels were significantly lower in CD patients compared with UC/IBD-U patients. Higher levels of inflammatory markers were associated with lower vedolizumab trough levels.

INTRODUCTION

In pediatric-onset inflammatory bowel disease (PIBD) patients that do not respond to anti-tumor necrosis factor (TNF), vedolizumab (VDZ), a biological agent that is still off-label for pediatric patients, is recommended.[1] VDZ is a monoclonal antibody directed against α4β7 integrin, which is expressed on a discrete subset of memory T-helper lymphocytes involved in the intestinal inflammation that characterizes IBD.[2] Since 2014, VDZ is registered for adult IBD patients after placebo-controlled trials demonstrated its efficacy in ulcerative colitis (UC) and Crohn disease (CD) patients above 18 years.[2-5] Several cohort studies in adults have confirmed VDZ effectiveness and have shown its favorable safety profile.[6-8] Data on VDZ use in PIBD patients show that the use of VDZ is safe but that it has variable efficacy.[9-12] As the efficacy of VDZ is based on drug exposure, rather than the administrated dose, the variation in response to VDZ may be explained by differences in PIBD phenotype or disease activity affecting VDZ trough levels. VDZ drug monitoring has been described in a limited number of adult IBD patients suggesting that albumin and body weight are factors that influence VDZ trough levels.[13] A recent meta-analysis found that 54% of patients with IBD with secondary loss of response to VDZ may benefit from dose optimization.[14] The exact positioning of VDZ drug level monitoring and optimal drug levels, however, remain to be defined. Despite these findings in adults, to date, data on VDZ trough levels in children with IBD are lacking. We aimed to report VDZ trough levels over time and assess independent clinical factors that influence vedolizumab trough levels in PIBD patients.

METHODS

Study design and patient management

In this retrospective study, children and adolescents aged up to 18 years receiving VDZ therapy were studied. All patients were included in a single tertiary hospital in the Netherlands between 2015 and 2018. Patients with UC, CD or IBD unclassified (IBD-U) were eligible if they had received at least 3 intravenous infusions as induction therapy with VDZ, including those who received VDZ combined with other immunosuppressive or immunomodulatory medication. According to local guidelines, patients received VDZ infusions at week 0, 2 and 6 (induction), and every 8 weeks thereafter (maintenance). Children >40 kg received 300 mg VDZ and children <40 kg received a weight-based dose of 5 mg/kg. Most patients also received bridging therapy with oral prednisolone (1mg/kg, maximum of 40 mg) and were tapered with 5 mg per week, based on physician decision and clinical response to VDZ. If disease control during maintenance treatment was insufficient, the interval of VDZ infusions was adjusted to every 6 or 4 weeks. The need

for VDZ treatment optimization was assessed by the physician based on clinical data, laboratory results, and/or endoscopic evaluation. Before every infusion, erythrocyte sedimentation rate (ESR), albumin, C-reactive protein (CRP), hemoglobin, hematocrit, thrombocytes and leucocytes as well as fecal calprotectin levels (Calpro ELISA) were assessed. Clinical disease activity was scored at every infusion by the appropriate clinical disease activity indexes, PUCAI (Pediatric Ulcerative Colitis Activity Index)[15] or PCDAI (Pediatric Crohn disease Activity Index) .[16] Endoscopic evaluation was performed when clinically indicated, before and/or after start of VDZ treatment. Mucosal healing was defined as a Mayo endoscopic score of zero in UC and the endoscopic absence of ileal or colonic ulcerations in case of CD. Accordingly, active disease was defined as the absence of mucosal healing.

Vedolizumab trough levels

Serum samples were collected before each infusion and stored for retrospective determination of VDZ trough levels. Due to batched analysis, trough levels were not available for clinical decision-making. VDZ trough levels were determined via a quantitative ELISA assay using rabbit anti-VDZ antibodies to capture VDZ and rabbit anti-VDZ F(ab′)2 fragments, similar to the previously described method for natalizumab (Sanquin Laboratories, Amsterdam, the Netherlands).[17] The lower limit of quantification (LLOQ) in serum is 100 ng/mL; inter-assay precision and accuracy are 1 to 4% and 87 to 115%, respectively. Anti-VDZ antibodies were also measured as previously described.[17] The lower limit of detection was based on mean >3 standard deviations measured in a panel of 30 sera from healthy donors and 45 sera from IBD patients who were treatment-naïve for VDZ.

Outcome measures and definitions

Primary outcome was the identification of independent clinical factors that influence VDZ trough levels. Secondary outcomes were therapy response, mucosal healing rates, need for surgical intervention, and the occurrence of serious adverse events. Therapy response was evaluated based on clinical remission and corticosteroid-free remission (CSFR) rates. CSFR was defined as a PUCAI <10 or PCDAI <12.5, without corticosteroid treatment or the need of a surgical intervention.

Statistical analysis

Continuous variables were reported as means and standard deviations (SD) and compared by *t* test if normally distributed. Continuous variables not following a normal distribution were analyzed by the Mann-Whitney *U*-test and presented as median and interquartile range (IQR). Categorical variables were presented as absolute frequencies and percentages and compared by the X^2-test or Fisher exact test. Kaplan-Meier survival analyses were performed to evaluate duration of VDZ therapy, time to CSFR and time to

surgery. Three linear mixed models were constructed, the first to identify independent predictors at baseline, before the start of VDZ, of VDZ trough levels over time. For both models, covariates were selected based on clinical relevance and findings in studies with adult IBD patients. Fixed effects were days on VDZ, IBD diagnosis (CD or UC/IBDU), and the following parameters at start of VDZ: age, body surface area (BSA), CRP, ESR, albumin and fecal calprotectin levels. The second mixed model was constructed to identify independent predictors during the course of VDZ treatment of VDZ trough levels. Fixed effects included the following time variable covariates: days on VDZ, IBD diagnosis (CD or UC/IBDU), BSA, dose (mg/kg), interval between infusions in days, ESR, CRP, albumin and fecal calprotectin levels. Random slopes were tested, but not included because this did not significantly improve the model. The third linear mixed model was constructed to calculate mean maintenance trough levels for patients who received VDZ infusions every 4 weeks or every 8 weeks. This interval was included as fixed effect. In all 3 models, random slopes were tested but not included because this did not significantly improve the model. A P-value <0.05 was considered statistically significant and no corrections for multiple testing were performed. Calculations were performed using IBM SPSS Statistics 24.0 (IBM Corp, Armonk, NY).

RESULTS

Patient characteristics

Twenty-six PIBD patients were included at a median age of 12.7 years (IQR 10.1 – 14.5). Sixty-five percentage (n=17) of patients were diagnosed with UC/IBD-U (14 UC, 3 IBD-U) and 9 with CD (Table 1). Although UC/IBD-U patients were not significantly younger than CD patients at the start of VDZ therapy, their weight was significantly lower (49 vs 76 kg, P=0.001). All children had been previously exposed to either infliximab (85%), adalimumab (4%) or both (11%). Five out of 17 UC/IBD-U patients had a primary nonresponse to corticosteroids as well as anti-TNF. According to the local treatment protocol, oral prednisone was used as induction and bridging therapy in 18/26 patients (median duration 14 weeks; IQR 6-25). Four patients with a body weight below 40 kg (3 UC/IBD-U patients and 1 CD patient) received the nonstandard weight-based dose of 5 mg/kg, the lowest being 110 mg.

Table 1: Baseline characteristics

Characteristics		All IBD patients (n=26)	CD (n=9)	UC / IBD-U (n=17)	p-value
Gender, n (% male)		13 (50)	6 (67)	7 (41)	0.216
Ethnicity, n (% Caucasian)		9 (35)	3 (33)	6 (35)	0.920
Age at diagnosis, years (IQR)		12.7 (10.1–14.5)	14.0 (10.9-14.3)	12.2 (9.7-14.6)	0.634
Findings at start of vedolizumab therapy					
Age, years (IQR)		15.0 (12.4-16.9)	15.5 (13.0-17.1)	13.8 (12.1-16.6)	0.458
Disease duration, years (IQR)		1.7 (1.1 – 2.4)	2.2 (0.9-3.3)	1.5 (1.1-2.2)	0.396
Weight, kg (IQR)		51.3 (41.7-66.9)	76.0 (69.9-77.7)	49.0 (34.8-59.2)	**0.001**
Body surface area, m^2 (IQR)		2.3 (1.6-3.0)	2.71 (1.8-3.8)	2.2 (1.4-2.7)	0.136
PCDAI		-	27.5 (15.7-37.5)	-	
PUCAI		-	-	35.0 (20.0-52.5)	
Location CD, n (%)	*L1*	-	1 (11)	-	
	L2	-	5 (55)	-	
	L3	-	3 (33)	-	
	L4a/b	-	4 (44)	-	
Behavior CD, n (%)	*B1*	-	8 (89)	-	
	B2	-	1 (11)	-	
	B3	-	-	-	
Perianal disease, n (%)		2 (8)	2 (22)	-	
Growth delay*, n (%)		6 (23)	2 (22)	4 (24)	
Location UC/IBD-U, n (%)	*E1*	-	-	-	
	E2	-	-	6 (35)	
	E3	-	-	-	
	E4	-	-	11 (65)	
Severity UC/IBD-U, n (%)	*S0*	-	-	12	
	S1	-	-	5	
Endoscopy performed (n)		15	5	10	
	Mayo score 1 *Mayo score 2* *Mayo score 3*			1 3 6	
	Active disease†		n=4		
ESR, mm/hr. (IQR)	N=19	20 (11-28)	27 (14-37)	18 (9-21)	0.272
CRP, mg/L (IQR)	N=24	2.5 (0.3-16.3)	14.0 (0.3-26.5)	2.1 (0.3-11.0)	0.726
FCP, µg/g (IQR)	N=10	721 (553-825)	579 (NA)	721 (562-827)	0.711

Table 1: Baseline characteristics (*continued*)

Characteristics		All IBD patients (n=26)	CD (n=9)	UC / IBD-U (n=17)	p-value
Indication to start vedolizumab, n (%)	*IFX failure*	22 (85)	6 (67)	16 (94)	0.053
	Adalimumab failure	1 (4)		1 (6)	
	Failure IFX and Adalimumab	3 (11)	3 (33)		
Reason failure anti-TNF therapy, n (%)	*Low level, ADA*	3 (11)	2 (22)	1 (6)	0.809
	Adequate level, loss of response	19 (73)	5 (56)	14 (82)	
	Low level, no ADA	2 (8)	1 (11)	1 (6)	
	Side effects	2 (8)	1 (11)	1 (6)	

P-values in bold denote significance. *P*-values are calculated using a Pearson's χ^2 test for categorical variables, Mann-Whitney *U*-test for continuous variables and a Kruskal Wallis Test for ordinal variables. ADA = anti-drug antibodies; CD = Crohn disease; IBD = inflammatory bowel disease; IBD-U = IBD-unclassified; IFX = infliximab; IQR = interquartile range; NA = not available; PCDAI = pediatric Crohn Disease activity index; PUCAI = pediatric ulcerative colitis disease activity index; UC = ulcerative colitis

*Defined as a height z-score at diagnosis or subsequently significantly less than expected z-score; or current height z-score significantly less than height z-score at diagnosis (reduction in height z-score since diagnosis is >0.75)

†Defined as the presence of ileal/or colonic ulcerations

Follow-up and therapy response

Median follow-up duration of all PIBD patients in this study was 37 weeks (IQR 20-66). At week 14, 4/16 UC/IBD-U patients and none of the CD patients were in CSFR. After 22 weeks, 2/6 CD patients with available follow-up had reached CSFR (Figure 1, Supplemental Table 1, Supplemental Digital Content, *http://links.lww.com/MPG/B877*). In 8 UC/IBD-U patients and 2 CD patients, dosing interval was shortened for clinical reasons during maintenance treatment. In total, 34.6% (n=9) had to undergo surgery due to therapy failure, including 6 UC/IBD-U patients and 3 CD patients. Endoscopic evaluation was performed in 16 patients (13 UC/IBD-U, 3 CD) after a median period of 18 weeks (IQR 14-27) on VDZ therapy. Twenty-five percentage was in clinical remission at the moment of endoscopy. Mucosal healing was seen in 4/13 (31%) UC/IBD-U patients and none of the CD patients.

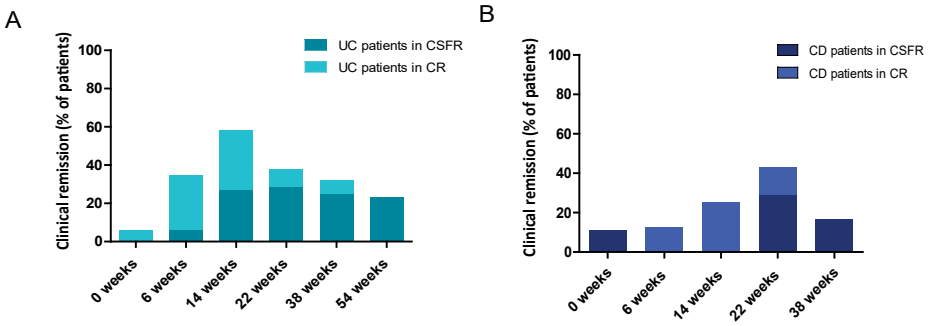

Figure 1. Clinical remission rates per time point during vedolizumab therapy. (A) Percentage of patients with UC/IBD-U in corticosteroid-free remission (CSFR) and clinical remission (CR) at different time points after start of vedolizumab therapy. (B) Percentage of Crohn's disease patients in CR and CSFR at different time points after start of vedolizumab. Percentages are based on all patients who were still receiving vedolizumab therapy or discontinued vedolizumab therapy at an earlier time point. Patients who were lost to follow-up were excluded from this group.

CD = Crohn's disease; CR = clinical remission defined as a PUCAI<10 or a PCDAI<12.5; CSFR = corticosteroid-free remission defined as clinical remission and no use of corticosteroids at that time point; IBD-U = IBD-unclassified; UC = ulcerative colitis.

Complete information on the first year of follow-up after start of VDZ was available in 19 out of 26 patients (Figure 2). At week 22, 88% of UC/IBD-U patients (n=14) and 75% (n=6) of CD patients were still using VDZ. After one year, 9 of 19 (47%) PIBD patients remained on VDZ treatment (8 UC/IBD-U, 1 CD) (Figure 2). In one CD patient, VDZ was stopped because of severe exercise intolerance and fatigue accompanied by tachycardia, which was possibly related to VDZ treatment.

Trough levels

In 22 PIBD patients, VDZ trough levels were measured during induction as well as maintenance treatment, resulting in 134 trough level measurements. During induction, mean trough levels were 32.1 µg/mL (SD 8.5) at week 2 and 29.9 µg/mL (SD 17.8) at week 6. The lowest trough levels were measured at start of maintenance treatment (week 14). Mean trough levels during both induction and maintenance therapy were numerically higher in UC/IBD-U patients than in CD patients (Figure 3A). Mean trough levels were, after correction for repeated measurements, 13.5 µg/mL in UC/IBD-U patients (SD 5.6) and 9.6 µg/mL in CD patients (SD 10.8) in patients receiving VDZ every 8 weeks. If VDZ was given every 4 weeks mean trough levels were 28.6 µg/mL in UC/IBD-U patients (SD 5.6) and 13.0 µg/mL in CD patients (SD 5.6) (Figure 3B). Antibodies to VDZ were measured in all samples, but none were positive for antibodies to VDZ.

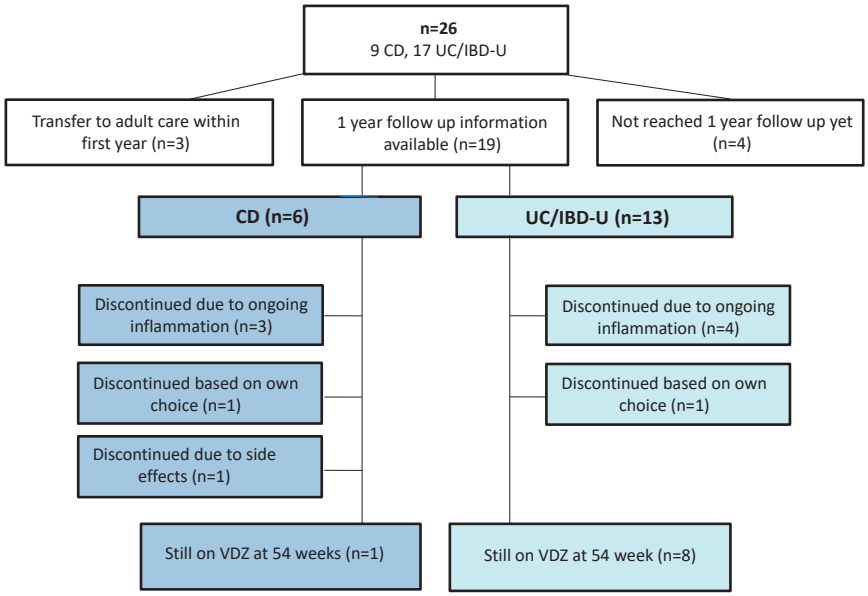

Figure 2. Flow chart of included patients. CD = Crohn disease; IBD-U = IBD-unclassified; UC = ulcerative colitis; VDZ = vedolizumab.

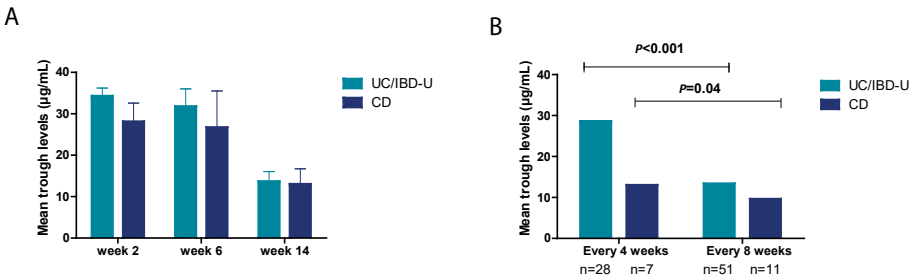

Figure 3. Mean vedolizumab trough levels. (A) Mean vedolizumab trough levels ± standard deviation (SD) per time point during induction therapy (B) Mean vedolizumab trough levels during maintenance therapy (weeks 14-176). Depicted for patients with normal dosing interval (every 8 weeks) and intensified dosing interval (every 4 weeks). The difference in trough levels following the different dosing intervals was evaluated for each diagnosis. *P* values were considered significant if <0.05.

Factors that influence vedolizumab trough levels

A multivariate analysis that assessed the association of characteristics prior to the start of VDZ with VDZ trough levels over time showed that higher BSA was associated with lower VDZ trough levels (β –12.8; 95% CI –10.7 to 4.9, *P*=0.002). With regards to laboratory measurements, a lower serum albumin before the start of VDZ was associated with lower VDZ trough levels (β 1.52, 95% CI 0.42 to 2.62, *P*=0.008), whereas CRP, ESR and fecal calprotectin before start of VDZ showed no significant association with

trough levels over time. Findings from a second multivariate analysis to assess factors during VDZ therapy associated with VDZ trough levels showed that CD patients had significantly lower trough levels than UC/IBD-U patients (β 15.2; 95% CI –1.1 to 29.2; *P*=0.036, Supplemental Table 2). Also, higher fecal calprotectin levels (β –0.009; 95% CI –0.02 to –0.003; *P*=0.007), higher CRP (β –0.4; 95% CI –0.72 to –0.04; *P*=0.027) and more days between infusions were associated with lower trough levels (β –0.77; 95% CI –0.9 to 0.64; *P*<0.001).

Trough levels as predictor of response

Mean trough levels at 14 weeks after start of VDZ were similar in patients who continued VDZ therapy at the end of follow up (as a proxy for maintenance of remission) and patients who discontinued VDZ treatment (10.5 µg/mL, SD 7.5 vs 16.3 µg/mL, SD 7.8, respectively; *P*=0.166, Supplemental Table 3, Supplemental Digital Content, *http://links.lww.com/MPGB877*). Shortening the dose interval led to increased trough levels in all patients, including those that eventually discontinued VDZ treatment (β –0.61, 95% CI –0.77 to –0.45; *P*<0.001) or were not in CSFR at week 52 (β –0.47, 95% CI –0.62 to –0.41; *P*<0.001).

DISCUSSION

In adult patients with IBD, accumulating evidence for the role of therapeutic drug monitoring in VDZ treatment is emerging. But other than for anti-TNF, findings are not straightforward and the available data is limited. Most of the currently available studies are based on data from the clinical GEMINI trials[3-5,18], and only on few real-world cohorts.[19-22] Our study, describing a real-world cohort of anti-TNF refractory PIBD patients, is the first to report VDZ trough levels in children with IBD.

The mean VDZ trough level in adult UC patients as measured by the GEMINI 1 study during induction therapy (27.9 µg/mL at week 6, n= 654, SD 15.5) was numerically lower than the mean trough level we found in our pediatric cohort of UC/IBD-U patients (31.8 µg/mL, n=12, SD 14.6).[3] Numerical differences were similar during maintenance therapy, showing levels in 77 adults that were lower (11.2 µg/mL, SD 7.2) than those of the children in our study (13.5 µg/mL, SD 5.6). This may be explained by the lower median body weight of UC/IBD-U patients in our cohort compared with the adult GEMINI study population, considering children received the standard dosing if they were >40 kg. Trough levels of CD patients in our cohort during induction were comparable with those found by Sandborn *et al*.[4] (26.8 µg/mL, SD 17.5, n=827, week 6). We, however, observed lower trough levels during maintenance therapy (13.0 ± 9.1 vs 9.6 ± 10.8 µg/mL), which

could be a result of ongoing inflammation in these patients during maintenance treatment.[20,21,23] Multivariate analysis in our cohort, taking inflammatory markers such as CRP and calprotectin into account, showed VDZ trough levels in pediatric CD patients are significantly lower than those in pediatric UC/IBD-U patients. This might be due to the transmural inflammation in CD (vs more superficial in UC), and subsequent increased disease-mediated clearance of VDZ in the affected tissue. The VDZ mechanism of action in different IBD subtypes is, however, not fully understood. Studies based on GEMINI trial data did not show a significant difference in trough levels between UC/IBD-U and CD patients.[18] In a population model, characterizing the pharmacokinetic properties of VDZ, they found a similar linear clearance for UC and CD patients.[13,17]

In our cohort, only a small number of UC patients and none of the CD patients were in CSFR 14 weeks after the start of VDZ therapy. Despite the relatively long duration of corticosteroid use, it seems that CD patients are less likely to respond to VDZ and need a longer duration on VDZ therapy in order to improve clinically. These findings are in line with findings in another PIBD cohort. They showed that after a median follow-up of 24 weeks, UC patients were more likely to be in remission (39%) than CD patients (24%).[9] The remission rates reported in adult studies are higher than the rates observed in the children in our cohort,[17,24] which may be explained by inclusion of anti-TNF refractory PIBD patients only, whereas this was not the case in the adult studies. This is supported by studies showing significantly better outcomes in anti-TNF naïve IBD patients.[25-27] Although an accelerated clearance because of immunogenicity is a frequently reported explanation for loss of response to anti-TNF, our data do not suggest that nonresponse or loss of response to VDZ can be explained by the formation of antibodies to VDZ.[28] This is consistent with studies in adults that indicate immunogenicity to occur in <5% of cases.[17,29]

Accumulating evidence of an exposure-efficacy relationship is emerging in adult IBD patients.[18-21] Ungaro et al.[23] included 258 IBD patients, and found significantly higher VDZ concentrations if patients were in clinical, biochemical and endoscopic remission. Lower trough levels could very well be a reflection of disease activity and increased clearance.[13] This is in line with findings in our cohort showing that higher CRP and fecal calprotectin levels are associated with lower trough levels. On the contrary, in another cohort of 73 IBD patients, VDZ trough levels were not associated with clinical, biological or endoscopic outcomes.[30] A systematic review and meta-analysis by Singh et al.[31] showed that in UC patients, VDZ trough levels are significantly higher in patients that are in clinical and endoscopic remission; however, for CD patients no significant differences were found. Due to the heterogeneity in the available adult studies and their findings, optimal therapeutic ranges for VDZ have not yet been determined.[32]

Our findings indicate that there is an important role for therapeutic drug monitoring of VDZ in this pediatric population that has very limited treatment options left. Following a multivariate approach to repeated measures in our cohort, we found IBD diagnosis to be a significant predictor of trough levels. The finding of CD diagnosis as an independent predictor of lower trough levels in our cohort indicates that pediatric CD patients may profit from therapeutic drug monitoring and higher dosing of VDZ. Our statistical analysis did not result in a significant difference in trough levels between patients who were in CSFR and those who were not, which is likely to be because of the number of patients included in this study.

There are limitations to this study, of which some can be addressed in future research. The most important limitation being the retrospective design of the study and the small number of included PIBD patients. A larger cohort is needed to assess the exposure-efficacy relationship, but because of the off-label use of VDZ in this pediatric population studies in a large group of PIBD patients are extremely challenging. Importantly, as we collected a large number of through levels during follow-up, the small cohort did not limit our analysis of factors that influence VDZ trough levels. A second limitation is the long duration of corticosteroid treatment as induction and bridging therapy, which may affect the interpretation of the effectiveness of VDZ therapy.

To our best knowledge, we are the first to present data on VDZ trough levels in children with IBD. We hereby show that VDZ trough levels are comparable to those in adults and provide insight in which clinical factors influence VDZ trough levels in children with IBD. A pharmacokinetic/ pharmacodynamic model in PIBD patients, including patients using lower doses of VDZ, would improve our knowledge on clearance of VDZ, as well as the relation between drug levels and response in these children. Larger prospective cohorts are needed to validate our findings and optimize dosing and treatment guidelines regarding VDZ therapy in PIBD patients.

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SUPPLEMENTARY MATERIAL

Supplemental Table 1: Remission rates per time point during vedolizumab therapy in UC/IBD-U and CD patients

UC/IBD-U	Week 0	Week 2	Week 6	Week 14	Week 22	Week 38	Week 54
All patients[†] (n)	**17**	**17**	**17**	**16**	**16**	**16**	**13**
Patients in CSFR, % (n)	0%	0% (0) [‡]	5.9% (1)	26.7% (4) [‡]	28.6% (4) [§]	25% (3) [¶]	23.1% (3)
Patients in clinical remission, % (n)	5.9% (1)	28.6% (4) [¶]	37.5% (6)	35.7% (5) [§]	35.7% (5) [§]	47.6% (4) [¶]	23.1% (3) [‡]
Using steroids, % (n)	76.5% (13)	70.6% (12)	58.8% (10)	43.8% (7)	25% (4)	19% (3)	7.7% (1)
Patients on VDZ therapy (n)	**17**	**17**	**16**	**14**	**14**	**12**	**8**

CD	Week 0	Week 2	Week 6	Week 14	Week 22	Week 38	Week 54
All patients[†] (n)	**9**	**9**	**9**	**8**	**7**	**7**	**6**
Patients in CSFR[‡], % (n)	11.1% (1)	12.5% (1) [‡]	0% (0) [‡]	0%	28.6% (2)	16.7% (1) [‡]	NA
Patients in clinical remission[§], % (n)	11.1% (1)	25% (2) [‡]	12.5% (1) [‡]	25% (2)	42.9% (3)	16.7% (1) [‡]	NA
Using steroids, % (n)	44.4% (4)	44.4% (4)	44.4% (4)	37.5% (3)	14.3% (1)	0%	0%
Patients on VDZ therapy (n)	**9**	**9**	**9**	**8**	**6**	**2**	**1**

[†]Defined as all patients who were still receiving vedolizumab therapy or discontinued vedolizumab therapy at an earlier time point. Patients who were lost to follow up were excluded from this group. Clinical remission was defined as a PUCAI<10 or a PCDAI <12.5 Corticosteroid-free remission (CSFR) was defined clinical remission and no use of corticosteroids at that time point.

[‡] One value missing

[§] Two values missing

[¶] Three or more values missing

Abbreviations: UC, ulcerative colitis; CD, IBD-U, IBD-unclassified; Crohn's disease; NA, not available

Supplemental Table 2: Linear mixed model analysis of parameters influencing vedolizumab trough levels

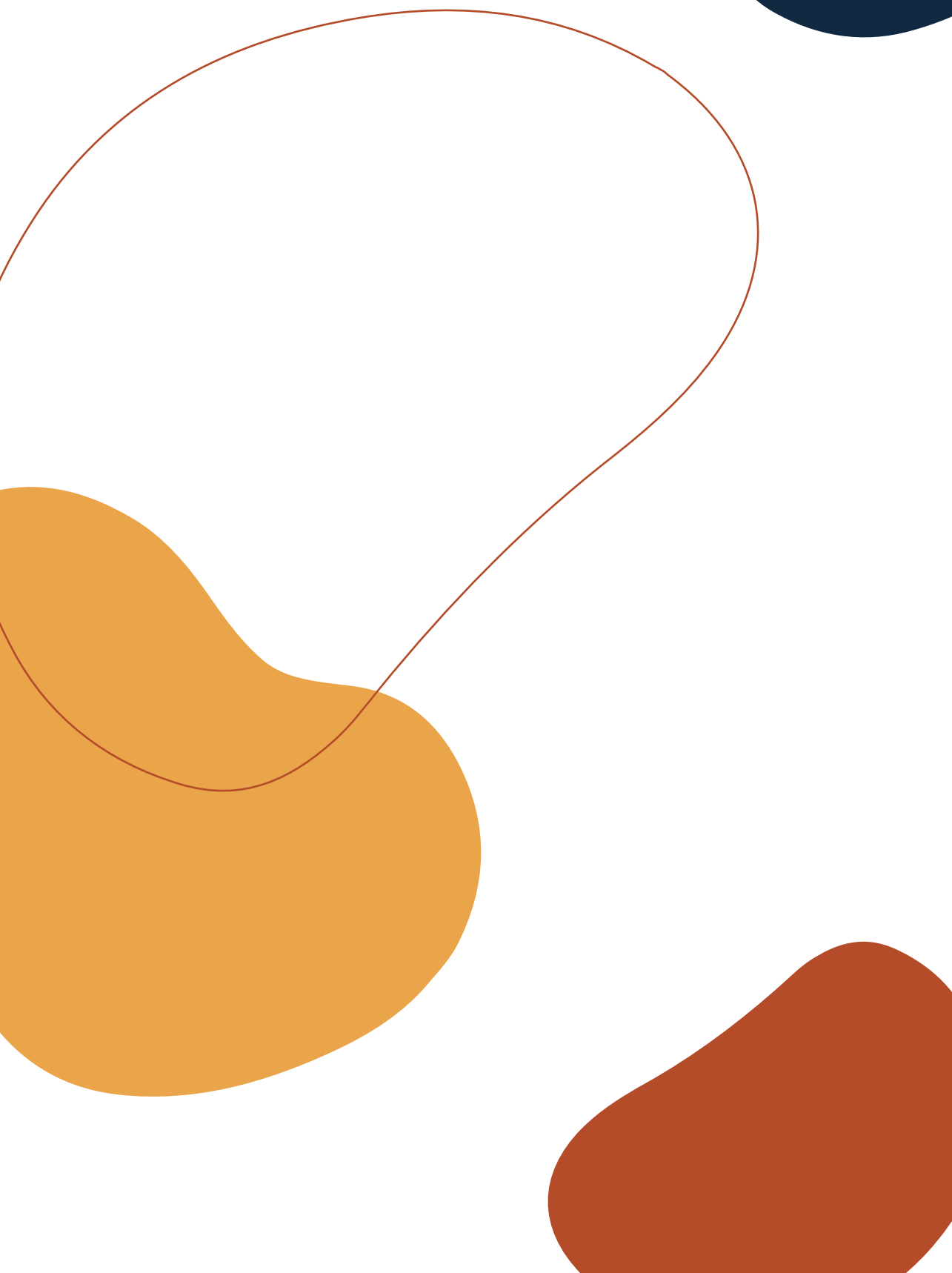
	B	P value	95%CI
Intercept	16.1	0.617	-48.5-80.1
UC/IBDU diagnosis	15.2	**0.036**	-1.1-29.2
Fcal levels	-0.009	**0.007**	-0.02- -0.003
Time	0.01	0.032	0.001-0.02
Dose (mg/kg)	0.50	0.817	-.90- -0.64
Dosing interval	-0.77	**<.001**	-0.9- -0.64
CRP	-0.4	**0.027**	-.72- -.04
BSA	-3.9	0.276	-11.2- 3.4
Albumin	0.53	0.237	-0.4-1.4
ESR	0.10	0.246	-0.7-0.025

A multivariate analysis was performed using a linear mixed model. Interval between vedolizumab doses, C-reactive protein level, fecal calprotectin level and diagnosis were considered statistically significant. Abbreviations: BSA, Body Surface Area; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Fcal, fecal calprotectin level

Supplemental Table 3: Trough levels per outcome

Outcome	Mean trough levels at week 6 (n=19), µg/ml, SD			Mean trough levels at week 14 (n=17), µg/ml, SD		
	Yes	No	p-value	Yes	No	p-value
Surgery	30.5 (19.8)	29.0 (16.0)	0.863	13.6 (7.8)	13.4 (8.6)	0.905
Treatment failure	24.8 (13.3)	34.6 (20.7)	0.241	16.3 (7.8)	10.5 (7.5)	0.166
CSFR at one year	39.1 (33.2)	28.2 (14.6)	0.343	19.8 (7.1)	12.6 (7.8)	0.238
Interval adjustment	40.5 (18.7)	22.2 (13.1)	**0.022**	10.9 (8.8)	16.5 (5.9)	0.149

Abbreviations: CSFR, corticosteroid free remission; SD, Standard Deviation.



07

Predicting outcomes in pediatric Crohn's disease for management optimization: systematic review and consensus statements from the Pediatric Inflammatory Bowel Disease-Ahead program

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ABSTRACT

Background and aims: A better understanding of prognostic factors within the heterogeneous spectrum of pediatric Crohn's disease (CD) should improve patient management and reduce complications. We aimed to identify evidence-based predictors of outcomes with the goal of optimizing individual patient management.

Methods: A survey of 202 experts in pediatric CD identified and prioritized adverse outcomes to be avoided. A systematic review of the literature with meta-analysis, when possible, was performed to identify clinical studies that investigated predictors of these outcomes. Multiple national and international face-to-face meetings were held to draft consensus statements based on the published evidence.

Results: Consensus was reached on 27 statements regarding prognostic factors for surgery, complications, chronically active pediatric CD, and hospitalization. Prognostic factors for surgery included CD diagnosis during adolescence, growth impairment, *NOD2/CARD15* polymorphisms, disease behavior, and positive anti-*Saccharomyces cerevisiae* antibody status. Isolated colonic disease was associated with fewer surgeries. Older age at presentation, small bowel disease, serology (anti-*Saccharomyces* cerevisiae antibody, antiflagellin, and OmpC), *NOD2/CARD15* polymorphisms, perianal disease, and ethnicity were risk factors for penetrating (B3) and/or stenotic disease (B2). Male sex, young age at onset, small bowel disease, more active disease, and diagnostic delay may be associated with growth impairment. Malnutrition and higher disease activity were associated with reduced bone density.

Conclusions: These evidence-based consensus statements offer insight into predictors of poor outcomes in pediatric CD and are valuable when developing treatment algorithms and planning future studies. Targeted longitudinal studies are needed to further characterize prognostic factors in pediatric CD and to evaluate the impact of treatment algorithms tailored to individual patient risk.

INTRODUCTION

Pediatric-onset Crohn's disease (CD) is heterogeneous. Beyond stricturing (B2), internal penetrating (B3) disease and need for surgery, complications in pediatric CD include perianal fistulizing disease, linear growth impairment, malnutrition, pubertal delay, and decreased bone mineral density (BMD). Early intensified treatment may reduce the development of complications[1] and thus identification of prognostic factors in pediatric CD can improve patient management.

The international pediatric inflammatory bowel disease (PIBD) Ahead program (PIBD-Ahead) aimed to identify evidence-based predictors of poor outcomes in PIBD, with the goal of optimally individualizing management based on knowledge of risk factors. The results specific to CD are reported here.

METHODS

Scope and purpose

PIBD-Ahead encompassed several stages, aiming to systematically reach international consensus on the predictors of poor outcomes in PIBD. First, a steering committee (SC), consisting of two cochairs (AMG and DT) and 15 members (the other authors), determined which undesirable outcomes were most important to predict. Pediatric gastroenterologists involved in the care of children with inflammatory bowel disease (IBD) internationally were approached through the online PIBD network (https://www.pibd-net.org/) or personal contacts to participate in a survey, wherein scale-based questions were used to determine disease outcomes, which, if preventable with biologics, would mandate early interventions.

Thereafter, a systematic review of the literature was performed to identify studies examining predictors of the chosen outcomes. Pooling of the effects between predictors and key outcomes was performed by using meta-analysis, where possible. Finally, after a series of national and international meetings with large groups of PIBD experts, consensus statements were formulated based on the evidence.

Literature inclusion criteria

We considered randomized controlled trials, prospective and retrospective cohort studies, and case-control studies that examined pediatric patients (as defined by individual studies) for inclusion in the review. Studies that reported on any patient or disease factor as a predictor of at least 1 of the outcomes of interest identified below

were eligible. Studies were excluded if they were not available in English (for feasibility reasons and given that most major journals make articles available in English), or if they were available only in abstract form given that data from abstracts and full articles can be inconsistent.

Systematic search and meta-analysis

In a face-to-face meeting in Prague (May 2017), the scope of the literature review was finalized by the SC. Databases searched included Cochrane, Embase, and PubMed from January 1992 to May 2017. Search strings and eligibility criteria were developed specifically for each database (see Supplementary Materials). Additional relevant publications were retrieved based on review of reference lists of included studies and as suggested during the national meetings through discussion with leaders in the field. Bibliographic fellows (MA, AR, EOM, and NC) reviewed all abstracts in duplicate to determine which full texts to retrieve. Full texts were also reviewed in duplicate (MA, AR, EOM, and NC). At both stages, disagreements were resolved by consensus with input from 1 of the principal investigators (AMG, DT).

Data were extracted independently and in duplicate (MA, AR, and EOM) onto standardized case report forms. Extracted data included the following: study characteristics (design, single/multicenter, number of participants), participant characteristics (IBD type, age, sex), outcome(s) and predictor(s) examined (including definitions), and follow-up duration/timing of outcome assessment. For studies included in meta-analyses, effect estimates, expressed either as 2x2 tables (number of participants with and without the predictor who experienced the outcome), odds ratio (OR) and/or hazard ratio (HR), were extracted, as well as whether the results were unadjusted or adjusted. Otherwise, studies were reviewed qualitatively for whether they showed a significant association between a predictor and outcome. Study authors were not contacted for missing data, given the large number of included studies.

Risk of bias was assessed for all studies by a single rater (MA, AR, EOM) using the Newcastle-Ottawa Scale, as appropriate for observational studies (no randomized controlled trials were identified). The Newcastle-Ottawa Scale is based on 8 factors (total score range 0–9) across 3 domains, namely selection, comparability, and outcome/exposure. We defined a high-quality study as a total score of 8–9, moderate quality as 5–7, and low quality as 0–4.

We decided *a priori* that we would attempt to meta-analyze only the most clinically pertinent and homogeneous outcomes, which, by consensus, we identified to be surgery and B2/B3 complications. Studies examining these outcomes were not pooled if

they were believed to be too clinically heterogeneous. For dichotomous outcomes, the pooled measure of treatment effect was OR and, for time-to-event outcomes, the pooled measure of treatment effect was HR, both expressed with 95% confidence intervals (CIs). Results were pooled by using random effects in all cases, because we expected at least some clinical heterogeneity among studies. This was accomplished by using inverse variance and DerSimonian and Laird methods. Statistical heterogeneity was evaluated across pooled studies using the I^2 statistic. Heterogeneity was also explored graphically by examining outliers in forest plots. ORs and HRs were considered separately and, where both were available, both were presented. Univariate and multivariable effect estimates were also generally considered separately. However, univariate and multivariable effect estimates were pooled if point estimates were similar (provided that adjustment did not substantially alter the association between predictor and outcome) or statistical heterogeneity was low (I^2 ≤40%).[2] We had planned to assess publication bias graphically using funnel plots, but this was not possible because of insufficient study numbers (<10) per outcome. Analyses were performed using R, version 4.0.0 [R Foundation for Statistical Computing, Vienna, Austria].

Consensus process

The consolidated report and draft statements were reviewed by the SC, and the validity of the statements was discussed at national face-to-face meetings organized by AbbVie in 27 countries, including Argentina, Australia, Austria, Bahrain, Belgium, Canada, Czech Republic, Denmark, France, Germany, Greece, Hungary, Ireland, Israel, Italy, the Netherlands, Qatar, Russia, Saudi Arabia, Singapore, South Africa, South Korea, Spain, Sweden, Switzerland, and the United Kingdom. Comments received during the meetings were considered by the SC during a second face-to-face meeting of the SC in September 2017 in Barcelona, Spain, where the statements were finalized.

At the final February 2018 consensus meeting in Vienna, Austria, the SC and national representatives (53 participants) voted on the statements. A statement was accepted if ≥80% of participants voted 4 (agree) or 5 (strongly agree) on a scale of 1–5 (with 1, 2, and 3 indicating strongly disagree, disagree, and uncertain, respectively). Statements not achieving agreement were further revised and subjected to repeat vote until consensus was reached for all statements. In general, soft wording, such as "may predict", has been used when only 1 positive study was available or when there was more than 1 positive study, but also with negative conflicting studies.

RESULTS

The international survey of outcome selection was completed by 202 practicing pediatric gastroenterologists from 33 countries. Based on the survey, the SC concluded that the most important undesirable outcomes to predict in CD could be categorized as disease complications (including B2 and B3 disease), intestinal resection, perianal fistulizing disease, chronically active inflammatory disease, significant growth impairment, and bone disease. B2 and B3 complications and intestinal resection were selected for meta-analysis.

The results of the search are presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) diagram in Supplementary Figure 1. A total of 101 studies were included, of which 42 were included in the quantitative meta-analysis. Study characteristics and risk of bias for studies examining predictor-outcome combinations included in meta-analyses are shown in Table 1 and 2, respectively. The equivalent data for studies examining predictor-outcome combinations not included in meta-analyses are shown in Supplementary Tables 1 and 2. All included studies were observational. Thirty-one studies were high quality, 45 were moderate quality, and 25 were low quality.

Figure 1 tabulates the final consensus statements. Table 3 presents the extracted numeric data for predictor-outcome pairs included in meta-analyses. Table 4 presents an intuitive summary of each outcome. A summary of the most pertinent literature is provided below each statement (for a full review of each predictor, see the Supplementary Materials).

Prognostic factors for surgery

Statement 1.1. Diagnosis in adolescence (>13 years of age), compared with younger age, may predict increased risk of bowel surgery within 5 years of diagnosis (94% agreement).

Thirteen studies[3-15] assessed age as a possible predictor of bowel surgery; of these 4 found older age (>13 years) to be a significant predictor of surgery.[4-7] The largest cohort with significant findings included 989 children aged 0–17 years and found an adjusted OR of 1.12 per 1-year increase in age (95% CI 1.06–1.18, *P*<.0001).[6]

Table 1. Characteristics of studies examining predictor-outcome combinations included in meta-analysis

Study	Study design	Population IBD type Age, sex	Predictors examined (definition, exposed vs unexposed)	Outcomes examined (definition)	Follow-up duration
Aloi *et al* (2013)[11]	Retrospective, single center	36 pediatric CD Mean 14.7 (±4.12) y, 67% M	Disease location ASCA+ (IgA or IgG)	B2 (early stricture within 3 months of diagnosis) Surgery Intensified treatment	Mean 2.48 (SD 4.12) y
Ammoury and Pfefferkom (2011)[20]	Retrospective, single center	81 pediatric CD Mean 11.6 (range 4–18) y, 63% M	Esophageal involvement	Surgery	Mean 3.5 y (range 6 mo–10 y)
Amre *et al* (2006)[17]	Retrospective, single center	139 pediatric CD Mean 11.2 (SD 3.4) y, 52% M	Sex Disease location (SB only, colon only, SB and LB) ASCA (IgA, IgG, positivity, and titer)	B3 (fistula or abscess) Surgery (ileocecal resection, perianal abscess drainage ± fistulectomy)	Mean 5.8 (SD 3) y
Attard *et al* (2004)[19]	Retrospective, single center	134 pediatric CD Mean 12.0 (SEM 1.2) y	Jejunoileitis	Surgery Hospitalization	N/A
Birimberg-Schwartz *et al* (2016)[33]	Retrospective, multicenter	406 pediatric IBD (mixed cohort) Mean 10.5 (SD 3.9) y, 54% M	Serology (ASCA, pANCA)	Surgery Intensified treatment (biologic or calcineurin inhibitor)	Median 2.8 (IQR 1.6-4.2) y
Chhaya *et al* (2015)[12]	Retrospective, multicenter	1595 pediatric CD	Age (0–9 vs 10–13 vs 14–16 vs 17–24 y) Sex	Surgery (resection, stricturoplasty, stoma creation)	Mean 4.3 y
Cucchiara *et al* (2007)[22]	Retrospective, multicenter	200 pediatric CD Mean 12 (SD 4) y, 58% M	Genetics (NOD2/CARD15 variant)	Surgery (resection)	Median 2.8 y (range 1 d-16.7 y)
De Greef *et al* (2013)[8]	Retrospective, multicenter	155 pediatric CD Median 12.5 (range 1.6-18) y, 55% M	Gestational age, family history of IBD, disease severity at diagnosis, disease location/behavior Height and BMI z-score at diagnosis	Height and BMI z-score over follow-up PCDAI, PGA, surgery (IBD-related), medication use	Median 2.7 (range 0.3-8.2) y
Desir *et al* (2004)[34]	Combined retrospective and prospective, single center	61 pediatric CD Mean 10.7 (3.4) y, 49% M	ASCA (IgA, IgG, positivity, and titer)	B3 (fistula or abscess) Surgery (small or large bowel) Relapse	Mean 4.9 (SD 2.1) y

Table 1. Characteristics of studies examining predictor-outcome combinations included in meta-analysis (*continued*)

Study	Study design	Population IBD type Age, sex	Predictors examined (definition, exposed vs unexposed)	Outcomes examined (definition)	Follow-up duration
Dubinsky *et al* (2006)[47]	Prospective, multicenter	167 pediatric CD Median 12 (range 1–18) y, 47% M	ASCA, OmpC, I2 and/or CBir1 Antibody sum score	B2 or B3	Median 18 (range 1–200) mo
Dubinsky *et al* (2008)[21]	Prospective, multicenter	536 pediatric CD Median 12 (range 0.6–18) y, 56% M	ASCA, OmpC, CBir1	B2 or B3 Surgery (small or large bowel resection, perianal surgery)	Median 32 mo
Eidelwein *et al* (2007)[35]	Retrospective, single center	137 pediatric CD, mixed cohort Mean 12.6 (SD 4.1) y, 47% M (Black) Mean 11.6 (SD 4.5) y, 52% M (White)	Race (Black vs White)	B2 or B3 Growth (weight- and height-for-age z-score) Medication use Surgery (colectomy, intestinal resection, ileostomy, fistulectomy)	Mean 5.3 (SD 3.0) y (Black) Mean 4.8 (SD 3.2) y (White) (Growth at 1 y)
Fabian *et al* (2017)[41]	Retrospective, single center	63 pediatric CD Median 12 (range 11–15) y, 57% M	Age (continuous)	Complications (stricture that cannot be passed or with upstream dilatation, internal fistula or abscess, perianal fistula or anti-TNFα use)	1 y
Ferraris *et al* (2006)[25]	Retrospective, multicenter	134 pediatric CD Median 12 (IQR 9.5–13) y, 51% M	Genetics (NOD2/CARD15 variant)	B2, B3 Surgery (abdominal surgery)	N/A
Gupta *et al* (2006)[6]	Retrospective, multicenter	989 pediatric CD Mean 11.5 (SD 3.8) y, 57% M	Sex, age (0–2, 3–5, 6–12, 13–17 y) Ethnicity (Caucasian, Black, Asian/Pacific Islander, Hispanic, other) Poor growth (at presentation, not further defined) Disease location, severity (PCDAI) Granuloma, serologies	Surgery (partial SB resection, partial/total colectomy)	Mean 3.6 (SD 3.1) y
Gupta *et al* (2008)[39]	Retrospective (registry), multicenter	989 pediatric CD Mean 11.5 (SD 3.8) y, 57% M	Age (6–17 vs 0–5 y) Poor growth (at presentation, not further defined)	B2, B3 (fistula, abscess), perianal fissure Medication use Growth failure (height-for-age or height velocity <5th percentile) Compression fracture or osteopenia/osteoporosis Intensified treatment	Median 2.8 y (range 1 d – 16.7 y)

Table 1. Characteristics of studies examining predictor-outcome combinations included in meta-analysis (*continued*)

Study	Study design	Population IBD type Age, sex	Predictors examined (definition, exposed vs unexposed)	Outcomes examined (definition)	Follow-up duration
Gupta *et al* (2010)[46]	Retrospective (registry), multicenter	989 pediatric CD Mean 11.5 (SD 3.8) y, 57% M	Disease location (isolated SB vs SB + colonic vs isolated colonic)	B2, B3	Median 2.8 y (range 1 d – 16.7 y) CI reported at 10 y
Henderson *et al* (2015)[7]	Retrospective, multicenter	181 CD Median 11.6 y (9.5–13.1), 57% M	Age (0–9 vs 10–16 y) CRP at diagnosis	Surgery	Median 5.2 y
Herman *et al* (2017)[51]	Retrospective, single center	209 pediatric CD Median 14.2 (IQR 12–16) y, 58% M	Perianal disease (fistulizing or non-fistulizing)	B2 or B3	Median 8.5 (IQR 5.2–11.7) y
Ideström *et al* (2005)[49]	Retrospective, single center	58 pediatric CD Median 10.9 (range 2.8–16.9) y, 62% M	Genetics (NOD2/CARD15 variant)	B2 Surgery (luminal for stricture/fistula, not perianal)	Median 4.2 (range 0.9–9.7) y
Jakobsen *et al* (2014)[30]	Case control	244 pediatric CD (mixed IBD cohort) Median 13.4 (11.6–14.0) y, 54% M	Genetics (NOD2/CARD15 variant)	Surgery	Median 4.7 y (3–7) y (entire IBD cohort)
Kugathasan *et al* (2004)[27]	Prospective, multicenter	163 pediatric CD (138 with CARD15 data) Mean 12.4 (range 3–18) y, 58% M	Genetics (NOD2/CARD15 variant)	B2, B3 Surgery (ileocolonic or ileal resection)	Mean 39 (range 6–88) mo
Kugathasan *et al* (2017)[40]	Prospective, multicenter	913 pediatric CD Median 12.3–15.6 y, 62% M	Age (continuous) Race (Black vs other) Disease location (ileal vs ileocolonic vs isolated colonic) Antimicrobial serologies Genetics (NOD2/CARD15 variant)	B2, B3	Median 40–47 mo
Lacher *et al* (2010)[28]	Prospective, multicenter	171 pediatric CD Mean 11.8 (SD 3.2) y, 67% M	Genetics (NOD2/CARD15 variant)	B2, B3 Surgery (intestinal resection)	Median 4.76 (range 0.25–13.14) y

Table 1. Characteristics of studies examining predictor-outcome combinations included in meta-analysis (*continued*)

Study	Study design	Population IBD type Age, sex	Predictors examined (definition, exposed vs unexposed)	Outcomes examined (definition)	Follow-up duration
Leonor *et al* (2007)[9]	Retrospective, single center	280 pediatric CD Median 11.9 (IQR 11.5–12.28) y, 60% M	Sex, ethnicity Disease location (small bowel disease vs ileocolon or colon)	Surgery (SB resection, subtotal/total colectomy, abscess I/D, Hartmann diversion of biopsy fistula in ano)	Median 3.27 (IQR 3.02–3.52) y
Li *et al* (2013)[45]	Retrospective, single center	107 pediatric IBD Mean 11.2 (± 4.1) y	Race (SA vs other)	B3 (fistula) Medication use	Mean 4 (± 2.9) y Min 1 y
Malmborg *et al* (2015)[42]	Retrospective, multicenter	161 pediatric CD 32% <10 y, 59% M	Age (>10 vs <10 y) Disease location (ileal or ileocolonic vs colonic)	B2 or B3 (or surgery)	Median 8.8 y
Na *et al* (2015)[50]	Retrospective, single center	65 pediatric CD Mean 8.6 ± 8.6 y, 58% M	Genetics (NOD2/CARD15 variant)	B2 or B3	N/A
Posovszky *et al* (2013)[29]	Prospective, single center	85 pediatric CD Median 22 (17–35) y group 1; 20 (15–26) y group 2, 54% M	Genetics (NOD2/CARD15 variant)	B2, B3 Surgery	Min 2 y
Rieder *et al* (2012)[32]	Prospective, single center	59 pediatric CD Mean 152 (SD 43) mo, 61% M	gASCA+	B2 or B3 (or perianal fistula) Surgery	N/A
Rinawi *et al* (2016)[44]	Retrospective, single center	174 pediatric CD 13% <10 y, 74% 10–17 y, 13% 17–18 y	Age, sex Disease location (ileal vs other), microscopic involvement, granulomas Perianal disease (tags/fissures) Growth impairment (G1 vs G0 as per Paris classification)	B2, B3 Perianal disease Disease extension	Median 16.4 (± 4.4) y Min 10 y

Table 1. Characteristics of studies examining predictor-outcome combinations included in meta-analysis (*continued*)

Study	Study design	Population IBD type Age, sex	Predictors examined (definition, exposed vs unexposed)	Outcomes examined (definition)	Follow-up duration
Rinawi *et al* (2016)[16]	Retrospective, single center	482 pediatric CD, 13.8 ±3 y	Sex Disease location (ileal, ileocolonic or colonic), disease behavior Growth impairment (G1 vs G0 as per Paris classification)	Surgery (intestinal surgery, stricturoplasty or fistulectomy)	Median 8.6 ± 6.6 y
Russell *et al* (2005)[26]	Retrospective, multicenter	167 pediatric CD Median 11.5 y, 54% M	Genetics (NOD2/CARD15 variant)	B2, B3 Surgery (any except exam under anesthesia)	2 y
Savoye *et al* (2012)[4]	Retrospective, multicenter	309 pediatric CD Median 14 (range 12–16) y, 54% M	Sex, age Disease location, behavior, perianal disease Diagnostic delay Growth delay, EIM	"Disabling" CD – growth delay (BMI, weight or height <–2 SDS), or 1 intestinal resection or 2 perianal interventions	Median 8 (range 7–12) y, min 5 y
Schaefer *et al* (2010)[5]	Prospective, multicenter	498 pediatric CD 5% 0–5y, 56% 6–12 y, 39% 13–16y, 58% M	Age, sex, ethnicity Family history of IBD Disease severity, disease behavior, distal disease (between transverse colon and rectum) vs other	Surgery (intestinal resection with anastomosis or ostomy, including subtotal/total colectomy, stricturoplasty or appendectomy)	Median 2 (95% CI 1.75–2.25) y
Shaoul *et al* (2009)[18]	Retrospective, single center	128 pediatric CD Mean 12.8 ± 3.8 y, 62% M	Age (<10, 10–12, >12 y) Genetics (NOD2/CARD15 – multiple alleles or heterozygote) Disease location Ethnicity (Sephardic vs Ashkenazi Jews)	B2, B3 Surgery	Mean 4.9 ± 3.6 y Min 2 y
Strisciuglio *et al* (2014)[23]	Retrospective, single center	74 pediatric CD Median 11 (range 0.7–17.9) y, 66% M	Genetics (NOD2/CARD15 variant)	B2, B3 Surgery Number of relapses	Min 1 y
Sun *et al* (2003)[24]	Retrospective, single center	55 pediatric CD Mean 11.2 (range 1–17.5) y	Genetics (NOD2/CARD15 variant)	B2, B3 Surgery (intestinal resection)	N/A

Table 1. Characteristics of studies examining predictor-outcome combinations included in meta-analysis (*continued*)

Study	Study design	Population IBD type Age, sex	Predictors examined (definition, exposed vs unexposed)	Outcomes examined (definition)	Follow-up duration
Sykora *et al* (2006)[43]	Prospective, multicenter	46 pediatric CD Mean 15.3 (SD 2.8) y, 54% M	Age (continuous) Disease location (isolated SB vs SB + colonic vs isolated colonic) Genetics (TNFα polymorphism)	B2, B3 (internal fistula, inflammatory mass/ abscess, perianal fistula) Surgery (luminal resection)	N/A
Tomer *et al* (2003)[48]	Retrospective, single center	101 pediatric CD Mean 11.8 (0.3–18) y, 66% M	Genetics (NOD2/CARD15 variant)	B2, B3	Mean 49 mo (range 28 d – 141 mo)
Vernier-Massouille *et al* (2008)[10]	Retrospective, multicenter	404 pediatric CD Median 14 (range 12–16) y, 54% M	Sex, age Disease location (ileal or ileocolonic vs colonic), disease behavior Perianal disease Growth delay (BMI ≤–2 SD)	Surgery (partial SB resection, partial/total colectomy)	Median 84 (range 52–124) mo
Zwintscher *et al* (2015)[14]	Retrospective (health administrative database), multicenter	7845 pediatric (<20 y) CD, mixed cohort Mean 15.6 (SD 3.9) y, 51% M	Sex, age (0–5 vs 6–10 vs 11–15 vs 16–20 y) Perianal disease (fistula, abscess, fissure)	B3 (complex fistula, entero-enteral fistula) Perianal disease Growth failure (ICD-9 code) Surgery	N/A

ASCA, anti-*Saccharomyces cerevisiae* antibodies; BMI, body mass index; CD, Crohn's disease; CI, cumulative incidence; CRP, C-reactive protein; d, days; EIM, extraintestinal manifestations; IBD, gASCA, anti-glycan ASCA; ICD-9, International Classification of Diseases, Ninth revision; I/D, incision and drainage; IQR, interquartile range; LB, large bowel; M, male; Min, minimum; mo, months; N/A, not available; pANCA, perinuclear antineutrophil cytoplasmic antibody; PCDAI, Pediatric Crohn's Disease Activity Index; PGA, Physician Global Assessment; SA, South Asian; SB, small bowel; SDS, standard deviation scores; SEM, standard error of the mean; y, year

Table 2. Risk of bias for studies examining outcomes included in meta-analysis

Study	Representativeness of exposed cohort	Representativeness of non-exposed cohort	Ascertainment of exposure	Outcome not present at start	Comparability of cohorts (up to 2 stars)	Outcome assessment	Follow-up long enough	Loss to follow-up	Overall risk of bias (number of stars)
Aloi *et al* (2013)[11]	1	1	1	0	0	1	1	1	6
Ammoury and Pfefferkom (2011)[20]	1	1	1	1	0	1	1	1	7
Amre *et al* (2006)[17]	1	1	1	1	2	1	1	1	9
Attard *et al* (2004)[19]	1	1	1	1	0	1	0	1	6
Birimberg-Schwartz *et al* (2016)[33]	1	1	1	1	1	1	1	1	8
Chhaya *et al* (2015)[12]	1	1	1	1	2	1	1	1	9
Cucchiara *et al* (2007)[58]	1	1	0	0	1	1	1	1	6
De Greef *et al* (2013)[8]	1	1	1	1	0	1	1	1	7
Desir *et al* (2004)[34]	1	1	1	1	2	1	1	1	9
Dubinsky *et al* (2006)[47]	1	1	1	1	0	1	1	1	7
Dubinsky *et al* (2008)[21]	1	1	1	1	0	1	1	1	7
Eidelwein *et al* (2007)[35]	1	1	1	1	0	1	1	1	7
Fabian *et al* (2017)[41]	1	1	1	1	2	1	0	1	8
Ferraris *et al* (2006)[25]	1	1	1	0	0	1	0	1	5
Gupta *et al* (2006)[6]	1	1	1	1	2	1	1	1	9
Gupta *et al* (2008)[39]	1	1	1	0	0	1	0	1	5
Gupta *et al* (2010)[46]	1	1	1	0	0	1	1	1	6
Henderson (2015)[7]	1	1	1	1	2	1	1	1	9
Herman *et al* (2017)[51]	1	1	1	1	0	1	1	1	7
Jakobsen *et al* (2014)[30]	1	1	1	1	2	1	1	1	9
Idesström *et al* (2005)[49]	1	1	1	0	0	1	1	1	6
Kugathasan *et al* (2004)[27]	1	1	1	0	1	1	1	1	7
Kugathasan *et al* (2017)[40]	1	1	1	1	2	1	1	1	9
Lacher *et al* (2010)[28]	1	1	1	0	0	1	1	1	7
Leonor *et al* (2007)[9]	1	1	1	1	1	1	1	0	7
Li *et al* (2013)[45]	1	1	1	1	0	0	0	1	5
Malmborg *et al* (2015)[42]	1	1	1	1	2	1	1	1	9
Na *et al* (2015)[50]	1	1	1	0	0	1	0	1	5
Posovszky *et al* (2013)[29]	1	1	1	0	0	1	1	1	6
Rieder *et al* (2012)[32]	1	1	1	0	1	1	0	1	6
Rinawi *et al* (2016, DLD)[44]	1	1	1	1	1	1	1	1	8
Rinawi *et al* (2016, IBD)[16]	1	1	1	1	2	1	1	1	9
Russell *et al* (2005)[26]	1	1	1	0	2	1	1	1	8
Savoye *et al* (2012)[4]	1	1	1	1	1	1	1	0	7
Schaefer *et al* (2010)[5]	1	1	1	1	2	1	1	0	8
Shaoul *et al* (2009)[18]	1	1	1	0	0	1	1	1	6
Strisciuglio *et al* (2014)[23]	1	1	1	0	0	1	0	1	5
Sun *et al* (2003)[24]	1	1	1	0	0	1	0	1	5
Sykora *et al* (2006)[43]	1	1	1	0	0	1	0	1	5
Tomer *et al* (2003)[48]	1	1	1	0	0	1	1	1	6
Vernier-Massouille *et al* (2008)[10]	1	1	1	1	2	1	1	1	9
Zwintscher *et al* (2015)[14]	1	1	1	0	1	0	0	1	5

Based on Newcastle-Ottawa Scale. All columns, 0 or 1 stars except comparability (0 to 2); the last column indicates the total number of stars.

Question 1: What are the prognostic factors of surgery?
Statement 1.1. Diagnosis in adolescence (>13 years of age), compared with younger age, may predict increased risk of bowel surgery within 5 years of diagnosis
Statement 1.2. Growth impairment at diagnosis predicts increased risk of bowel surgery
Statement 1.3. Disease location may predict surgery; isolated colonic disease is associated with fewer surgeries
Statement 1.4. Inconclusive evidence exists for sex as a predictor for surgery; presence of NOD2/CARD15 variants, stricturing and/or internal penetrating (B2/B3) phenotype, and positive anti-Saccharomyces cerevisiae antibodies (ASCA) status predict surgery; ethnicity and presence of granulomas at diagnosis do not predict surgery
Question 2: What are the prognostic risk factors of complications?
Stricturing (B2) and/or penetrating (B3) disease
Statement 2.1. Children who develop CD at an older age may be at increased risk of developing internal penetrating (B3) complications, but not stricturing (B2) disease
Statement 2.2. CD patients of Black ethnicity/race are more likely than White patients to develop penetrating (B3) disease
Statement 2.3. CD patients with small bowel disease (ie, L1 or L3 +/– L4b) have an increased risk of developing stricturing complications (B2) and may be at an increased risk of developing penetrating complications (B3)
Statement 2.4. Anti-microbial serologies predict progression to stricturing and/or internal penetrating complications: **Statement 2.4.1. Antimicrobial serologies predict progression to stricturing (B2) and/or internal penetrating (B3) complications: ASCA positivity predicts progression to internal penetrating (B3) complications and may predict progression to stricturing (B2) complications; a higher ASCA immunoglobulin (Ig) A titer predicts progression to penetrating (B3) complications ;** **Statement 2.4.2. Antiflagellin (CBir1) positivity predicts progression to stricturing (B2) and/or internal penetrating (B3) complications; OmpC positivity may predict progression to stricturing (B2) and/or internal penetrating (B3) complications ;** **Statement 2.4.3. Seropositivity for ≥1 microbial serologies predicts progression to stricturing (B2) and/or internal penetrating (B3) disease; a higher number of positive serologies and higher titers may confer a greater risk**
Statement 2.5. Polymorphisms in the NOD2/CARD15 gene predict ileal disease location and may predict stricturing (B2) disease, but location is inadequately controlled for
Statement 2.6. The presence of perianal disease may predict stricturing (B2) and/or internal penetrating (B3) complications
Statement 2.7. Sex, family history of IBD, disease activity at baseline, granulomas, upper GI tract involvement, presence of extraintestinal manifestations, and diagnostic delay do not predict disease location, stricturing (B2) and/or internal penetrating (B3) complications
Perianal disease
Statement 2.8. Older age at CD onset may be associated with an increased risk of developing perianal disease
Statement 2.9. Children and adolescents of Black and South Asian ethnicity with CD are at a greater risk of developing perianal disease
Statement 2.10. Bacterial serology and sex may be associated with the development of perianal disease; genetics, antineutrophil cytoplasmic antibody (ANCA) positivity, anthropometric parameters, disease location, disease behavior, extraintestinal manifestations, diagnostic delay, and disease activity do not predict the development of perianal disease
Linear growth impairment
Statement 2.11. Male sex, younger age at disease onset, and isolated small bowel disease may be associated with a greater risk of linear growth impairment
Statement 2.12. More active disease (assessed at baseline or over time) predicts linear growth impairment
Statement 2.13. Diagnostic delay is a risk factor for linear growth impairment
Statement 2.14. *NOD2/CARD15* polymorphisms may be associated with low weight, and extraintestinal manifestations may be associated with linear growth impairment; pubertal status at disease onset, family history of IBD, ethnicity, gestational age, upper GI tract involvement, oral involvement, granulomas, disease behavior, perianal disease, and presenting symptoms do not predict linear growth impairment
Bone disease
Statement 2.15. Low height, weight, and body mass index predict reduced BMD
Statement 2.16. Higher clinical disease activity (assessed by Pediatric CD Activity Index [PCDAI]) at baseline and over time may predict reduced BMD
Statement 2.17. Sex, disease location, disease behavior, extraintestinal manifestations, granulomas, and perianal disease do not predict BMD
Question 3: What are the prognostic risk factors of chronically active inflammatory disease?
Chronically active inflammatory disease
Statement 3.1. ASCA positivity may predict the need for more intensive therapy
Statement 3.2. Microscopic ileocolonic involvement at diagnosis may be associated with subsequent macroscopic ileocolonic disease
Statement 3.3. Disease activity and disease behavior (ie, B2 and/or B3), but not age and sex, may predict more intensive therapies or a poor response to therapies; there is no strong evidence for a predictive value of ethnicity
Statement 3.4. No strong evidence exists to identify predictive factors of future disease activity or disease severity
Statement 3.5. No strong evidence exists for predictors of disease relapse and the number of relapses
Statement 3.6. Stricturing and/or internal penetrating (B2/B3) phenotype and the presence of granulomas and increased visceral adipose tissue may predict hospitalizations; small bowel involvement, TNF polymorphisms, NOD2 variants, and age do not predict hospitalization

Figure 1. Summary of Consensus Recommendations for the Management of Inflammatory Disease

Table 3. Findings from individual studies examining predictor-outcome combinations included in meta-analysis

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect		Unadjusted relative effect			Adjusted relative effect		
				Events/ exposed	Events/ unexposed	OR (95% CI)	HR (95% CI)	p-value	OR (95% CI)[1]	HR (95% CI)	p-value
Growth impairment as a predictor of surgery											
Gupta *et al* (2006)[6]	Surgery	Growth impairment (not further defined)	128/956				1.99 (1.18–3.37)	**0.01**		2.16 (1.24–3.77)	**0.007**
*De Greef *et al* (2013)[8]	Surgery	Height- and BMI-for-age z-score at diagnosis	17/155					NS			
Rinawi *et al* (2016)[16]	Surgery	Growth impairment (as per Paris classification)	143/482	42/107	101/375		1.6 (1.1–2.3)	**0.011**			NS
*Savoye *et al* (2012)[4]	Surgery (composite outcome)	Growth delay BMI, weight or height <–2 SDS	47/309					**<0.05**			
*Zwintscher (2015)[14]	Surgery	Growth impairment (as per ICD-9)	2,113/ 12,465						1.21 (0.86–1.71)		0.279
Disease location as a predictor of surgery											
*Ammoury and Pfefferkom (2011)[20]	Surgery	Esophageal involvement	9/81					0.09			
Amre *et al* (2006)[17]	Surgery	Colon only vs other	35/139	4/32	31/107			0.07			
*Attard *et al* (2004)[19]	Surgery	Jejunum or proximal ileum	/134	11/23	12/111	3.7		**<0.03**			
*De Greef *et al* (2013)[8]	Surgery	Disease location	17/155					NS			
Gupta *et al* (2006)[6]	Surgery	L2 (colonic) vs L1 (isolated ileal)	/600	/144	/456		0.56 (0.27–1.16)	0.12			
*Leonor *et al* (2007)[9]	Surgery	Disease location	55/280					NS			
*Henderson *et al* (2015)[7]	Surgery	Disease location	/465					NS			
Rinawi *et al* (2016)[16]	Surgery	Colon only vs other for proportions (2x2); L2 vs L1 for HR	143/482	7/58	136/424			**0.003**		0.70 (0.51–0.96)	**0.03**

Table 3. Findings from individual studies examining predictor-outcome combinations included in meta-analysis (*continued*)

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect		Unadjusted relative effect			Adjusted relative effect		
				Events/ exposed	Events/ unexposed	OR (95% CI)	HR (95% CI)	p-value	OR (95% CI)[1]	HR (95% CI)	p-value
Schaefer *et al* (2010)[5]	Surgery	Transverse colon to rectum vs other	57/854	/674	/180					0.35 (0.19–0.64)	**0.0007**
*Savoye *et al* (2012)[4]	Surgery (composite outcome)	UGI disease	47/309					NS			
*Shaoul *et al* (2009)[18]	Surgery	(Ileo)colonic disease	38/128					**<0.04**			
Vernier-Massouille *et al* (2008)[10]	Surgery	L2 vs L1	176/353				0.60 (0.33-1.10)	0.1			
Sex as a predictor of surgery											
Aloi *et al* (2013)[11]	Surgery	Male vs female	4/36	3/25	1/11			NS			
Amre *et al* (2006)[17]	Surgery	Male vs female	35/139	15/72	20/67			NS			
Chhaya *et al* (2015)[12]	Surgery	Male vs female	/1,595				0.90 (0.69–1.17)	0.43			
Dubinsky *et al* (2008)[21]	Surgery	Male vs female	140/796							0.59 (0.38–0.91)	**<0.009**
Gupta *et al* (2006)[6]	Surgery	Male vs female	128/989	63/566	65/423			NS		0.65 (0.46–0.93)	**0.02**
Leonor *et al* (2007)[9]	Surgery	Male vs female	55/280	35/167	20/113			NS			
Rinawi *et al* (2016)[16]	Surgery	Male vs female	143/482	86/280	57/202		1.05 (0.75–1.47)	0.78		0.98 (0.68–1.41)	0.92
Schaefer *et al* (2010)[5]	Surgery	Male vs female	57/854	36/498	21/356			NS			
Vernier-Massouille *et al* (2008)[10]	Surgery	Male vs female	/394				0.96 (0.71–1.30)	0.77			NS
*Zwintscher *et al* (2015)[14]	Surgery	Male vs female	2,113/ 12,465						1.17 (1.06–1.30)		**0.001**

Table 3. Findings from individual studies examining predictor-outcome combinations included in meta-analysis (*continued*)

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect		Unadjusted relative effect			Adjusted relative effect		
				Events/ exposed	Events/ unexposed	OR (95% CI)	HR (95% CI)	p-value	OR (95% CI)[1]	HR (95% CI)	p-value
NOD2/CARD15 polymorphisms as a predictor of surgery											
Cucchiara *et al* (2007)[58]	Surgery	NOD2/CARD15 variant	50/196	23/75	27/121			NS			
*Dubinsky *et al* (2008)[21]	Surgery	NOD2/CARD15 variant						NS			
Ferraris *et al* (2006)[25]	Surgery	NOD2/CARD15 variant	12/134	4/50	8/84	0.83 (0.24–2.90)		1			
*Jakobsen *et al* (2014)[30]	Surgery	Genetic variants including NOD2/CARD15 variant	/244					NS			
Kugathasan *et al* (2004)[27]	Surgery	NOD2/CARD15 variant	/163							7.78 (2.74–22.1)	**<0.0005**
Lacher *et al* (2010)[28]	Surgery	NOD2/CARD15 variant	32/171	21/78	11/93	2.75 (1.23–6.14)		**0.017**			
*Posovsky *et al* (2013)[29]	Surgery	NOD2/CARD15 variant	/85	/37	/48			NS			
Russell *et al* (2005)[26]	Surgery	NOD2/CARD15 variant	45/167	18/33		4.45 (1.98–10.00)		**0.0002**			
*Shaoul *et al* (2009)[18]	Surgery	NOD2/CARD15 variant	38/128	/48	/77			NS			
Strisciuglio *et al* (2014)[23]	Surgery	NOD2/CARD 15 variant	10/74	2/16	8/58			0.89			
Sun *et al* (2003)[24]	Surgery	NOD2/CARD15 variant	17/55	13/36	4/19			0.26			
Stricturing disease (B2) as a predictor of surgery											
De Greef *et al* (2013)[8]	Surgery	B2	20/155			6.8 (1.8–25.3)	**0.001**				
Schaefer *et al* (2010)[5]	Surgery	B2	57/854							6.60 (3.39–12.86)	**<0.0001**
Vernier-Massouille *et al* (2008)[10]	Surgery	B2	176/394	/96						2.54 (1.59–4.05)	**<0.01**

Table 3. Findings from individual studies examining predictor-outcome combinations included in meta-analysis (*continued*)

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect		Unadjusted relative effect			Adjusted relative effect		
				Events/ exposed	Events/ unexposed	OR (95% CI)	HR (95% CI)	p-value	OR (95% CI)[1]	HR (95% CI)	p-value
Internal penetrating disease (B3) as a predictor of surgery											
Schaefer *et al* (2010)[5]	Surgery	B3	57/854							3.70 (1.80–7.60)	**0.0005**
Vernier-Massouille *et al* (2008)[10]	Surgery	B3	176/394	/11						1.28 (0.33–4.89)	0.72
Stricturing and/or internal penetrating disease (B2/B3) as a predictor of surgery											
Rinawi *et al* (2016)[16]	Surgery	B2 and/or B3	143/482	51/115	92/367	2.38 (1.54–3.69)				2.44 (1.69–3.53)	**<0.001**
Antimicrobial serologies as a predictor of surgery											
Amre *et al* (2006)[17]	Surgery	ASCA+ (IgA or IgG)	35/139	24/75	11/64			0.05		1.80 (0.84–3.85)	**<0.05**
*Birimberg-Schwartz *et al (2016)*[33]	Surgery	pANCA-/ASCA+	6/146					0.326			
*Desir *et al* (2004)[34]	Surgery	ASCA IgG	/154			2.34 (0.29–18.5)					
Dubinsky *et al* (2008)[21]	Surgery	ASCA+	61/563			2.2 (1.5–3.2)		**0.0001**		3.2 (1.1–9.5)	**<0.04**
Gupta *et al* (2006)[6]	Surgery	ASCA+	/161	7/63	/98		3.43 (1.00–11.76	0.05			
Rieder *et al* 2012)[32]	Surgery	gASCA+	20/59		/22				1.4 (0.4–5.0)[2] 1.9 (0.55–6.4)[3] 2.5 (0.64–9.4)[4]		0.59 0.32 0.19
Rinawi *et al* (2016)[44]	Surgery	ASCA+	94/170	25/32	69/138		3.10 (1.34–7.19)	**0.008**			NS

Table 3. Findings from individual studies examining predictor-outcome combinations included in meta-analysis (*continued*)

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect		Unadjusted relative effect			Adjusted relative effect		
				Events/ exposed	Events/ unexposed	OR (95% CI)	HR (95% CI)	p-value	OR (95% CI)[1]	HR (95% CI)	p-value
Russell *et al* (2009)[31]	Surgery	ASCA+	49/197	27/82	22/115	2.11 (1.10–4.06)		**0.03**			
Age as a predictor of stricturing (B2) disease											
*Gupta *et al* (2008)[39]	B2	Age (6–17 vs 0–5 y)	/989	/857	/83		2.15 (0.99–4.69)	0.05			
*Kugathasan *et al* (2017)[40]	B2	Age (continuous)	54/913							1.07 (0.97–1.17)	0.16
*Shaoul *et al* (2009)[18]	B2	Age (<10, 10–12, >12 y)	20/128					NS			
Race as a predictor of stricturing (B2) disease											
*Kugathasan *et al* (2017)[40]	B2	Black vs other	54/913	9/121	45/792			0.45		1.08 (0.52–2.22)	0.84
Disease location as a predictor of stricturing (B2) disease											
*Aloi *et al* (2013)[11]	B2	Disease location	/36					NS			
Gupta *et al* (2010)[46]	B2	Ileal or ileocolonic vs colon only	/600	103/456	16/144		CI at 10 y 39.3 (14.1–80.6) (ileal) vs 18.7 (13.1–26.3) (ileocolonic) vs 11.4 (4.9–25) (colon only)	**0.02**			
Kugathasan *et al* (2017)[40]	B2	Ileal or ileocolonic vs colon only for proportions; isolated ileal vs other for HR	54/913	44/690	10/223			0.30		1.60 (0.88–2.91)	0.12
Antimicrobial serologies as a predictor of stricturing (B2) disease											
*Aloi *et al* (2013)[11]	B2	ASCA+ (IgA or IgG)	/36					NS			

Table 3. Findings from individual studies examining predictor-outcome combinations included in meta-analysis (*continued*)

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect		Unadjusted relative effect			Adjusted relative effect		
				Events/ exposed	Events/ unexposed	OR (95% CI)	HR (95% CI)	p-value	OR (95% CI)[1]	HR (95% CI)	p-value
*Kugathasan *et al* (2017)[40]	B2	ASCA IgA+	54/913	22/218	32/695			**0.003**		1.69 (0.94–3.07)	0.0816
*Kugathasan *et al* (2017)[40]	B2	CBir1+	54/913	32/341	22/572			**<0.001**		2.30 (1.26–4.20)	**0.007**
NOD2/CARD15 polymorphisms as a predictor of stricturing (B2) disease											
Ferraris *et al* (2006)[25]	B2	NOD2/CARD15 variant	22/134	8/50	14/84	1.03 (0.39–2.69)		0.95			
*Ideström *et al* (2005)[49]	B2	NOD2/CARD15 variant	7/58	/5	/53			NS			
Kugathasan *et al* (2004)[27]	B2	NOD2/CARD15 variant	25/138	20/58	5/80			**0.0001**	7.9 (2.94–25.21)[4]		**0.0001**
*Kugathasan *et al* (2017)[40]	B2	NOD2/CARD15 variant	54/913					0.14			
Lacher *et al* (2010)[28]	B2	NOD2/CARD15 variant	29/171	23/78	6/93	6.06 (2.32–15.83)		**<0.0001**			
*Na *et al* (2015)[50]	B2	NOD2/CARD15 variant						NS			
Posovszky *et al* (2013)[29]	B2	NOD2/CARD15 variant	21/85	15/37	6/48			**0.005**			
Russell *et al* (2005)[26]	B2	NOD2/CARD15 variant	7/167	3/33	4/134			0.14			
Shaoul *et al* (2009)[18]	B2	NOD2/CARD15 (multiple alleles or heterozygote, any variant)	20/125	8/48	12/77			0.87			
Strisciuglio *et al* (2014)[23]	B2	NOD2/CARD15 variant	8/74	5/16	3/58			**0.01**			
Sun *et al* (2003)[24]	B2	NOD2/CARD15 variant	24/55	18/36	6/19	2.17 (0.67–6.96)		0.4			
Tomer *et al* (2003)[48]	B2	NOD2/CARD15 variant	2/101	1/29	1/72			**0.5**			

Table 3. Findings from individual studies examining predictor-outcome combinations included in meta-analysis (*continued*)

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect		Unadjusted relative effect			Adjusted relative effect		
				Events/ exposed	Events/ unexposed	OR (95% CI)	HR (95% CI)	p-value	OR (95% CI)[1]	HR (95% CI)	p-value
Age as a predictor of internal penetrating (B3) disease											
*Gupta *et al* (2008)[39]	B3 (fistula)	Age (6–17 vs 0–5 y)	/989	/857	/83		2.67 (1.15–6.15)	**0.02**			
*Gupta *et al* (2008)[39]	B3 (abscess)	Age (6–17 vs 0–5 y)	/989	/857	/83		7.66 (2.36–24.9)	**0.001**			
*Kugathasan *et al* (2017)[40]	B3	Age (continuous)	24/913							1.45 (1.17–1.80)	**0.0008**
*Shaoul *et al* (2009)[18]	B3	Age (<10, 10–12, >12)	8/128					NS			
*Zwintscher *et al* (2015)[14]	B3 (complex fistula)	Age (0–5 vs 6–10 vs 11–15 vs 16-–20 y)	98/7,845								0.994
*Zwintscher *et al* (2015)[14]	B3 (entero-enteral fistula)	Age (0–5 vs 6–10 vs 11–15 vs 16–20 y)	293/ 7,845								0.994
Race as a predictor of internal penetrating (B3) disease											
Kugathasan *et al* (2017)[40]	B3	Black vs White	24/913	9/121	15/792			**0.001**		3.19 (1.39–7.31)	**0.0061**
Li *et al* (2013)[45]	B3	SA vs White	15/107	3/13	12/94		CI 15.4 (4.1–4.8) vs 4.4 (1.7–11.4)	**0.02**			
Disease location as a predictor of internal penetrating (B3) disease											
*Gupta *et al* (2010)[46]	B3	Ileal or ileocolonic vs colon only	/600	/456	/144			0.13			
*Kugathasan *et al* (2017)[40]	B3	Ileal or ileocolonic vs colon only for proportions; isolated ileal vs other for HR	24/913	21/690	3/223			0.18		1.23 (0.51–2.95)	0.64

Table 3. Findings from individual studies examining predictor-outcome combinations included in meta-analysis (*continued*)

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect		Unadjusted relative effect			Adjusted relative effect		
				Events/ exposed	Events/ unexposed	OR (95% CI)	HR (95% CI)	p-value	OR (95% CI)[1]	HR (95% CI)	p-value
Antimicrobial serologies as a predictor of internal penetrating (B3) disease											
Amre *et al* (2006)[17]	B3	ASCA IgA+	31/139	23/67	8/72			**0.002**		2.84 (1.20–6.72)	**<0.05**
*Desir *et al* (2004)[34]	B3	ASCA IgA+	13/61						0.51 (0.08–3.08)		NS
Kugathasan *et al* (2017)[40]	B3	ASCA IgA+	24/913	14/218	10/695			**0.0002**		2.68 (1.19–6.04)	**0.0171**
*Amre *et al* (2006)[17]	B3	ASCA IgA titer	31/139							1.20 (1.08–1.34)	**<0.005**
*Desir *et al* (2004)[34]	B3	ASCA IgA titer	13/61						1.04 (0.29–3.76)		NS
Amre *et al* (2006)[17]	B3	ASCA IgG+	31/139	17/59	14/80			0.12		2.38 (1.09–5.17)	**<0.05**
Desir *et al* (2004)[34]	B3	ASCA IgG+	13/61						0.72 (0.14–4.22)		NS
*Amre *et al* (2006)[17]	B3	ASCA IgG titer	31/139							1.12 (0.99–1.28)	NS
*Desir *et al* (2004)[34]	B3	ASCA IgG titer	13/61						0.91 (0.29–2.75)		NS
*Amre *et al* (2006)[17]	B3	ASCA IgA+ or IgG+	31/139	23/75	8/64			**0.01**		2.33 (0.99–5.50)	NS
*Kugathasan *et al* (2017)[40]	B3	CBir1+	24/913	16/341	8/572			**0.005**		3.01 (1.31–6.93)	**0.0097**

Table 3. Findings from individual studies examining predictor-outcome combinations included in meta-analysis (*continued*)

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect		Unadjusted relative effect			Adjusted relative effect		
				Events/ exposed	Events/ unexposed	OR (95% CI)	HR (95% CI)	p-value	OR (95% CI)[1]	HR (95% CI)	p-value
Perianal disease as a predictor of internal penetrating (B3) disease											
*Zwintscher *et al* (2015)[14]	B3 (complex fistula)	Perianal disease (abscess, fissure, fistula)	98/7,845						3.50 (1.98–6.20)		**<0.001**
*Zwintscher *et al* (2015)[14]	B3 (entero-enteral fistula)	Perianal disease (abscess, fissure, fistula)	293/ 7,845						0.30 (0.15–0.63)		**0.001**
NOD2/CARD15 polymorphisms as a predictor of internal penetrating (B3) disease											
Ferraris *et al* (2006)[25]	B3	NOD2/CARD15 variant	14/134	7/50	7/84	1.8 (0.58–5.55)		0.3			
Kugathasan *et al* (2004)[27]	B3	NOD2/CARD15 variant	24/138	8/58	16/80			0.34	0.64 (0.24–1.58)[4]		0.345
*Kugathasan *et al* (2017)[40]	B3	NOD2/CARD15 variant	54/913					0.39			
Lacher *et al* (2010)[28]	B3	NOD2/CARD15 variant	2/171	2/78	0/93			0.24			
*Na *et al* (2015)[50]	B3	NOD2/CARD15 variant						NS			
Posovszky *et al* (2013)[29]	B3	NOD2/CARD15 variant	21/85	6/37	3/48			0.16			
Russell *et al* (2005)[26]	B3	NOD2/CARD15 variant	24/167	7/33	17/134			0.22			
Shaoul *et al* (2009)[18]	B3	NOD2/CARD15 (multiple alleles or heterozygote, any variant)	8/125	5/48	3/77			0.16			
Strisciuglio *et al* (2014)[23]	B3	NOD2/CARD15 variant	4/74	4/16	0/58			**0.01**			
Sun *et al* (2003)[24]	B3	NOD2/CARD15 variant	12/55	7/36	5/19	0.68 (0.18–2.51)		0.82			
Tomer *et al* (2003)[48]	B3	NOD2/CARD15 variant	19/101	3/29	16/72			0.18			

Table 3. Findings from individual studies examining predictor-outcome combinations included in meta-analysis (*continued*)

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect		Unadjusted relative effect			Adjusted relative effect		
				Events/ exposed	Events/ unexposed	OR (95% CI)	HR (95% CI)	p-value	OR (95% CI)[1]	HR (95% CI)	p-value
Age as a predictor of stricturing and/or internal penetrating (B2/B3) disease											
*Fabian *et al* (2017)[41]	B2 or B3 (or perianal fistula or anti-TNF)	Age (continuous)	19/63						RR 0.95 (0.85–1.05)		0.29
*Malmborg *et al* (2015)[42]	B2 or B3 (or anti-TNF use)	Age (>10 vs <10 y)	/161	/51	/110		1.81 (0.83–3.99)	0.14		1.00 (0.35–2.85)	0.99
*Rinawi *et al* (2016)[44]	B2 or B3	Age (continuous)	80/174				1.02	0.47			NS
*Sykora *et al* (2006)[43]	B2 or B3 (or perianal fistula)	Age	16/46					NS			
Race as a predictor of stricturing and/or internal penetrating (B2/B3) disease											
*Eidelwein *et al* (2007)[35]	B2 or B3	Race (Black vs White)	21/137	10/34	11/103			**0.01**			
Disease location as a predictor of stricturing and/or internal penetrating (B2/B3) disease											
Gupta *et al* (2010)[46]	B2 or B3	Ileal or ileocolonic vs colon only	/600	207/456	32/144		CI at 10 y 57.7 (33.5–83.6) (ileal) vs 42.5 (32.9–53.7) (ileocolonic) vs 22.4 (14.4–33.8) (colon only)	**0.0009**			
*Malmborg *et al* (2015)[42]	B2 or B3 (or anti-TNF use)	Ileal or ileocolonic vs colon only	/161	/130	/31		1.38 (0.63–3.03)	0.44			
Rinawi *et al* (2016)[44]	B2 or B3	Ileal or ileocolonic vs other for proportions; isolated ileal vs other for HR	80/173	63/127	17/46		1	0.52			

Table 3. Findings from individual studies examining predictor-outcome combinations included in meta-analysis (*continued*)

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect		Unadjusted relative effect			Adjusted relative effect		
				Events/ exposed	Events/ unexposed	OR (95% CI)	HR (95% CI)	p-value	OR (95% CI)[1]	HR (95% CI)	p-value
Sykora *et al* (2006)[43]	B2 or B3 (or perianal fistula)	Isolated SB or SB + colonic vs colon only	16/46	14/41	2/5			0.80			
Antimicrobial serologies as a predictor of stricturing and/or internal penetrating (B2/B3) disease											
Dubinsky *et al* (2006)[47]	B2 or B3	Seropositive (ASCA, OmpC, I2 and/or CBir1+)	10/167	8/97	2/70			**0.03** (log-rank)			
Dubinsky *et al* (2008)[21]	B2 or B3	Seropositive (ASCA, OmpC and/or CBir1+)	37/536	32/363	5/173			**0.01**			
*Dubinsky *et al* (2008)[21]	B2 or B3	Antibody sum score (1–3 for each positive antibody vs 0)	37/536				1.1 (0.3–3.7) 5.5 (2.0–15.2) 6.0 (1.7–20.5)	NS **0.005** **<0.005**			
*Dubinsky *et al* (2008)[21]	B2 or B3	ASCA+	37/536					NS			
*Dubinsky *et al* (2008)[21]	B2 or B3	OmpC+	37/536				2.4 (1.2–4.9)	**0.01**			
*Dubinsky *et al* (2008)[21]	B2 or B3	CBir1+	37/536				2.5 (1.2–5.2)	**<0.02**			
*Rieder *et al* (2012)[32]	B2 or B3 (or perianal fistula)	gASCA+	/59	/37	/22				7.4 (1.4–38.2)[2] 3.9 (1.08–13.8)[3] 2.5 (0.68–9.0)[4]	**0.016** **0.038** 0.17	

Table 3. Findings from individual studies examining predictor-outcome combinations included in meta-analysis (*continued*)

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect		Unadjusted relative effect			Adjusted relative effect		
				Events/ exposed	Events/ unexposed	OR (95% CI)	HR (95% CI)	p-value	OR (95% CI)[1]	HR (95% CI)	p-value
Perianal disease as a predictor of stricturing and/or internal penetrating (B2/B3) disease											
Herman *et al* (2017)[51]	B2 or B3	Perianal disease (fistulizing or non-fistulizing)	29/209	18/71	11/138			**0.001**			
Rinawi *et al* (2016)[44]	B2 or B3	Perianal disease (tags/fissures)	80/174	10/22	70/152		0.97	0.92			

*Denotes specific predictor-outcome pairs that could not be meta-analyzed due to heterogeneity or insufficient data, including lack of CD-specific data. *P* values in **bold** indicate significance. ASCA, anti-*Saccharomyces cerevisiae* antibodies; BMI, body mass index; CI, cumulative incidence; gASCA, anti-glycan ASCA; HR, hazard ratio; ICD-9, International Classification of Diseases, Ninth revision; NS, not significant; OR, odds ratio; pANCA, perinuclear antineutrophil cytoplasmic antibody; RR, relative risk; SA, South Asian; SB, small bowel; SDS, standard deviation scores; TNF, tumor necrosis factor; UGI, upper gastrointestinal

[1] Unless otherwise stated to be RR

[2] Adjusted for disease location

[3] Adjusted for disease duration

[4] Adjusted for age

Table 4. Summary of outcomes and respective predictors in pediatric CD

Outcomes	Predictors	Possible predictors	No association
Surgery	• Growth impairment • Presence of genetic variants • ASCA (+)	• Adolescent diagnosis • Disease location	• Ethnicity • Presence of granulomas • Sex
Stricturing (B2)/ Penetrating (B3) disease	• Ethnicity (B3) • Isolated small bowel disease (B2) • ASCA (+) and higher ASCA IgA titer (B3) • CBir1 (+) (B2/B3) • ≥1 microbial seropositivity (B2/B3) • *NOD2/CARD15* polymorphisms (B2)	• Older age at diagnosis (B3) • Isolated small bowel disease (B3) • Perianal disease (B2/B3)	• Older age at diagnosis (B2) • ASCA-IgA (B2) • Sex (B2/B3) • Family history of IBD (B2/B3) • Disease activity at baseline (B2/B3) • Granulomas (B2/B3) • Upper GI tract involvement (B2/B3) • EIM (B2/B3) • Diagnostic delay (B2/B3)
Perianal disease	• Ethnicity	• Older age at CD onset • Bacterial serology • Sex	• Genetics • ANCA (+) • Anthropometric parameters • Disease location • Disease behavior • EIM • Diagnostic delay • Disease activity
Linear growth impairment	• More active disease at baseline or over time • Diagnostic delay	• Male sex • Younger age at CD onset • Isolated small bowel disease • *NOD2/CARD15* polymorphisms • EIM	• Pubertal status • Family history of IBD • Ethnicity • Gestational age • Upper GI tract involvement • Oral involvement • Granulomas • Disease behavior • Perianal disease • Presenting symptoms
Bone disease	• Poor nutritional status (via height, weight, BMI)	• Higher clinical disease activity (PCDAI at baseline and over time)	• Sex • Disease location • Disease behavior • EIM • Granulomas • Perianal disease
Chronically active inflammatory disease		• ASCA positivity • Microscopic ileocolonic involvement • Disease activity • Disease behavior (B2/B3)	• Age • Sex • Ethnicity

Table 4. Summary of outcomes and respective predictors in pediatric CD (*continued*)

Outcomes	Predictors	Possible predictors	No association
Hospitalization		• Disease behavior (B2/B3) • Granulomas • Increased visceral adipose tissue	• Age • Small bowel involvement • *TNF* polymorphisms • *NOD2* variants
Future disease activity or severity	N/A		
Number of relapses	N/A		

ANCA, anti-neutrophil cytoplasmic antibody; ASCA, anti-*Saccharomyces cerevisiae* antibodies; B2, stricturing disease; B3, penetrating disease; BMI, body mass index; CD, Crohn's disease; EIM, extraintestinal manifestations; GI, gastrointestinal; IBD, inflammatory bowel disease; Ig, immunoglobin; N/A, not available; PCDAI, Pediatric Crohn's Disease Activity Index; TNF, tumor necrosis factor.

Statement 1.2. Growth impairment at diagnosis predicts increased risk of bowel surgery (81% agreement).

Five studies evaluated the association of growth impairment with the risk of bowel surgery, of which 3 showed a significant association.[4, 6, 8, 14, 16] Two meta-analyzable studies showed a 1.72-fold higher risk for surgery in patients with growth impairment (pooled HR, 1.72; 95% CI, 1.27–2.33; *P*=.0004; n=1,438; I^2=0%) (Figure 2A).[6, 16] One of the 2 negative studies had a mixed PIBD cohort rather than CD only.[14]

Statement 1.3. Disease location may predict surgery; isolated colonic disease is associated with fewer surgeries (84% agreement).

Twelve studies evaluated disease location as a predictor for the risk of surgery.[4-10, 16-20] Four meta-analyzable studies showed a significantly lower risk of surgery in patients with isolated colonic disease (pooled HR, 0.57; 95% CI, 0.43–0.78; *P*=.0003; n=2,289; I^2=24%) (Figure 2B).[5, 6, 10, 16] The pooled unadjusted OR from a smaller analysis of 2 studies with no heterogeneity further supported this (pooled OR, 0.30; 95% CI, 0.15–0.58; *P*=.0003; n=621; I^2=0%) (Supplementary Figure 2A).[16, 17] Conversely, this indicates that the presence of small bowel disease (isolated or with colonic disease) increases the risk of surgery. Of the studies that could not be included in the meta-analysis, 3 reported disease location to not be a significant risk factor.[7-9] Attard *et al*.[19] found jejunal involvement and disease in the proximal ileum to be associated with an increased surgery risk (unadjusted HR, 3.7; *P*<.03), but upper gastrointestinal (GI) disease and esophageal involvement were not found to be significant risk factors by 2 other studies.[4, 20]

Statement 1.4. **Inconclusive evidence exists for sex as a predictor for surgery; presence of *NOD2/CARD15* variants, stricturing and/or internal penetrating (B2/B3) phenotype, and positive anti-*Saccharomyces cerevisiae* antibodies (ASCA) status predict surgery; ethnicity and presence of granulomas at diagnosis do not predict surgery** (90% agreement).

Ten studies [5, 6, 9-12, 14, 16, 17, 21] evaluated the association between sex and surgery. Meta-analysis of 6 studies[5, 6, 9, 11, 16, 17] found no significant risk for sex (pooled OR, 0.95; 95% CI, 0.73–1.22; *P*=.27; n=2,780; I^2=22%) (Figure 2C). A smaller analysis of 5 studies with greater heterogeneity showed a decreased risk of surgery with male sex but bordered the null (pooled HR, 0.82; 95% CI, 0.68–0.99; *P*=.04; n=4,256; I^2=36%) (Supplementary Figure 2B).[6, 10, 12, 16, 21] The largest study, not included in the meta-analysis, reported male sex to be a significant risk factor in a mixed IBD cohort.[14] Conversely, Dubinsky et al.[21], also not included in the meta-analysis, reported an increased risk for females in a multivariable analysis (HR, 1.69; 95% CI,1.07–2.17; *P*<.009). The 2 remaining studies did not report a significantly increased risk for either sex.[10, 12]

Eleven studies evaluated the presence of a *NOD2/CARD15* variant as a predictor of surgery,[18, 21-30] of which 3 found a significant association.[26-28] The largest cohort of 186 patients with childhood-onset CD found a higher risk for surgery in those with a 3020insC mutation (adjusted HR [aHR], 5.83; 95% CI, 2.62–12.98; *P*<.0001).[27] The data from 6 studies could be pooled, which resulted in a 2-fold increased risk (pooled OR, 2.02; 95% CI, 1.23–3.32; *P*=.006; n=797; I^2=35%) (Figure 2D).[22-26, 28]

Disease behavior was evaluated as a risk factor for surgery in 4 studies.[5, 8, 10, 16] Pooled HR of 2.55 for B3 disease behavior (95% CI, 0.95–6.88; *P*=.06; n=1,248; I^2=46.0%) (Figure 2E)[5, 10] and a pooled HR of 3.97 (95% CI, 1.56–10.10; *P*=.004; n=1,248; I^2=81.1%) (Figure 2F) for B2 disease behavior was found.[5, 10] Rinawi et al.[16] found children with B2/B3 disease to be at increased risk of surgery (aHR 2.54, 95% CI 1.59–4.05, *P*<.001).[16]

Five[6, 16, 17, 21, 31] out of 8 studies[6, 16, 17, 21, 31-34] evaluating the association between ASCA status and surgery showed a significant association. The pooled OR for 5 meta-analyzable studies was 2.31 (95% CI, 1.74–3.06; *P*<.0001; n=1128; I^2=0%) (Figure 2G).[16, 17, 21, 31, 32] The pooled HR for 4 of these studies also showed a significantly increased risk of surgery (HR, 2.59; 95% CI, 1.63–4.11; *P*<.0001; n=1033; I^2=0%) (Supplemental Figure 2C).[6, 16, 17, 21] Of the 3 studies without a significant association,[32-34] 1 included both CD and ulcerative colitis (UC).[33] Ethnicity did not predict the risk of surgery.[5, 6, 9, 35] Presence of granulomas was not associated with the risk of surgery.[6, 16, 36-38]

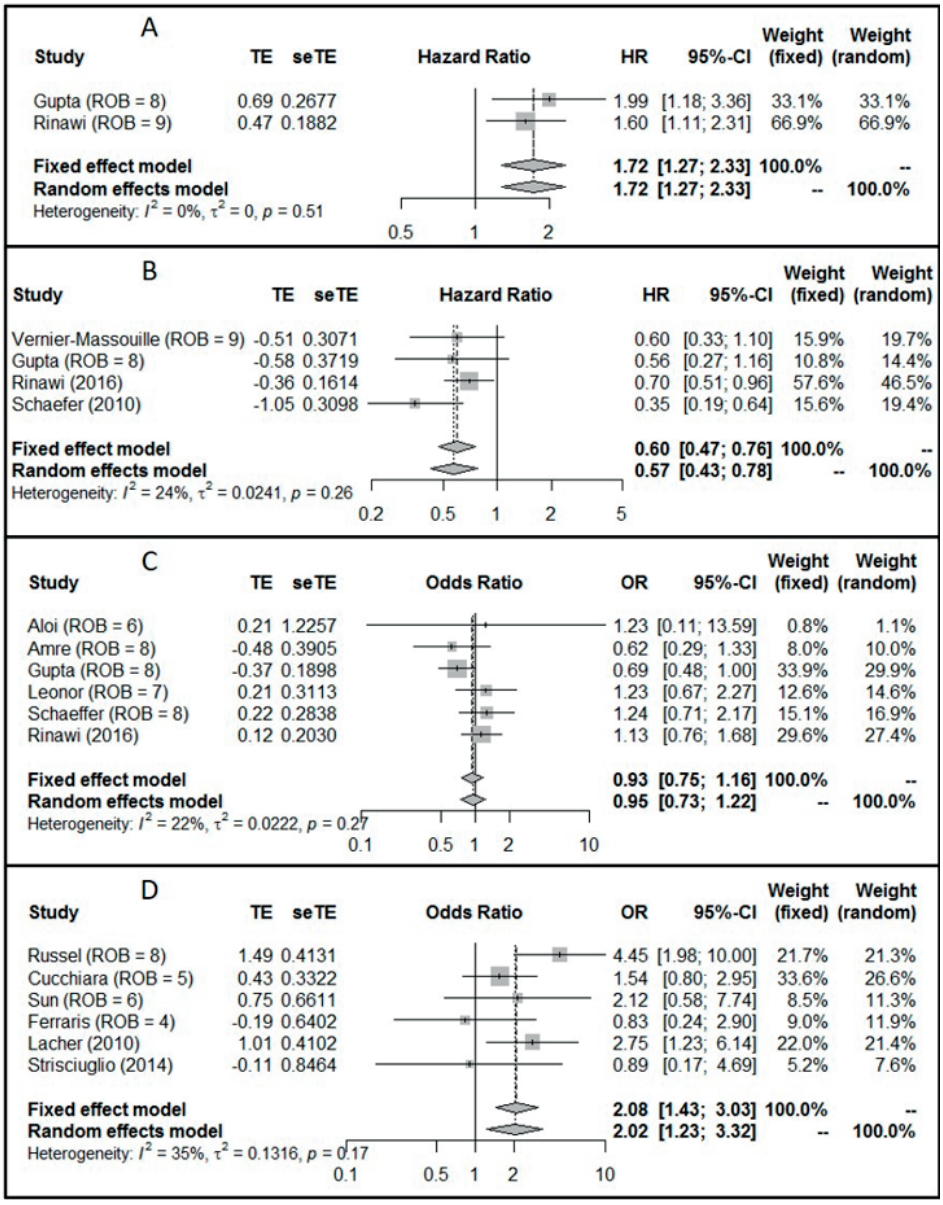

Figure 2. Forest plots for predictors of surgery in pediatric CD: A – poor growth; B – isolated colonic disease; C – male sex; D – NOD2/CARD15 variant;

ROB, risk of bias; seTE, standard error of treatment estimate; TE, estimate of treatment effect.

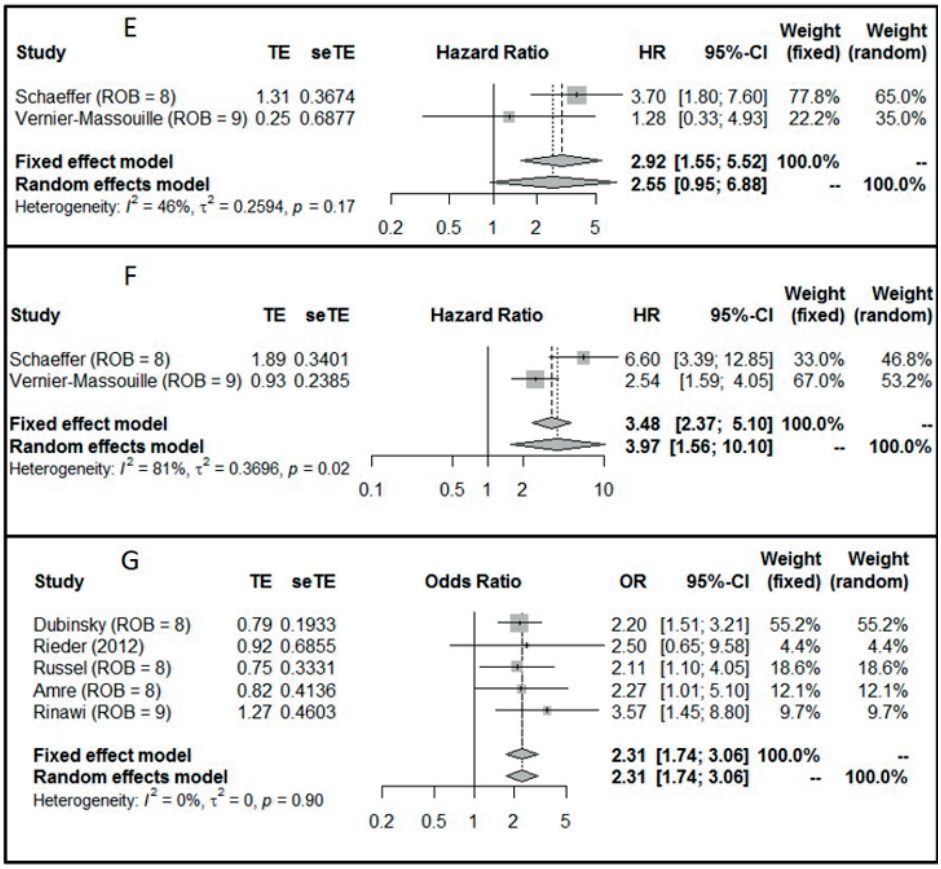

Figure 2. Forest plots for predictors of surgery in pediatric CD: E – B3 behavior; F – B2 behavior; G – ASCA positivity.

ROB, risk of bias; seTE, standard error of treatment estimate; TE, estimate of treatment effect.

Prognostic risk factors for complications in pediatric Crohn's disease

Statement 2.1. Children who develop CD at an older age may be at increased risk of developing internal penetrating (B3) complications, but not stricturing (B2) disease (94% agreement).

Three studies[18, 39, 40] found no association between age and progression to B2 disease, none of which could be meta-analyzed because of differing methods (univariate vs multivariable Cox regression) and age definitions. Two[39, 40] of 4 studies,[14, 18, 39, 40] including the Risk Stratification and Identification of Immunogenetic and Microbial Markers of Rapid Disease Progression in Children with Crohn's Disease (RISK) study,[40] a large (n=913) prospective inception cohort of pediatric CD, found an association between older age during childhood and increased risk of B3 complications. The RISK study was the only prospective and high-quality study among the 4. No association was reported between age and progression to the combined outcome of B2 or B3 complications in 4 studies.[41-44] Meta-analysis was not possible due to differences in age definitions and differences in the effect estimates used in individual studies.

Statement 2.2. CD patients of Black ethnicity/race are more likely than White patients to develop penetrating (B3) disease (82% agreement).

When pooled, 2 studies, including the RISK cohort, found non-White children to be at higher risk of progressing to penetrating complications than White children (pooled OR, 3.46; 95% CI, 1.67–7.17; *P*=.0009; n=1,020; I^2=0%) (Figure 3A).[40, 45] The RISK study compared Black children to White children in a large cohort and adjusted analysis (HR, 3.19; 95% CI, 1.39-7.31). By comparison, the study by Li *et al*.[45] examined a small South Asian cohort (n=13) in an unadjusted analysis and did not find a significant association (OR, 2.05; 95% CI, 0.49-8.53). In a third study including 105 children with inflammatory CD, Black children progressed more rapidly to the combined outcome of B2 or B3 complications (OR, 3.48; 95% CI, 1.32–9.17; *P*=.011; n=137).[35] In these studies, follow-up duration ranged from 3 to 10 years.

Statement 2.3. CD patients with small bowel disease (ie, L1 or L3 +/– L4b) have an increased risk of developing stricturing complications (B2) and may be at an increased risk of developing penetrating complications (B3) (85% agreement).

Three studies examined the association between disease location and stricturing complications. Although the RISK study found no association in adjusted analyses for isolated ileal disease (aHR, 1.60; 95% CI, 0.88–2.91; *P*=.12),[40] when unadjusted results for any small bowel involvement from this study were pooled with a second study,[46] any small bowel disease was a significant risk factor for B2 behavior (pooled OR, 1.93; 95% CI, 1.22–3.05; *P*=.005; n=1,513; I^2=6%) (Figure 3B). A smaller (n=36) uncontrolled study found no such association.[11] Four studies reported on disease location and the com-

bined outcome of B2 or B3 complications; 3 could be meta-analyzed,[43, 44, 46] revealing an increased risk with ileal involvement (isolated ileal or ileocolonic) compared to isolated colonic disease (pooled OR, 2.16; 95% CI, 1.26–3.71; *P*=.005; n=819; I^2=36%) (Figure 3C). The fourth study, which could not be meta-analyzed, was retrospective and reported B2/B3 as a composite outcome that also included anti-tumor necrosis factor (TNF) use (HR, 1.38; 95% CI, 0.63–3.03; *P*=.44).[42] Neither of the 2 studies to examine disease location and B3 complications found a significant association.[40, 46] They could not be meta-analyzed.

Statement 2.4.1. Antimicrobial serologies predict progression to stricturing (B2) and/or internal penetrating (B3) complications: ASCA positivity predicts progression to internal penetrating (B3) complications and may predict progression to stricturing (B2) complications; a higher ASCA immunoglobulin (Ig) A titer predicts progression to penetrating (B3) complications (94% agreement).

The literature on antimicrobial serology and progression to complicated CD in children is difficult to interpret, given the heterogeneity of tests investigated. Overall, it appears that an association exists, particularly between ASCA positivity and B3 disease. The RISK study identified a trend toward an association between ASCA-IgA and B2 disease in an adjusted survival analysis (aHR, 1.69; 95% CI, 0.94–3.07).[40] A much smaller and unadjusted analysis identified no association between ASCA positivity and early B2 complications.[11] Furthermore, the RISK study identified a clearly increased risk of B3 complications with ASCA-IgA positivity (aHR, 2.68; 95% CI, 1.19–6.04), which remained similar in magnitude when pooled with another adjusted study (pooled HR, 2.75; 95% CI, 1.53–4.97; *P*=.0008; n=1,052; I^2=0%) (Figure 3D).[17, 40] The pooled unadjusted OR for these 2 studies was 4.45 (95% CI, 2.43–8.16; *P*<.0001; I^2=0%) (Supplementary Figure 2D). A large adjusted study also showed an association between ASCA-IgA titer and B3 disease (HR, 1.20; 95% CI, 1.08–1.34; *P*=.0009; n=139).[17] The 1 study that did not support an association between ASCA-IgA (positivity or titer) and B3 disease was substantially smaller and did not use survival analysis.[34] On the other hand, for ASCA-IgG positivity, 2 studies found no association with B3 disease (pooled OR, 1.58; 95% CI, 0.75–3.36; *P*=.231; n=200; I^2=2.7%) (Figure 3E).[17, 34] Both studies were individually negative when examining ASCA-IgG titer as well.

Statement 2.4.2. Antiflagellin (CBir1) positivity predicts progression to stricturing (B2) and/or internal penetrating (B3) complications; OmpC positivity may predict progression to stricturing (B2) and/or internal penetrating (B3) complications (94% agreement).

The RISK study observed a strong association between CBir1 positivity and B2 as well as B3 complications.[40] Similarly, in a longitudinal cohort of 536 children, CBir1 and, separately, OmpC positivity, both predicted B2 or B3 complications over time.[21]

Statement 2.4.3. Seropositivity for ≥1 microbial serologies predicts progression to stricturing (B2) and/or internal penetrating (B3) disease; a higher number of positive serologies and higher titers may confer a greater risk (94% agreement).

The pooled results from 2 studies support an increased risk of developing B2 or B3 complications with any antimicrobial seropositivity (eg, ASCA, anti-OmpC, or anti-CBir1) compared with negative status for all serologies (pooled OR, 3.20; 95% CI, 1.41–7.26; *P*=.0055; n=703; I^2=0%) (Figure 3F).[21, 47]

Statement 2.5. Polymorphisms in the *NOD2/CARD15* gene predict ileal disease location and may predict stricturing (B2) disease, but location is inadequately controlled for (90% agreement).

Twelve studies explored the association between *NOD2* and B2 complications, including 9 that could be meta-analyzed, which showed an increased risk of B2 disease (pooled OR, 3.10; 95% CI, 1.70–5.65; *P*=.0002; n=1,050; I^2=55%) (Figure 3G).[18, 23-29, 48] The 3 studies that could not be pooled found no association.[40, 49, 50] Because most of these studies did not adjust for disease location, it is unclear whether *NOD2*'s association with B2 disease stems directly from its association with ileal location. A meta-analysis of 9 of the 11 studies that assessed the association between *NOD2* and B3 complications showed no increased risk (pooled OR, 1.48; 95% CI, 0.78–2.81; *P*=.23; n=1,050; I^2=48%) (Figure 3H).[18, 23-29, 48] The 2 additional studies that could not be meta-analyzed were also negative.[40, 50]

Statement 2.6. The presence of perianal disease may predict stricturing (B2) and/or internal penetrating (B3) complications (89% agreement).

Two studies yielded conflicting findings on perianal disease as a predictor of B2 or B3 complications.[44, 51] When pooled, although the effect estimate was in the direction of an increased risk of B2/B3 disease in children with perianal disease, this did not achieve statistical significance (pooled OR, 1.98; 95% CI, 0.51–7.74; *P*=.32; n=383; I^2=80%) (Figure 3I). Notably, there was substantial heterogeneity in this analysis. An administrative database study reported an increased risk of internal fistulae (rectourethral, rectovaginal, or enterovesical) in the setting of perianal disease (OR, 3.50; 95% CI, 1.98–6.20; n=12,465); although, in the same study, perianal disease was associated with a decreased risk of entero-enteric fistulae (OR, 0.30; 95% CI, 0.15–0.63).[14]

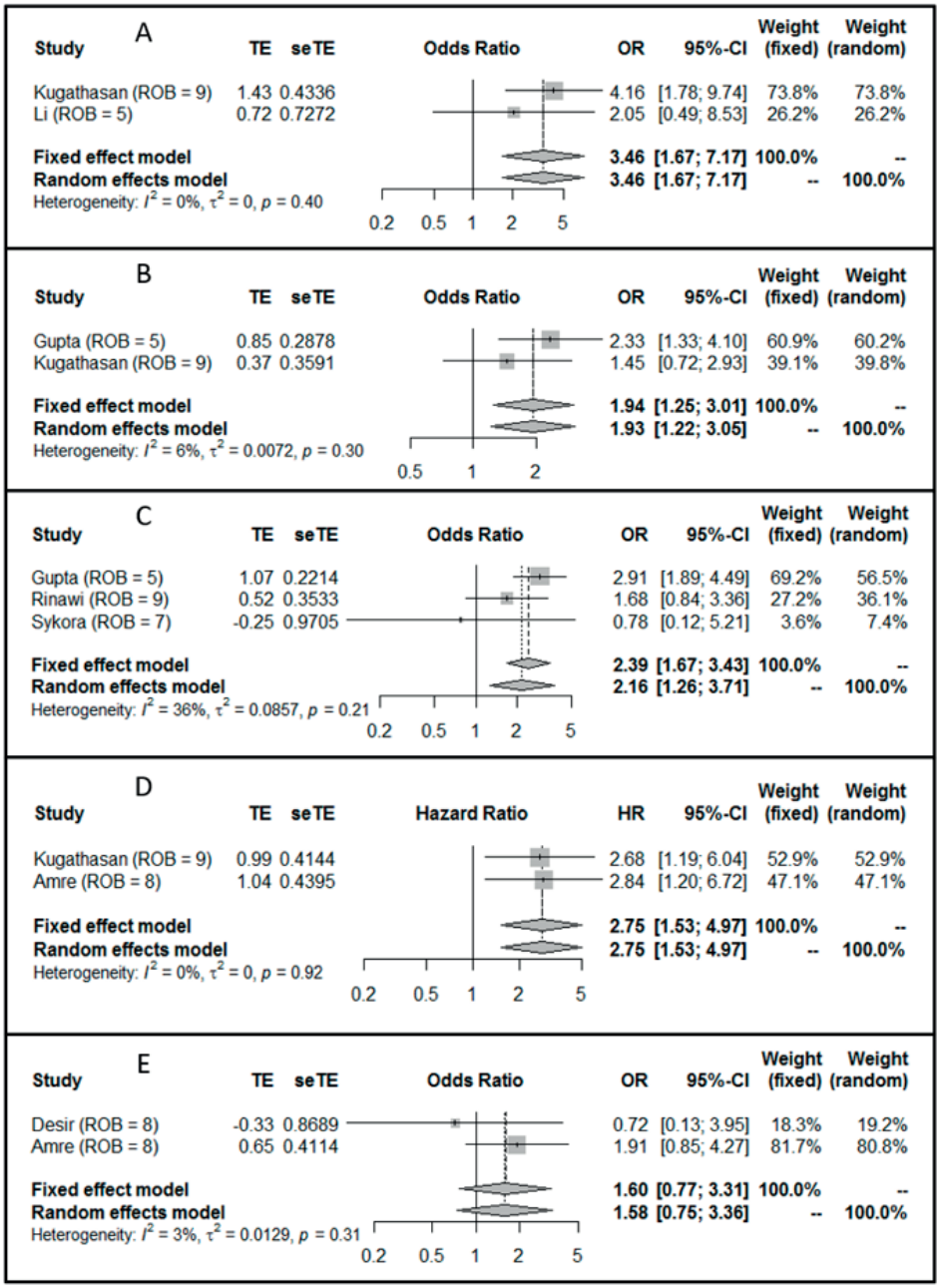

Figure 3. Forest plots for predictors of B2/B3 complications in pediatric CD: A – non-White ethnicity/race as a predictor of B3 complications; B – small bowel disease (±colonic) as a predictor of B2 complications; C – small bowel disease (±colonic) as a predictor of B2 or B3 complications; D – ASCA-IgA positivity as a predictor of B3 complications; E – ASCA-IgG positivity as a predictor of B3 complications;
ROB, risk of bias; seTE, standard error of treatment estimate; TE, estimate of treatment effect.

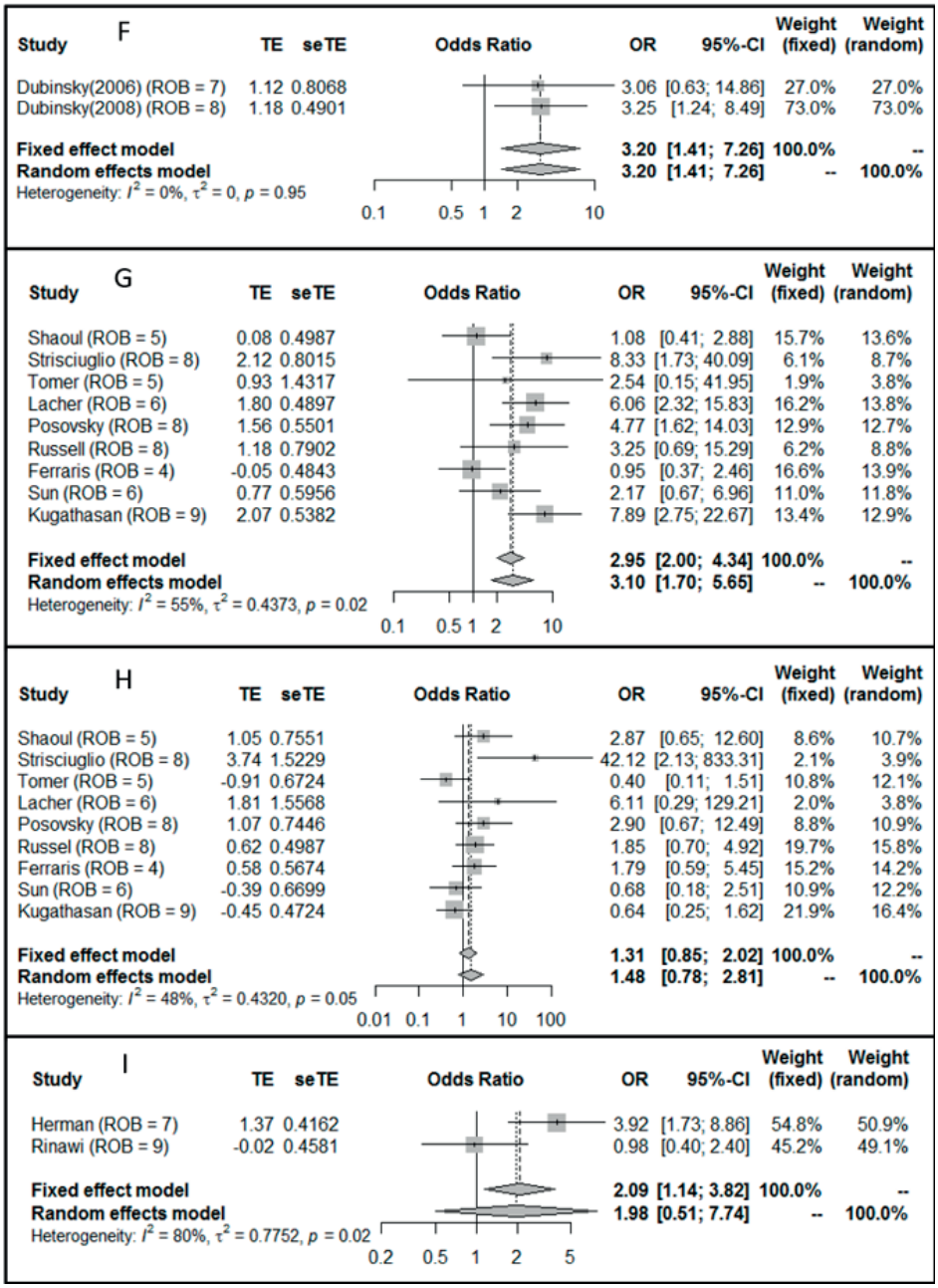

Figure 3. Forest plots for predictors of B2/B3 complications in pediatric CD: F – antimicrobial seropositivity as a predictor of B2 or B3 complications; G – NOD2 polymorphisms as a predictor of B2 complications; H – NOD2 polymorphisms as a predictor of B3 complications; I – perianal disease as a predictor of B2 or B3 complications.

ROB, risk of bias; seTE, standard error of treatment estimate; TE, estimate of treatment effect.

Statement 2.7. Sex, family history of IBD, disease activity at baseline, granulomas, upper GI tract involvement, presence of extraintestinal manifestations, and diagnostic delay do not predict disease location, stricturing (B2) and/or internal penetrating (B3) complications (83% agreement).

Sex was not found to predict B2/B3 complications in 7 of 8 studies examining this association.[11, 41-44, 52, 53] Similarly, family history of IBD (0/3 studies positive),[11, 42, 44] baseline clinical and biochemical disease activity (1 study positive,[43] 5 negative),[11, 41, 42, 44] granulomas (0/6 studies positive),[36-38, 41, 44, 54] extraintestinal manifestations (0/2 studies positive),[42, 44] diagnostic delay (0/1 study positive),[44] and upper GI tract involvement (0/3 studies positive)[41-43] were not associated with progression to complicated CD.

Statement 2.8. Older age at CD onset may be associated with an increased risk of developing perianal disease (97% agreement).

The oldest age group (17–21 years of age) at disease onset of 7,076 patients in the ImproveCareNow Network had a higher rate of perianal disease than younger children (HR, 1.13; 95% CI, 1.10–1.15).[55] In a second study, including 215 children, older age at diagnosis was also associated with more perianal disease over time.[44] Furthermore, Gupta *et al*.[39] observed a trend toward more perianal disease in children >5 years of age (vs younger children). In contrast, children with and without perianal disease did not differ in terms of age in the RISK study.[40]

Statement 2.9. Children and adolescents of Black and South Asian ethnicity with CD are at a greater risk of developing perianal disease (92% agreement).

Black[55] (adjusted OR 2.47, *P*=.017) and South Asian[45] children were at higher risk of developing perianal disease than White children.

Statement 2.10. Bacterial serology and sex may be associated with the development of perianal disease; genetics, antineutrophil cytoplasmic antibody (ANCA) positivity, anthropometric parameters, disease location, disease behavior, extraintestinal manifestations, diagnostic delay, and disease activity do not predict the development of perianal disease (86% agreement).

ASCA, antilaminaribioside carbohydrate antibodies, antimannobioside carbohydrate antibodies, and anti-L antibodies were associated with the composite outcome of perianal disease or B2/B3 complications in 1 study.[32] In the RISK cohort, children with perianal disease at diagnosis were more likely to be ASCA IgA/IgG, CBir1, granulocyte-macrophage colony-stimulating factor, and OmpC-positive, and the proportion of males was greater among children with perianal disease.[40] However, both these studies examined perianal disease in a cross-sectional manner. Only 1[55] of 3[44, 53] additional studies found an association between sex and risk of perianal disease. Two of these additional

studies[44, 55] examined the development of perianal disease over time, and the other was cross-sectional in nature.[53]

Overall, genetics (2 studies positive,[56, 57] 9 negative, including for *NOD2*),[22, 23, 27-29, 49, 50, 58, 59] ANCA positivity (0/2 studies positive),[40, 60] anthropometric parameters (0/3 studies positive),[44, 55, 61] disease location (0/3 studies positive),[40, 44, 55] disease behavior (0/1 study positive),[44] extraintestinal manifestations (0/1 study positive),[44] diagnostic delay (0/1 study positive),[44] and disease activity (0/3 studies positive)[40, 44, 55] did not predict the development of perianal disease over time.

Statement 2.11. Male sex, younger age at disease onset, and isolated small bowel disease may be associated with a greater risk of linear growth impairment (100% agreement).

Although 5 studies found no association between sex and growth,[4, 62-65] 4 other large and well-designed studies did observe males to be at higher risk of linear growth impairment.[53 66 67, 68] The studies on age in relation to growth impairment are conflicting. Four found no association,[39, 53, 63, 68] though 2 were mixed IBD studies.[63, 68] In 4 additional studies, younger age at diagnosis predicted growth impairment,[4, 62, 65, 67] and a single study observed the opposite.[69] These differences may relate to varying definitions for growth impairment as well as failure to adjust for pubertal status. Three growth-focused studies found small bowel disease (vs colonic location) to be associated with growth impairment,[65, 66, 70] whereas 5 others of poorer quality did not report this association.[4, 8, 62, 63, 71]

Statement 2.12. More active disease (assessed at baseline or over time) predicts linear growth impairment (92% agreement).

Some studies supported an association between more active disease and poorer growth, although most were cross-sectional rather than truly predictive. Specifically, 2 studies observed an association between more severe clinical disease and impaired growth,[63, 70] whereas 2 did not.[8, 62] Four studies found an association between higher erythrocyte sedimentation rate and growth impairment,[68, 69, 72, 73] whereas 3 found no association between C-reactive protein or albumin and linear growth.[63, 69, 72]

Statement 2.13. Diagnostic delay is a risk factor for linear growth impairment (92% agreement).

Two studies focused on CD found an association between diagnostic delay and impaired growth.[66, 74] Two studies that did not differentiate between CD and UC found no such association.[68, 75]

Statement 2.14. *NOD2/CARD15* polymorphisms may be associated with low weight, and extraintestinal manifestations may be associated with linear growth impairment; pubertal status at disease onset, family history of IBD, ethnicity, gestational age, upper GI tract involvement, oral involvement, granulomas, disease behavior, perianal disease, and presenting symptoms do not predict linear growth impairment (94% agreement).

Three studies examined *NOD2/CARD15* in relation to growth,[26, 29, 70] only 1 of which was positive, reporting that 50% of children with at least 1 *NOD2/CARD15* variant were in the lowest weight percentile (<4%) compared with 16% of children without a variant.[26] One study observed an association between extraintestinal manifestations and lower height at last follow-up,[67] whereas another found no such association in a mixed IBD cohort.[68] Pubertal status at CD diagnosis (0/2 studies positive),[62, 71] family history of IBD (0/3 studies positive),[8, 62, 68] ethnicity (0/3 studies positive),[35, 62, 68] gestational age (0/1 study positive),[8] presence of granuloma (0/1 study positive),[38] perianal disease (0/2 studies positive),[4, 76] disease behavior (0/2 studies positive),[8, 62] specific IBD symptoms (0/1 study positive),[53] upper GI tract location (0/6 studies positive),[4, 62, 63, 67, 70, 77] and oral involvement (0/1 study positive)[78] were not associated with growth impairment.

Statement 2.15. Low height, weight, and body mass index predict reduced BMD (98% agreement).

All 10 studies that examined nutritional status/anthropometrics in relation to reduced BMD reported an association with either lower weight or lower height.[29, 79-87] For weight, 9 of 9 studies were positive,[29, 79-85, 87] and for height, 5 of 8 studies were positive,[79, 80, 83, 85, 88] whereas 3 were negative.[29, 81, 87] Importantly, most studies reporting on height were cross-sectional.

Statement 2.16. Higher clinical disease activity (assessed by Pediatric CD Activity Index [PCDAI]) at baseline and over time may predict reduced BMD (98% agreement).

Ten studies investigated disease activity in relation to bone outcomes, with heterogeneous results, possibly because several were cross-sectional.[29, 79, 81-83, 85, 87, 89-91] Five studies found an association between clinical disease activity and BMD,[29, 81, 82, 85, 89] whereas 5 other studies did not,[79, 83, 87, 90, 91] including 2 prospective studies.[87, 90]

Statement 2.17. Sex, disease location, disease behavior, extraintestinal manifestations, granulomas, and perianal disease do not predict BMD (84% agreement).

No association has been shown between sex and bone health in 7 pediatric studies,[29, 53, 79, 80, 83, 85, 92] whereas 2 showed contradictory associations.[88, 89] Disease location (0/3 studies positive),[29, 83, 87] behavior (0/1 study positive),[29] extraintestinal manifestations

(0/2 studies positive),[29, 85] presence of granuloma (0/1 study positive),[83] and perianal disease (0/1 study positive)[85] were not predictive of bone outcomes.

Prognostic risk factors for chronically active inflammatory pediatric Crohn's disease

Statement 3.1. ASCA positivity may predict the need for more intensive therapy (89% agreement).

Three studies examined ASCA positivity as a predictor for intensified therapy,[11, 33, 93] 2 of which identified a positive association.[33, 93]

Statement 3.2. Microscopic ileocolonic involvement at diagnosis may be associated with subsequent macroscopic ileocolonic disease (98% agreement).

One study of 212 children reported on microscopic ileocolonic involvement as an independent predictor of the subsequent development of macroscopic disease.[44] The need for an immunomodulator or anti-TNF within the first year, and number of flares and hospitalizations were associated with disease-extent progression, but only microscopic ileocolonic involvement remained significant in the multivariable analysis (HR, 4.32; 95% CI, 1.93–9.67).

Statement 3.3. Disease activity and disease behavior (ie, B2 and/or B3), but not age and sex, may predict more intensive therapies or a poor response to therapies; there is no strong evidence for a predictive value of ethnicity (83% agreement).

Three studies examined the association between PCDAI at diagnosis and subsequent treatment,[94-96] of which only 1 (n=240) reported an association with the need for immunomodulators by 1 year.[96] One of 2 studies found an association between B3 behavior and use of anti-TNF.[57, 95]

Only 2 of 10 studies reported an association between age and intensified treatment.[3, 11, 13, 39, 64, 97-101] The first, a prospective registry of 1,928 children, found that younger children (1–5 years) received corticosteroids and methotrexate more often than older children, but with a similar rate for biologics.[100] The other study found that younger children (0–5 years) received steroids more often but with a similar rate for immunomodulators or biologics.[3]

Sex was not found to predict intensified therapy in 4 studies.[64, 97, 99, 101] One study reported an association between male sex and better response to steroids, but this was not maintained over time.[97]

Two studies evaluated ethnicity and intensified therapy. Although positive, they did not separate patients with CD from those with UC, and each assessed different ethnicities (South Asian[45] or Black[35] vs White).

Statement 3.4. No strong evidence exists to identify predictive factors of future disease activity or disease severity (81% agreement).

Of 3 studies investigating predictive factors of disease severity in pediatric CD,[8, 60, 65] 2 identified an association.[8, 65] The first study found an association between ileal/ileocolonic location and PCDAI or Physician Global Assessment.[8] In the second, the presence of TNF 308G/A genetic polymorphism was associated with a trend for severe disease, as represented by hospitalizations, surgery, and need of steroids or anti-TNF.[65] No association was found between ANCA serology and disease course.[60]

Statement 3.5. No strong evidence exists for predictors of disease relapse and the number of relapses (98% agreement).

Four[13, 23, 34, 102] of 6[77, 78] studies reported significant predictors for disease relapse (as defined by clinical activity score), including ASCA IgA positivity,[34] younger age at disease onset,[13] ATG16L1 risk allele homozygosity,[23] and a polymorphonuclear neutrophil CD64 index >1.0 (vs <1.0).[102] Gasparetto *et al*.[13] found children aged 5–10 years at diagnosis to relapse more frequently than children with disease onset at 11–16 years of age (mean ± standard deviation relapse per patient per year 1.4 ± 0.2 vs 0.85 ± 0.1, respectively; OR, 1.2; 95% CI, 1.01–1.65). However, because of study limitations of sample size, retrospective design, and heterogeneity in the results, these findings do not represent strong evidence for predictors of occurrence or number of disease relapses.

Statement 3.6. Stricturing and/or internal penetrating (B2/B3) phenotype and the presence of granulomas and increased visceral adipose tissue may predict hospitalizations; small bowel involvement, *TNF* polymorphisms, *NOD2* variants, and age do not predict hospitalization (88% agreement).

Predictors for hospitalizations were investigated in 7 studies, all with different predictors.[13, 19, 29, 37, 65, 100, 103] Age,[13, 100] proximal bowel involvement,[19] and the presence of *NOD2* variants[29] or TNF polymorphisms[65] were not associated with hospitalization. One study found that patients with granulomas were more likely to be hospitalized (HR 1.43, 95% CI 1.0–2.0), whereas they did not display an increased risk for bowel resections or flares.[37] Uko *et al*. [103] found increased visceral adipose tissue to be associated with hospitalizations (OR 1.9, 95% CI 1.2–3.4, *P*=.01) in a retrospective study. Although no studies evaluated the association between B2/B3 disease and hospitalization, the association of B2/B3 disease with surgery as mentioned in statement 1.4 reflects this association.

This was supported by a recent study showing that B2/B3 disease was associated with an increased risk for hospitalization (HR, 1.5; 95% CI, 1.1–2.1; *P*=.016).[104]

IMPLICATIONS FOR PRACTICE

The concept of severe CD in children is recognized to encompass not only progression to intestinal complications requiring extensive or repeated resection, but also chronically active disabling disease, which remains inflammatory. This may lead to other age-specific outcomes such as growth impairment and reduced bone density, which can further adversely affect children emotionally during a particularly sensitive time in their adolescence. Physicians intuitively risk-stratify patients soon after diagnosis and make treatment recommendations aiming to prevent these undesirable outcomes. However, evidence-based tools to stratify patient risk and tailor treatment selection accordingly are needed. This is particularly salient because there is good evidence of better outcomes resulting from earlier effective medical intervention in pediatric CD. This was shown in the RISK cohort, for example, in which early anti-TNFα treatment within 3 months of diagnosis was associated with improved clinical and growth outcomes at 1 year.[1]

This project represents the most comprehensive review of the available literature to this date in an attempt to develop evidence-based guidance on risk factors for severe pediatric CD. As such, it represents an important and contemporary addition to the literature. The involvement of a large number of pediatric IBD experts from around the world and the consensus approach are important strengths of this undertaking. There are, however, a number of limitations. First, despite the comprehensive search strategy, there was a paucity of large, prospective, pediatric-specific CD studies for several of the predictor-outcome pairs. Meta-analyses, in general, included a fairly small number of studies. In some cases, studies pooled CD and UC populations. This highlights the need for additional large and rigorously performed longitudinal studies in pediatric CD, both to further characterize prognostic factors and to evaluate the benefits of treatment algorithms that tailor treatment based on risk stratification informed by these risk factors. Additional limitations include the heterogeneity of the included studies. Sources of heterogeneity included definitions of predictors and outcomes, with growth being one example of a factor for which various definitions were used, as well as differences in the types of effect measures reported by individual studies. Although we made efforts to pool studies when justified based on similar definitions and types of effect measures, substantial heterogeneity remained for some analyses. In addition, we excluded non-English texts and were unable to contact study authors.

In summary, the present consensus statements offer clinicians evidence of associations between baseline characteristics and outcomes in children with CD. Antimicrobial antibodies may be associated with stricturing or internal penetrating CD and surgery, but biomarkers of equally disabling chronic inflammatory colonic disease or progressive perianal fistulizing disease are direly needed. As in adults, precision medicine is not yet a reality in pediatric CD. Nonetheless, the associations summarized and meta-analyzed through PIBD-Ahead provide some guidance to the physician making initial treatment decisions for the individual child.

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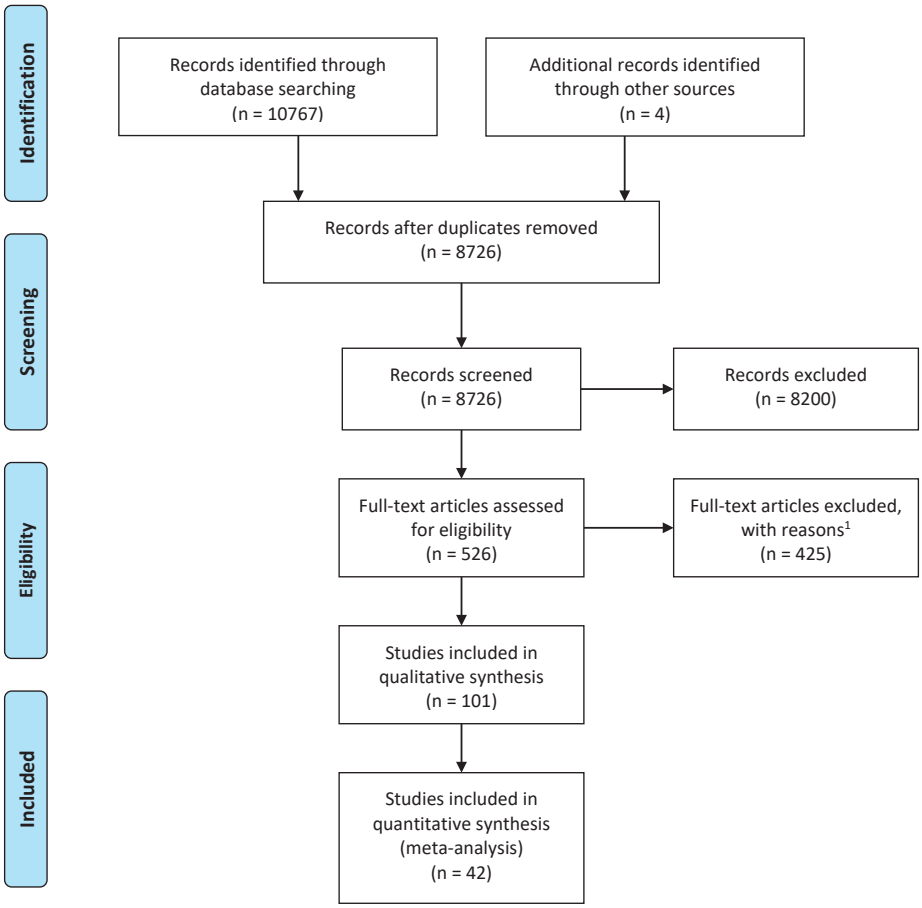
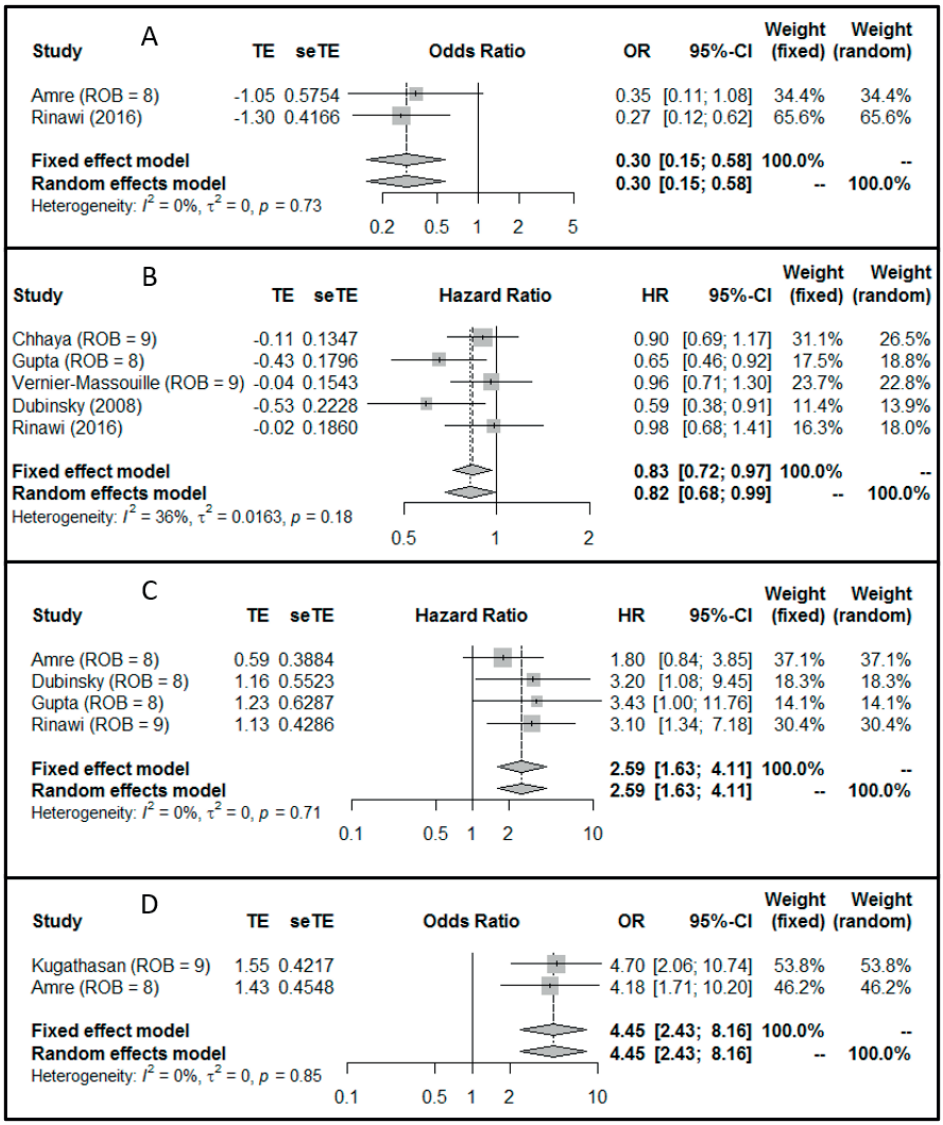


Supplemental Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram



Supplemental Figure 2. Additional forest plots for predictors of surgery and B2/B3 complications in pediatric CD: A – isolated colonic disease as a predictor of surgery; B – male sex as a predictor of surgery; C – ASCA positivity as a predictor of surgery; D – ASCA-IgA positivity as a predictor of B3 complications

08

Predicting outcomes in pediatric ulcerative colitis for management optimization: systematic review and consensus statements from the Pediatric Inflammatory Bowel Disease-Ahead program

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ABSTRACT

Background and aims: A better understanding of prognostic factors in ulcerative colitis (UC) could improve patient management and reduce complications. We aimed to identify evidence-based predictors for outcomes in pediatric UC, which may be used to optimize treatment algorithms.

Methods: Potential outcomes worthy of prediction in UC were determined by surveying 202 experts in pediatric UC. A systematic review of the literature, with selected meta-analysis, was performed to identify studies that investigated predictors for these outcomes. Multiple national and international meetings were held to reach consensus on evidence-based statements.

Results: Consensus was reached on 31 statements regarding predictors of colectomy, acute severe colitis (ASC), chronically active pediatric UC, cancer and mortality. At diagnosis, disease extent (6 studies, n=627; *P*=.035), Pediatric Ulcerative Colitis Activity Index score (4 studies, n=318; *P*<.001), hemoglobin, hematocrit, and albumin may predict colectomy. In addition, family history of UC (2 studies, n=557; *P*=.0004), extraintestinal manifestations (4 studies, n=526; *P*=.048), and disease extension over time may predict colectomy, whereas primary sclerosing cholangitis (PSC) may be protective. Acute severe colitis may be predicted by disease severity at onset and hypoalbuminemia. Higher Pediatric Ulcerative Colitis Activity Index score and C-reactive protein on day 3 and 5 of hospital admission predict failure of intravenous steroids. Risk factors for malignancy included concomitant diagnosis of primary sclerosing cholangitis, longstanding colitis (>10 years), male sex, younger age at diagnosis.

Conclusions: These evidence-based consensus statements offer predictions to be considered for a personalized medicine approach in treating pediatric UC.

INTRODUCTION

Pediatric-onset ulcerative colitis (UC) has a somewhat more severe phenotype than in adults.[1, 2] Disease is twice as often extensive,[3] and more often requires hospitalization[4, 5] as well as colectomy for medically refractory disease.[3, 6] Indeed, high cumulative rates of colectomy have been reported in children: 8% at 1 year, 26% at 5 years, and 20–41% at 10 years.[3, 6]

Children also have unique age-related considerations, including pubertal development, nutrition, and bone mineral density accretion, as well as unique psychosocial needs. Because of such differences, prognostic factors associated with pediatric UC should be examined separately from those of adults.

The international pediatric inflammatory bowel disease (PIBD) Ahead Program (PIBD-Ahead) was aimed at identifying evidence-based predictors for outcomes in PIBD. Here, we present the predictors of UC to guide evidence-based individualization of management in childhood-onset UC.

METHODS

PIBD-Ahead encompassed several stages, aiming to systematically reach international consensus on the predictors of poor outcomes in PIBD. The methods of this project have been described in the companion Crohn's disease (CD) article by Ricciuto *et al.*[7]. Briefly, a survey among international experts in pediatric gastroenterology and inflammatory bowel disease (IBD) was first performed to determine undesirable outcomes of interest to be predicted in pediatric UC. The survey aimed to identify outcomes that may justify treatment escalation to biologics to prevent the said outcomes. Chronically active colitis was defined as reported in the studies including any of the following repeatedly assessed over time: physician global assessment, Pediatric Ulcerative Colitis Activity Index (PUCAI), endoscopic grading, and intractability index (duration of active disease as a proportion of length of follow-up). The same variables may have served as both predictors and outcomes because they were analyzed independently. For instance, the occurrence of an episode of acute severe colitis (ASC) may predict poor disease outcome but also is a poor outcome by itself. Thereafter, a systematic literature review was performed to identify studies examining predictors of these outcomes. We included articles enrolling children of all ages, namely 0–18 years of age. Meta-analyses were conducted to pool the effects of predictors of colectomy, the key selected outcome. Selection of studies for meta-analyses was determined by data sufficiency and clinical relevance. To

reflect the degree of heterogeneity across studies, the I^2 method was used, describing the percentage of variability stemming from heterogeneity rather than chance.[8] To compensate for the heterogeneity, a random effects model was used. Pooling of study results used either odds ratio (OR) or hazard ratio (HR) based on the study methodology; some studies allowed the calculation of both measures. A series of national and international meetings were convened to formulate and validate consensus statements based on the identified evidence. At the final February 2018 consensus meeting in Vienna, Austria, the steering committee with national representatives (53 participants) voted on the statements. A consensus was reached if ≥80% of participants voted 4 (agree) or 5 (strongly agree) on a scale of 1–5. Statements not achieving agreement were further revised and revoted upon until consensus was reached for all statements. In general, soft wording such as "may predict" has been used when only 1 positive study was available or when more than 1 positive study was found but also with negative studies.

RESULTS

The international survey, which informed outcome selection, was completed by 202 pediatric gastroenterologists from 33 countries. It was concluded that the most important undesirable outcomes to prevent in children with UC are colectomy, ASC, chronically active disease, cancer and mortality. Because of the expected limited number of studies for the latter, these were evaluated for both CD and UC and are reported in this article.

The results of the search are presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) diagram (Supplementary Figure 1). Fifty-nine studies were included, of which 17 were included in the quantitative meta-analysis. Study characteristics and risk of bias for studies examining predictor-outcome combinations included in the meta-analysis are shown in Tables 1 and 2, respectively. The equivalent data for studies examining predictor-outcome combinations not included in the meta-analysis are shown in Supplementary Tables 1 and 2. All of the included studies were observational. 19 studies were high quality, 38 moderate quality, and 2 low quality.

Figure 1 tabulates the final consensus and Table 3 presents the extracted numeric data for predictor-outcome pairs included in meta-analyses. Table 4 presents an intuitive summary of each outcome. A brief summary of the most pertinent literature is provided below each statement (for a full review of each predictor, see the Supplementary Materials).

Table 1. Characteristics of studies included in meta-analysis

Study	Study design	Population by IBD type, age and sex	Predictors examined (definition, exposed vs unexposed)	Outcomes examined	Follow-up duration
Aloi *et al* (2013)[10]	Retrospective, single center	110 pediatric UC patients Median 10.2 y (range 1.2–18.3) 39/110 (39%) early onset (0–7 y)/71/110 (61%) 8–18 y 38% M	Age (EO ≤7 y vs later) Disease extension (involvement during F/U of at least one additional segment) Disease extent Disease severity at diagnosis EIM (skin, joint, and ocular manifestations, and PSC) Family history of IBD (first-degree relative UC/CD) Sex	Colectomy	Mean 48 mo (range 28–94)
Aloi *et al* (2015)[9]	Retrospective, single center	31 pediatric UC patients 10.6 y (SD 4.9) 48% M	Age (mean age) CRP Disease extension (according to Paris classification) Disease extent (E4 vs E1, E2, E3) Disease severity at diagnosis ESR (>25 mm/h) Hypoalbuminemia Sex	Colectomy	2 y
Assa *et al* (2018)[11]	Retrospective, single center	126 pediatric UC patients Median 13.7 y (IQR 11.1–15.8) 46% M	Disease extent Disease severity at diagnosis (ASC)	Colectomy	8.5 y (IQR 5.1–12)
Chhaya *et al* (2015)[25]	Retrospective (registry), multicenter	1,175 pediatric UC patients (0–25 y) 0–9 y 61/1,175 10–13 y 111/1,175 14–16 y 143/1,175 17–24 y 860/1,175 48% M	Age (10–13 y vs 17–24 y as reference) Sex (female vs male)	Colectomy	Mean 4.3 y/ person
Falcone *et al* (2000)[15]	Retrospective, single center	73 pediatric UC patients (1–18 y) Mean 11.3 y (SD 0.5) at first symptom 48% M	Family history of IBD Sex	Colectomy	Mean 5.4 y (SD 0.6, range 0.4–13.8)

Table 1. Characteristics of studies included in meta-analysis (*continued*)

Study	Study design	Population by IBD type, age and sex	Predictors examined (definition, exposed vs unexposed)	Outcomes examined	Follow-up duration
Gower-Rousseau *et al* (2009)[6]	Retrospective (EPIMAD registry), multicenter	113 pediatric UC patients (<17 y at diagnosis) Median 14 y (IQR 11–16) 39% M	Age (<10 y vs ≥10 y) CRP (<10 mg/L vs ≥10 mg/L) Disease extension (involvement w/ time of at least one additional segment) Disease extent (E3 vs E1) EIM (joint, skin, and ocular manifestations, and PSC) Family history of IBD (first-degree relative UC/CD) Family history of UC Sex	Colectomy	Median 77 mo (46–125)
Kelley-Quon *et al* (2012)[23]	Retrospective (PediIBDC registry), multicenter	407 pediatric UC patients Mean 10.6 (SD 4.4) 49% M	Age CRP (>5 mg/dL) ESR (>20 mm/h) Family history of IBD Family history of UC (first-degree relative with UC) Hemoglobin level (<10 g/dL) Hypoalbuminemia (<3.5 g/dL) Sex (male vs female)	Colectomy (predictors reported for overall colectomy rate and not colectomy at 2 years)	Mean 6.8 y (SD 4)
Lascurain *et al* (2016)[31]	Retrospective, multicenter, case control (PSC-IBD vs non–PSC-IBD)	37 PSC-IBD patients/148 non-PSC matched IBD controls (155 patients UC) Median 14.2 y (IQR 9.9–16.7)/Median 14.2 y (IQR 11.7–16.8) 64.9% M/56.1% M	Sex	Colectomy	Median 4.75 y (IQR 3.7–7.2)/ Median 5.19 y (3.1–7.8)
Ledder *et al* (2014)[26]	Retrospective, case control, multicenter	30 early-onset IBD <6 y (20 UC, 8 CD, 2 indeterminate)/60 later-onset 6–17y (19 UC, 39 CD, 2 indeterminate) Median 3 y (IQR 2.0–4.4)/Median 12.4 y (IQR 10.2–14.4) 63% M/66% M	Age (<6 y vs 7–16 y)	Colectomy (results for UC alone were presented)	Mean 4.9 y (SD 2.5)/ Mean 4.5 y (SD 2.5)

Table 1. Characteristics of studies included in meta-analysis (*continued*)

Study	Study design	Population by IBD type, age and sex	Predictors examined (definition, exposed vs unexposed)	Outcomes examined	Follow-up duration
Mataly *et al* (2013)[16]	Retrospective, single center	115 pediatric UC patients Mean 10.6 y (SD 5.1) 45% M	EIM (arthritis, aphthous stomatitis, arthralgia, erythema nodosum, skin lesions, and/or PSC) Sex	Colectomy	Median 4.4 y (±2.1)
McAteer *et al* (2013)[22]	Retrospective (Pediatric Health Information System database), multicenter	8,688 pediatric UC and indeterminate colitis patients (8,066 UC patients) Mean -NA, divided into categories 0–4, 5–10, 11–14, 15–17 y 48% M	Age (0–4 y, 5–10 y, 11–14 y, with 15–17 y reference) Hemoglobin level (anemia by ICD-9 category) Sex	Colectomy	Study period between 2004 and 2011
Moore *et al* (2011)[12]	Retrospective, single center	135 pediatric UC patients Mean 12.5 y (SD 4.1) 55% M	Age (mean) Disease extent (extensive if proximal to splenic flexure) ESR (mean)	Colectomy	NA
Nambu *et al* (2016)[27]	Retrospective, single center	63 pediatric UC patients 10 patients EO UC (0–7 y), 53 patients LO UC (8–15 y) 47% M	Age (0–7 y vs 8–15 y)	Colectomy	EO mean 42 mo (SD 40) LO mean 36.1 mo (SD 26.5)
Newby *et al* (2008)[28]	Retrospective, multicenter	210 pediatic IBD patients (74 UC, 116 CD, 20 indeterminate) UC median 11.96 (range 2.08–15.33) UC 60% M	Sex	Colectomy	UC Mean 3.3 y (range 1–6.83)
Piekkala *et al* (2013)[19]	Retrospective, case control, single center	51 pediatric UC patients Surgery group median 13.1 y (range 3.1–16) Disease control 12.1 y (2.8–16.6) Non IBD control 13.5 y (2.7–16.8) NA	Disease severity at diagnosis (PUCAI >65)	Colectomy	Median 6 y (range 3–11)

Table 1. Characteristics of studies included in meta-analysis (*continued*)

Study	Study design	Population by IBD type, age and sex	Predictors examined (definition, exposed vs unexposed)	Outcomes examined	Follow-up duration
Rinawi *et al* (2017)[14]	Retrospective, single center	188 pediatric UC patients Median 13.1 y (IQR 10.2–15.2) 55% M	Age (median) CRP (median) Disease extent (E4 and E3 each vs proctitis) EIM (undefined) Family history of IBD Hemoglobin level (median) Hypoalbuminemia (mean) Sex (female vs male)	Colectomy	Median 6.9 y (range 1–30)
Schechter *et al* (2015)[13]	Retrospective, multicenter	115 pediatric UC patients (2–18 y) Mean 11 y (SD 4.1) 50% M	Disease extent (extensive/pancolitis vs left sided/proctitis)	Colectomy	Median 23.1 mo (IQR 15.3–43.4)

ASC, acute severe colitis; CD, Crohn's disease; CRP, C-reactive protein; EIM, extraintestinal manifestations; EO, early onset; ESR, erythrocyte sedimentation rate; F/U, follow-up; IBD, inflammatory bowel disease; ICD-9, International Classification of Diseases, Ninth Revision; IQR, interquartile range; LO, late onset; M, male; mo, month; NA, not available; PediIBDC, Pediatric Inflammatory Bowel Disease Consortium; PSC, primary sclerosing cholangitis; PUCAI, Pediatric Ulcerative Colitis Activity Index; SD, standard deviation; UC, ulcerative colitis; y, year.

Table 2. Risk of bias of included studies in meta-analysis

Study	Representativeness of exposed cohort	Representativeness of non-exposed cohort	Ascertainment of exposure	Outcome not present at start	Comparability of cohorts (up to 2 stars)	Outcome assessment	Follow-up long enough	Loss to follow-up	Overall risk of bias (number of stars)
Aloi et al (2013)[10]	1	1	1	1	0	1	1	1	7
Aloi *et al* (2015)[9]	1	1	1	1	0	1	1	1	7
Assa *et al* (2018)[11]	1	1	1	1	2	1	1	1	9
Chhaya *et al* (2015)[25]	1	1	1	1	2	1	1	1	9
Falcone *et al* (2000)[15]	1	1	1	1	0	1	1	1	7
Gower-Roussea u *et al* (2009)[6]	1	1	1	1	2	1	1	1	9
Kelley-Quon *et al* (2012)[23]	1	1	1	1	2	1	1	1	9
Lascurain *et al* (2016)[31]	1	1	1	1	1	1	1	0	8
Ledder *et al* (2014)[26]	1	1	1	1	0	1	1	1	7
Mataly *et al* (2013)[16]	1	1	1	1	0	1	1	1	7
McAteer *et al* (2013)[22]	1	1	1	1	2	1	0	0	7
Moore *et al* (2011)[12]	1	1	1	1	2	1	1	0	8
Nambu *et al* (2016)[27]	1	1	1	1	0	1	1	0	6
Newby *et al* (2008)[28]	1	1	1	1	0	1	1	1	7
Piekkala *et al* (2013)[19]	1	1	1	1	0	1	1	0	6
Rinawi *et al* (2017)[14]	1	1	1	1	2	1	1	1	9
Schechter *et al* (2015)[13]	1	1	1	1	1	1	1	0	7

Based on Newcastle-Ottawa Scale. All columns, 0 or 1 stars except comparability (0 to 2), the last column indicates the total number of stars.

Question 1: What are the prognostic risk factors of colectomy?
Colectomy
Statement 1.1. At diagnosis, disease extent, PUCAI score (≥65 points), hemoglobin, hematocrit, and white blood cells (WBC) may predict colectomy; PUCAI score ≥65 during the subsequent 3 months, family history of UC, and extraintestinal manifestations may predict colectomy
Statement 1.2. At diagnosis, age, sex, endoscopic severity, erythrocyte sedimentation rate (ESR), hypoalbuminemia, C-reactive protein (CRP), ferritin, ethnicity, anthropometric measures (ie, growth, weight, and body mass index [BMI] z-scores), duration of symptoms prior to diagnosis, genetic polymorphisms, and antineutrophil cytoplasmic antibodies (ANCA) status do not predict colectomy
Statement 1.3. Primary sclerosing cholangitis (PSC) may be protective for colectomy (82% agreement).
Statement 1.4. Disease extension over time may predict the need for colectomy; neutrophilic infiltration of the stomach and duodenum (but not the esophagus) at diagnosis may predict the need for colectomy
Statement 1.5. Clostridium difficile infection may be associated with increased risk of colectomy
Question 2: What are the prognostic risk factors of acute severe colitis (ASC)?
Episodes of ASC
Statement 2.1. Disease severity at onset, evaluated by PUCAI or endoscopic assessment, may predict future ASC
Statement 2.2. Hypoalbuminemia at diagnosis may predict future ASC; no other blood tests (ie, hemoglobin, ESR, and CRP) during the first 3 months after diagnosis are predictors of ASC
Statement 2.3. Age and disease extent at diagnosis do not predict development of ASC
Short-term outcomes of children hospitalized with ASC
Statement 2.4. PUCAI scores on days 3 and 5 of hospital admission predict the need for treatment escalation in the short- and long-term period following intravenous corticosteroid treatment
Statement 2.5. Higher CRP at both days 3 and 5 of treatment predicts response to intravenous steroids; ESR and hemoglobin do not predict outcomes at any time
Statement 2.6. Shorter time from disease onset to ASC may predict nonresponse to intravenous steroids
Statement 2.7. Genetic polymorphisms and cytokine status may predict the outcome in ASC
Statement 2.8. Fecal inflammatory markers are weak predictors of steroid response and have limited value in addition to the PUCAI in ASC
Statement 2.9. Age, sex, disease extent, ANCA positivity, and family history of IBD do not predict outcomes of ASC
Question 3: What are the prognostic risk factors of chronically active UC?
Disease activity
Statement 3.1. Age at diagnosis and sex do not predict disease activity
Statement 3.2. Rectal sparing at diagnosis does not predict disease activity; no studies have evaluated the association between disease extent and disease activity in pediatrics
Statement 3.3. ANCA positivity may not predict disease activity or endoscopic inflammatory grading
Disease extension over time
Statement 3.4. Family history of IBD may predict disease extension over time
Statement 3.5. At diagnosis, age, sex, weight, height, ethnicity, PUCAI, ANCA positivity, disease extent at diagnosis, and routine laboratory measures (CRP, ESR, hemoglobin/hematocrit, albumin, WBC, and ferritin level) do not predict disease extension
Disease severity over time (ie, medication use, response to treatment, hospitalization, and relapse)
Statement 3.6. PUCAI score (≤10) at 3 months predicts sustained steroid-free remission; disease severity at diagnosis (assessed clinically or endoscopically) does not predict subsequent use of immunomodulators or biologics
Statement 3.7. Genetic polymorphisms, particularly in genes associated with the treatment pathways, and ethnicity may predict response to medications
Statement 3.8. Serology (ANCA/anti-Saccharomyces cerevisiae antibodies [ASCA]) may predict anti-TNF use, but not immunomodulator use
Statement 3.9. At diagnosis, age, sex, weight, height, family history of IBD, clinical/endoscopic disease severity, and laboratory blood tests (CRP, ESR, albumin, hemoglobin, platelets) do not predict medication intensification
Statement 3.10. Disease extent at diagnosis may predict medication use and response to treatment; it does not, however, predict relapse
Statement 3.11. Duration of symptoms prior to diagnosis does not predict response to subsequent treatment
Question 4: What are the prognostic risk factors of cancer and/or mortality in patients with childhood-onset IBD?
Statement 4.1. Concomitant diagnosis of PSC, longstanding colitis (>10 years), male sex, and younger age at IBD diagnosis are risk factors for any cancer; having a first-degree relative with any cancer before 50 years of age may be a risk factor for cancer in UC
Statement 4.2. Malignancy and infection (sepsis and opportunistic infections) may be risk factors for mortality, but no population-based studies are currently available

Figure 1. Summary of consensus recommendations for the management of inflammatory bowel disease

Table 3. Individual findings of studies included in meta-analysis

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect		Unadjusted relative effect			Adjusted relative effect		
				Events/ exposed	Events/ unexposed	OR (95% CI)	HR (95% CI)	p-value	OR (95% CI)[1]	HR (95% CI)	p-value
Colectomy vs age											
Aloi *et al* (2013)[10]	Colectomy	Age (≤7 y vs ≥8 y)	15/110	5/34	10/76						
*Aloi *et al* (2014)[29]	Intestinal resection	Age	10/31					NS			
Aloi *et al* (2015)[9]	Colectomy	Age (mean)	10/31			0.2 (0.12–5.9)		NS			
Chhaya *et al* (2015)[25]	Colectomy	Age (10–13 y vs 17–24 y as reference)	73/1175				1.89 (1.02–3.5)	0.04		1.56 (0.83–2.91)	0.17
*Falcone *et al* (2000)[15]	Colectomy	Age (<18 y vs ≥18 y)	37/73					NS			
Gower-Rousseau *et al* (2009)[6]	Colectomy	Age (<10 y vs ≥10 y)	27/113				1.85 (0.6–6.1)	0.32			
Kelley-Quon *et al* (2012)[23]	Colectomy	Age	57/406				0.99 (99% CI 0.87–1.13)	0.837			
*Ledder *et al* (2014)[26]	Colectomy	Age (< 6 y vs 6–17 y)	3	3/20	0/19						
*Mataly *et al* (2013)*[16]	Colectomy (partial/total)	Age	/115					NS			
McAteer *et al* (2013)[22]	Colectomy	Age (0–4 y, 5–10 y, 11–14 y, with 15–17 y reference) (All NS, results presented for 0–4 y vs 15–17y)	227/8,066						1.06 (0.61–1.85)		0.827

Table 3. Individual findings of studies included in meta-analysis (*continued*)

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect		Unadjusted relative effect			Adjusted relative effect		
				Events/ exposed	Events/ unexposed	OR (95% CI)	HR (95% CI)	p-value	OR (95% CI)[1]	HR (95% CI)	p-value
Moore *et al* (2011)[12]	Colectomy	Age (mean)	37/135				1.16 (1.05–1.29)	0.01		1.18 (1.06–1.32)	0.00 (imputed model)
Nambu *et al* (2016)[27]	Colectomy	Age (0–7 y vs 8–15 y)	11/63	1/10	10/53						
*Newby *et al* (2008)[28]	Major surgery	Age	/210					0.14			
Rinawi *et al* (2017)[14]	Colectomy	Age (median)	34/188				1.03 (0.94–1.13)	0.524			
*Schechter *et al* (2015)[13]	Colectomy	Age	4/115 at 12 months; 12/115 at last F/U					NS			
*Stordal *et al* (2004)[30]	Surgery	Age (mean)	3/14					NS			
Colectomy vs sex											
Aloi *et al* (2013)[10]	Colectomy	Sex	15/110			0.72 (0.22–2.34)		0.82			
Aloi *et al* (2015)[9]	Colectomy	Sex (male vs female)	10/31	5/15	5/16	1.2 (0.2–6.0)		NS			
Chhaya *et al* (2015)[25]	Colectomy	Sex (female vs male)	73/1,175				1.25 (0.79–1.99)	0.35			
Falcone *et al* (2000)[15]	Colectomy	Sex (male vs female)	37/73	21/35	16/38						
Gower-Rousseau *et al* (2009)[6]	Colectomy	Sex (male vs female)	27/113				0.8 (0.4–1.8)	0.6			
Kelley-Quon *et al* (2012)[23]	Colectomy	Sex (male vs female)	57/406	25/199	32/207		0.91 (99% CI 0.30–2.78)	0.827			

Table 3. Individual findings of studies included in meta-analysis (*continued*)

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect		Unadjusted relative effect			Adjusted relative effect		
				Events/ exposed	Events/ unexposed	OR (95% CI)	HR (95% CI)	p-value	OR (95% CI)[1]	HR (95% CI)	p-value
Lascurain *et al* (2016)[31]	Colonic Surgery	Sex (male vs female)	PSC-IBD 0.4 colonic surgeries/1,000 patient-years Non–PSC-IBD 0.54 surgeries/1,000 patient-years				1.9 (0.9–3.8)	0.054		2.1 (1.1–4.2)	0.034
Mataly *et al* (2013)[16]	Colectomy	Sex	20/115				2.1 (1.1–8.2)	0.04			
McAteer *et al* (2013)[22]	Colectomy	Sex (male vs female)	227/8,066						0.96 (0.74–1.26)		0.789
*Moore *et al* (2011)[12]	Colectomy	Sex	/135					NS (female trend)			
Newby *et al* (2008)[28]	Surgery	Sex (male vs female)	12/74	6/45	6/29						
Rinawi *et al* (2017)[14]	Colectomy	Sex (female vs male)	34/188	9/85 male	25/103		0.41 (0.19–0.87)	0.021		0.24 (0.1–0.57)	0.001
*Schechter *et al* (2015)[13]	Colectomy	Sex	4/115 at 12 months; 12/115 at last F/U					NS			
*Zwintscher *et al* (2015)[18]	Surgical intervention	Sex	NA/511 (31 UC)						0.85 (0.77–0.94)		0.001
Colectomy vs EIM											
Aloi *et al* (2013)[10]	Colectomy	EIM (skin, joint, and ocular manifestations, and PSC)	15/110			0.66 (0.17–2.54)		0.77			
*Falcone *et al* (2000)[15]	Colectomy	EIM (mostly arthralgia)	37/73					NS			

Table 3. Individual findings of studies included in meta-analysis (*continued*)

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect		Unadjusted relative effect			Adjusted relative effect		
				Events/ exposed	Events/ unexposed	OR (95% CI)	HR (95% CI)	p-value	OR (95% CI)[1]	HR (95% CI)	p-value
Gower-Rousseau *et al* (2009)[6]	Colectomy	EIM (joint, skin, and ocular manifestations, and PSC)	27/113				3.4 (1.2–10.0)	0.02		3.5 (1.2–10.5)	0.03
Mataly *et al* (2013)[16]	Colectomy	EIM (arthritis, aphthous stomatitis, arthralgia, erythema nodosum, skin lesions, and/or PSC)	20/115				1.4 (0.3–4.0)	NS			
Rinawi *et al* (2017)[14]	Colectomy	EIM (undefined)	34/188	12/39	22/127		2.03 (1.01–4.1)	0.05		1.9 (0.76–4.76)	0.171
Colectomy vs family history of IBD											
Aloi *et al* (2013)[10]	Colectomy	Family history of IBD (first-degree relative UC/CD)	15/110			0.45 (0.095–2.16)		0.49			
*Aloi *et al* (2015)[9]	Colectomy	Family history of IBD	10/31					NS			
Falcone *et al* (2000)[15]	Colectomy	Family history of IBD	37/73	5/9	32/64						
Gower-Rousseau *et al* (2009)[6]	Colectomy	Family history of IBD	27/113				2.4 (0.9–6.4)	0.08		2.1 (0.7–5.7)	0.15
Kelley-Quon *et al* (2012)[23]	Colectomy	Family history of UC (first degree)	57/406	21/120	36/286						
Rinawi *et al* (2017)[14]	Colectomy	Family history of IBD	34/188	9/43	25/145		1.25 (0.56–2.69)	0.562			
Colectomy vs family history of UC											
Gower-Rousseau *et al* (2009)[6]	Colectomy	Family history of UC	27/113				2.9 (0.9–9.7)	0.08			

Table 3. Individual findings of studies included in meta-analysis (*continued*)

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect		Unadjusted relative effect			Adjusted relative effect		
				Events/ exposed	Events/ unexposed	OR (95% CI)	HR (95% CI)	p-value	OR (95% CI)[1]	HR (95% CI)	p-value
Kelley-Quon *et al* (2012)[23]	Colectomy	Family history of UC (first degree)	57/406				1.81 (1.25–2.61)	<0.001			
Colectomy vs disease extent											
Aloi *et al* (2013)[10]	Colectomy	Disease extent (extensive disease E3)	15/110			7.4 (2.2–24.8)		0.001			
Aloi *et al* (2015)[9]	Colectomy	Disease extent (E4 vs E1, E2, E3)	10/31	7/18	3/13	1.6 (0.3–8.0)		NS			
Assa *et al* (2018)[11]	Colectomy	Disease extent (E3/E4 at diagnosis)	22/126	18/88	4/35			0.18			
*Falcone *et al* (2000)[15]	Colectomy	Disease extent (pancolitis)	37/73					S			
Gower-Rousseau *et al* (2009)[6]	Colectomy	Disease extent (E3 vs E1)	27/113	8/42	5/71		2.4 (0.8–6.6)	0.11		2.4 (0.8–6.8)	0.10
*Hochart *et al* (2017)[17]	Colectomy	Disease extent (E1 vs E2–E4)	NA/158					NS			
*Mataly *et al* (2013)[16]	Colectomy	Disease extent (proctitis)	20/115			1.4 (0.7–4.5)		NS			
Moore *et al* (2011)[12]	Colectomy	Extensive disease (proximal to splenic flexure) vs non-extensive disease	37/135	27/99	10/36		1.44 (0.56–3.74)				
Rinawi *et al* (2017)[14]	Colectomy	E4 and E3 each vs proctitis	34/188				0.33 (0.04–2.81)/3.44 (1.26–9.36)	0.309/0.016		0.4 (0.1–2.2)/5.3 (0.9–8.2)	

Table 3. Individual findings of studies included in meta-analysis (*continued*)

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect		Unadjusted relative effect			Adjusted relative effect		
				Events/ exposed	Events/ unexposed	OR (95% CI)	HR (95% CI)	p-value	OR (95% CI)[1]	HR (95% CI)	p-value
Schechter *et al* (2015)[13]	Colectomy	Disease extent (extensive/pancolitis vs left sided/proctitis)	4/115 at 12 months; 12/115 at last F/U	9/86	3/29			NS			
*Zwintscher *et al* (2015)[18]	Surgical intervention	Perianal disease				2.01 (1.63–2.48)		<0.001			
Colectomy vs Disease extension											
Aloi *et al* (2013)[10]	Colectomy	Disease extension (involvement during F/U of at least one additional segment)	15/110			2.4 (0.8–7.4)		0.12			
Aloi *et al* (2015)[9]	Colectomy	Disease extension (according to Paris classification)	10/31	2/10	8/21	0.4 (0.4–2.6)		NS			
Gower-Rousseau *et al* (2009)[6]	Colectomy	Disease extension (yes vs no)	27/113	13/35	1/36		13.3 (1.7–101.7)				
Colectomy vs disease severity											
Aloi *et al* (2013)[10]	Colectomy	Disease severity at diagnosis	15/110			3.63 (1.13–11.62)		0.05			
Aloi *et al* (2015)[9]	Colectomy	Disease severity at diagnosis	10/31			1.4 (0.2–7.2)		NS			
Assa *et al* (2018)[11]	Colectomy	Disease severity at diagnosis (ASC)	22/126	12/37	10/86		3.5 (1.5–8.2)	0.002			0.008 (only p-value provided)
Piekkala *et al* (2013)[19]	Colectomy	Disease severity at diagnosis (PUCAI >65)	24/51	11/15	4/36						
*Rinawi *et al* (2017)[14]	Colectomy	Disease severity at diagnosis (PUCAI)	34/188					S			

Table 3. Individual findings of studies included in meta-analysis (*continued*)

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect		Unadjusted relative effect			Adjusted relative effect		
				Events/ exposed	Events/ unexposed	OR (95% CI)	HR (95% CI)	p-value	OR (95% CI)[1]	HR (95% CI)	p-value
*Schechter *et al* (2015)[13]	Colectomy	Disease severity at diagnosis (PUCAI)	4/115 at 12 months; 12/115 at last F/U					NS			
Colectomy vs ESR											
Aloi *et al* (2015)[9]	Colectomy	ESR (>25 mm/h)	10/31	5/16	5/15	0.9 (0.2–4.1)		NS			
Kelley-Quon *et al* (2012)[23]	Colectomy	ESR (>20 mm/h)	57/406	8/86	49/320		0.36 (99% CI 0.09–1.55)	0.073			
Moore *et al* (2011)[12]	Colectomy	ESR (mean)	37/135				1.01 (1.001–1.03)	0.06			
*Schechter *et al* (2015)[13]	Colectomy	ESR (median)	4/115 at 12 months; 12/115 at last F/U					NS			
Colectomy vs CRP											
Aloi *et al* (2015)[9]	Colectomy	CRP (>10 mg/L)	10/31	6/18	4/13	1.1 (0.2–5.2)		NS			
Gower-Rousseau *et al* (2009)[6]	Colectomy	CRP (<10 mg/L vs ≥10 mg/L)	27/113			8.5 (1.9–39)					
Kelley-Quon *et al* (2012)[23]	Colectomy	CRP (>5 mg/dL)	57/406	3/14	54/392		2.75 (99% CI 0.75–10.15)	0.045			
Rinawi *et al* (2017)[14]	Colectomy	CRP (median)	34/188				1.04 (0.88–1.23)	0.629			
*Schechter *et al* (2015)[13]	Colectomy	CRP	4/115 at 12 months; 12/115 at last F/U					NS			
Colectomy vs albumin											
Aloi *et al* (2015)[9]	Colectomy	Albumin (<3.2 g/dL)	10/31	5/14	5/17	1.3 (0.2–6.0)		NS			

Table 3. Individual findings of studies included in meta-analysis (*continued*)

Study	Outcome	Predictor (definition, exposed vs unexposed)	Events	Absolute effect		Unadjusted relative effect			Adjusted relative effect		
				Events/ exposed	Events/ unexposed	OR (95% CI)	HR (95% CI)	p-value	OR (95% CI)[1]	HR (95% CI)	p-value
Kelley-Quon *et al* (2012)[23]	Colectomy	Albumin (<3.5 g/dL)	57/406	10/41	47/365		6.05 (99% CI 2.15–17.04)	<0.001			
*Moore *et al* (2011)[12]	Colectomy	Albumin	37/135					NS			
Rinawi *et al* (2017)[14]	Colectomy	Albumin (mean)	34/188				0.74 (0.4–1.4)	0.334			
*Schechter *et al* (2015)[13]	Colectomy	Albumin	4/115 at 12 months; 12/115 at last F/U					NS			
Colectomy vs hemoglobin											
Kelley-Quon *et al* (2012)[23]	Colectomy	Hemoglobin (<10 g/dL)	57/406				0.41 (99% CI 0.03–6.01)	0.389			
McAteer *et al* (2013)[22]	Colectomy	Anemia (ICD-9 category)	227/8,066						2.17 (1.64–2.87)		<0.001
*Moore *et al* (2011)[12]	Colectomy	Hematocrit	37/135					S			
Rinawi *et al* (2017)[14]	Colectomy	Hemoglobin (median)	34/188				1.03 (0.87–1.23)	0.731			
*Schechter *et al* (2015)[13]	Colectomy	Hemoglobin	4/115 at 12 months; 12/115 at last F/U					NS			

*Denotes specific predictor-outcome pairs that could not be meta-analyzed due to heterogeneity or insufficient data, including lack of UC-specific data.

ASC, acute severe colitis; CD, Crohn's disease; CI, confidence interval; CRP, C-reactive protein; EIM, extraintestinal manifestations; ESR, erythrocyte sedimentation rate; F/U, follow up; HR, hazard ratio; IBD, inflammatory bowel disease; ICD-9, International Classification of Diseases, Ninth revision; NS, not significant; OR, odds ratio; PSC, primary sclerosing cholangitis; PUCAI, Pediatric Ulcerative Colitis Activity Index; S, significant but no numerical data provided; UC, ulcerative colitis; y, year.

Prognostic factors for colectomy

Statement 1.1. At diagnosis, disease extent, PUCAI score (≥65 points), hemoglobin, hematocrit, and white blood cells (WBCs) may predict colectomy; PUCAI score ≥65 during the subsequent 3 months, family history of UC, and extraintestinal manifestations may predict colectomy (96% agreement).

The association between disease extent and colectomy was assessed in 11 studies.[6, 9-18] Seven studies individually reported no association[6, 9-14] but the other 4 were positive [10, 14, 15, 18] (OR of 6 studies, 1.71; 95% confidence interval [CI], 0.87–3.34; n=630; I^2=53%[6, 9-13]; HR of 3 studies, 1.81; 95% CI, 0.73–4.52; n=436; I^2=61%[6, 12, 14]) (Figure 2A).

Colectomy was predicted by disease severity at diagnosis (as measured by the PUCAI) in 4 meta-analyzable studies out of 6 studies that explored this association[9-11, 13, 14, 19] (OR, 4.50; 95% CI, 1.83–11.06; n=318; I^2=49%) (Figure 2B).[9-11, 19] The 2 other studies found that PUCAI score also predicted colectomy at 3 months.[13, 14] Similarly, in the Predicting Response to Standardized Pedeatric Colitis Therapy (PROTECT) study published after the completion of our systematic review, time to colectomy was associated with week 4 clinical remission (defined as PUCAI <10).[120, 21] Additionally, colectomy rate at 52 weeks was lower in those with mild disease (2/163; 1.2%) compared with moderate to severe disease (23/237; 9.7%; *P*=0.0006).

Findings were inconsistent across studies for the predictive utility of hemoglobin and hematocrit at diagnosis on colectomy rates[12-14, 22, 23] of which 2 were positive[12, 22] (OR of 2 studies, 1.26; 95% CI, 0.28-5.68; n=8,472; I^2=83%[22, 23]; HR of 2 studies, 1.03; 95% CI, 0.86–1.22; n=594; I^2=0%[14, 23]) (Figure 2B). After the completion of this study, the prospective PROTECT cohort similarly found that higher hemoglobin levels at diagnosis were associated with a favorable outcome at 52 weeks.[20]

All 6 studies[6, 9, 10, 14, 15, 23] assessing family history of IBD as a predictor for colectomy found no association; 5 were meta-analyzable (pooled OR of 4 studies, 1.27; 95% CI, 0.82–1.97; n=777; I^2=0%[10, 14, 15, 23]; pooled HR of 2 studies, 1.51; 95% CI, 0.80–2.82; n=301; I^2=0%[6, 14]) (Figure 3A). One other study included a mixed IBD population of 411 patients (244 UC, 129 CD, and 38 IBD unclassified), and showed no association between family history of IBD and need for surgery.[24] However, family history of only UC as opposed to any IBD was positive in 1[23] of 2 studies and in the meta-analysis (pooled HR of 2 studies, 1.89; 95% CI, 1.33–2.68; *P*=.0004; n=557; I^2=0%) (Figure 2D).[6, 23]

Association between extraintestinal manifestations and colectomy was explored in 5 studies; 1[6] found an association with colectomy, 1[14] found borderline significance on univariate analysis but not on multivariate analysis, and 3 found no association.[910, 15, 16]

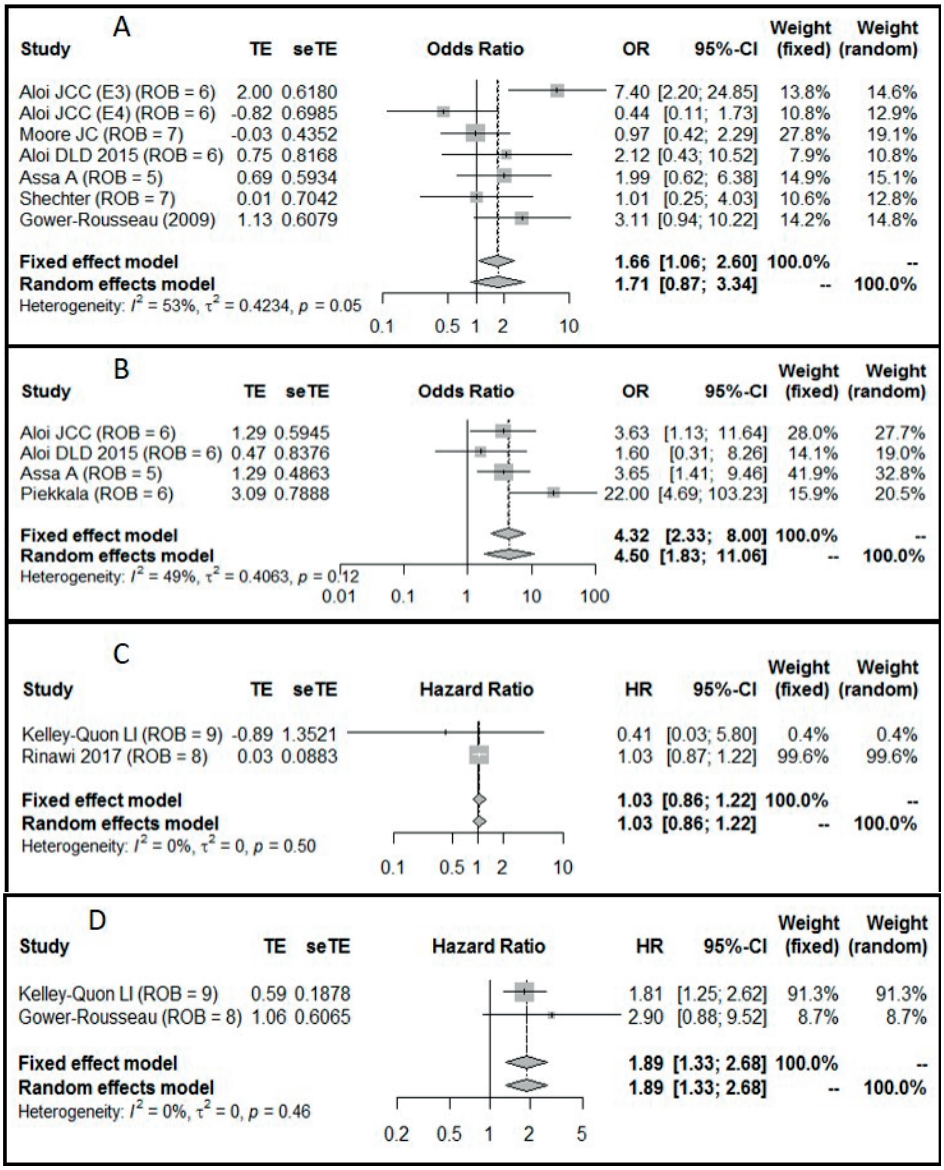

Figure 2. Forest plots for predictors that may be associated with colectomy in pediatric ulcerative colitis: A – disease extent; B – disease severity; C – hemoglobin; D – family history of UC; DLD, Digestive and Liver Disease; JCC, Journal of Crohn's and Colitis; ROB, risk of bias; seTE, standard error of treatment estimate; TE, estimate of treatment effect.

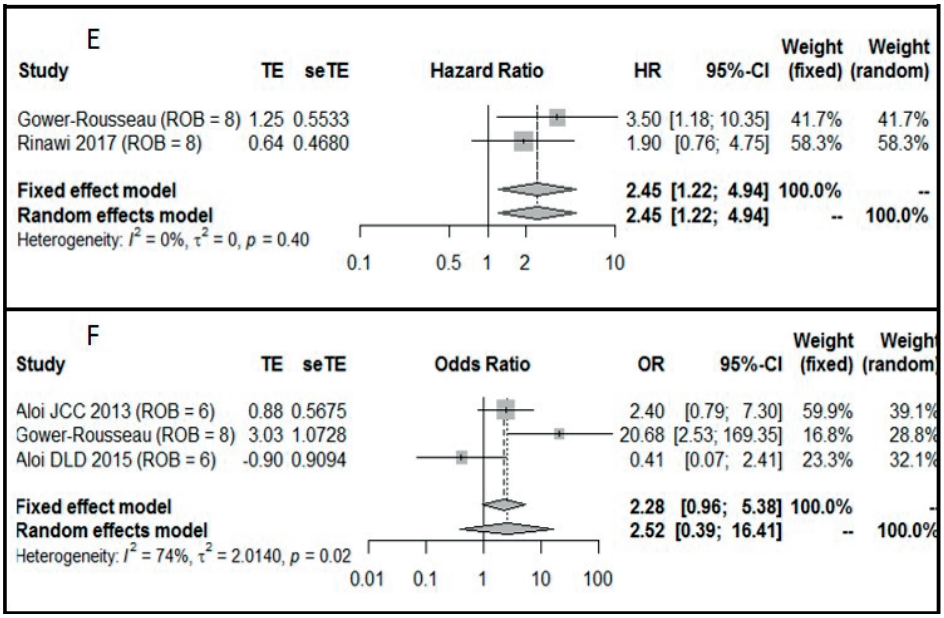

Figure 2. Forest plots for predictors that may be associated with colectomy in pediatric ulcerative colitis: E – extraintestinal manifestations; F – disease extension.
DLD, Digestive and Liver Disease; JCC, Journal of Crohn's and Colitis; ROB, risk of bias; seTE, standard error of treatment estimate; TE, estimate of treatment effect.

Meta-analysis of 4 of the studies found a positive association (pooled OR of 3 studies 1.50; 95% CI, 0.79–2.84; n=413; I^2=5%[10, 14, 16]; pooled HR of 2 studies, 2.45; 95% CI,1.22–4.94; n=301; I^2=0%[6, 14]) (Figure 2E).

Two studies[12, 23] were conflicting regarding WBC count at diagnosis, with the larger study of 406 patients not finding a significant result,[23] whereas a smaller study of 135 patients reported an increased risk with either elevated WBC count (mean 11.6 vs 9.5; *P*=0.008) or elevated absolute neutrophil count, as well as adjusted HR of 1.10 (95% CI, 1.02–1.19) for WBC count.[12]

Statement 1.2. At diagnosis, age, sex, endoscopic severity, erythrocyte sedimentation rate (ESR), hypoalbuminemia, C-reactive protein (CRP), ferritin, ethnicity, anthropometric measures (ie, growth, weight, and body mass index [BMI] *z*-scores), duration of symptoms before diagnosis, genetic polymorphisms, and antineutrophil cytoplasmic antibodies (ANCA) status do not predict colectomy (82% agreement).
Only 2[12, 25] of 16 studies on the topic[6, 9, 10, 13-16, 22, 23, 26-30] found an association between age and colectomy. Four meta-analyzable studies[9,10, 22, 27] were pooled for OR (0.97; 95% CI, 0.43–2.21; n=8,270; I^2=43%) and 5[6, 12, 14, 23, 25] for HR (1.07; 95% CI, 0.97–1.19; n=2,017; I^2=51%) (Figure 3B).

Sex was not associated with colectomy in 9[6, 9, 12, 13, 14, 22, 23, 25, 28] of 13 relevant studies,[6, 9, 12-16, 18, 22, 23, 25, 28, 31] while the remaining 4 studies[14, 16, 18, 31] indicated that boys may be more likely to undergo colectomy. Nonetheless, most studies were meta-analyzable and the pooled association was negative (OR of 8 studies, 1.17; 95% CI, 0.83–1.66; n=9,063; I^2=38%[9, 10, 14-16, 22, 23, 28]; HR of 5 studies, 1.48; 95% CI,0.89–2.47; n=2,094; I^2=63%[6, 14, 23, 25, 31]) (Figure 3C).

Endoscopic severity at diagnosis did not predict colectomy in 2 retrospective studies (n=115 and n=185).[13, 31] The prospective PROTECT pediatric study reached the same conclusion, in which baseline endoscopic severity was not associated with week 12 outcomes.[32]

Four studies[9, 13, 14, 23] did not find an association between ESR at diagnosis and colectomy, consistent with the meta-analysis results of 3 of the studies (OR of 2 studies, 0.63; 95% CI, 0.31–1.26; n=437; I^2=0%[9, 23]; HR of 2 studies, 0.78; 95% CI, 0.32–1.87; n=541; I^2=50%[12, 23]) (Figure 3D).

Hypoalbuminemia did not predict colectomy; only 1[23] of 5 studies[9, 12-14, 23] was positive. Three studies were meta-analyzable[9, 14, 23] (OR of 2 studies, 1.97; 95% CI, 0.99–3.93; n=437; I^2=0%[9, 23]; HR of 2 studies, 2.09; 95% CI, 0.27–16.35; n=594; I^2=94%[14, 23]) (Figure 3E).

Four[9, 13, 14, 23] of 5ive[6, 9, 13, 14, 23] studies found that CRP at diagnosis did not predict colectomy, consistent with the meta-analysis of 4 of these (OR of 3 studies, 2.5; 95% CI, 0.78–8.01; n=550; I^2=49%[6, 9, 23]; HR of 2 studies, 1.49; 95% CI,0.59–3.73; n=594; I^2=72%[14, 23]) (Figure 3F). Of note, in the only positive study, the rate of colectomy was higher among children whose CRP was greater than 10 mg/L at diagnosis.[6] A retrospective study found no association between ferritin at diagnosis and colectomy.[14]

Ethnicity did not predict colectomy in 4 studies.[14, 15, 23, 33] Six studies examined the association between anthropometric characteristics and colectomy.[12, 14, 18, 22, 23, 34] Only 1 retrospective study of 406 children reported an association between weight loss at diagnosis and colectomy.[23] Two large studies suggested that obesity does not predict colectomy.[22, 34]

Delay in diagnosis did not predict colectomy in 3 studies.[6, 16, 28] The predictive utility of genetic polymorphisms was examined in 6 studies.[35-40] However, reliable relationships are difficult to establish because different polymorphisms were assessed across studies. Specifically, *CARD15* polymorphisms,[35, 39] DLG5 polymorphisms,[39] the presence of TC haplotype of OCTN1/2 variants,[39] anti-tumor necrosis factor (TNF) variants,[38] and MDR1

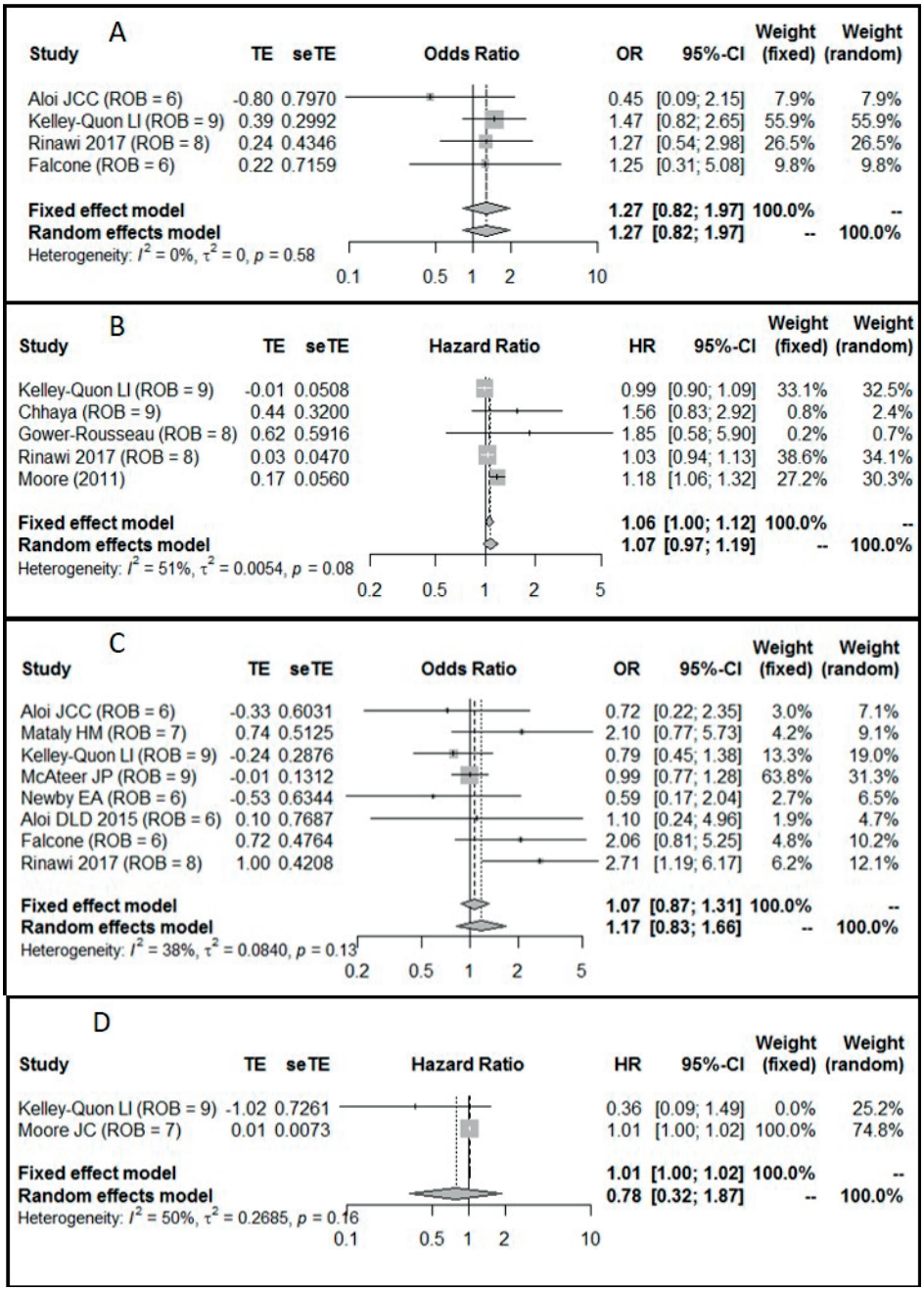

Figure 3. Forest plots for predictors that do not predict colectomy in pediatric ulcerative colitis: A – family history of inflammatory bowel disease; B – age; C – sex; D – erythrocyte sedimentation rate; E – albumin; F – C-reactive protein.

DLD, Digestive and Liver Disease; JCC, Journal of Crohn's and Colitis; ROB, risk of bias; seTE, standard error of treatment estimate; TE, estimate of treatment effect.

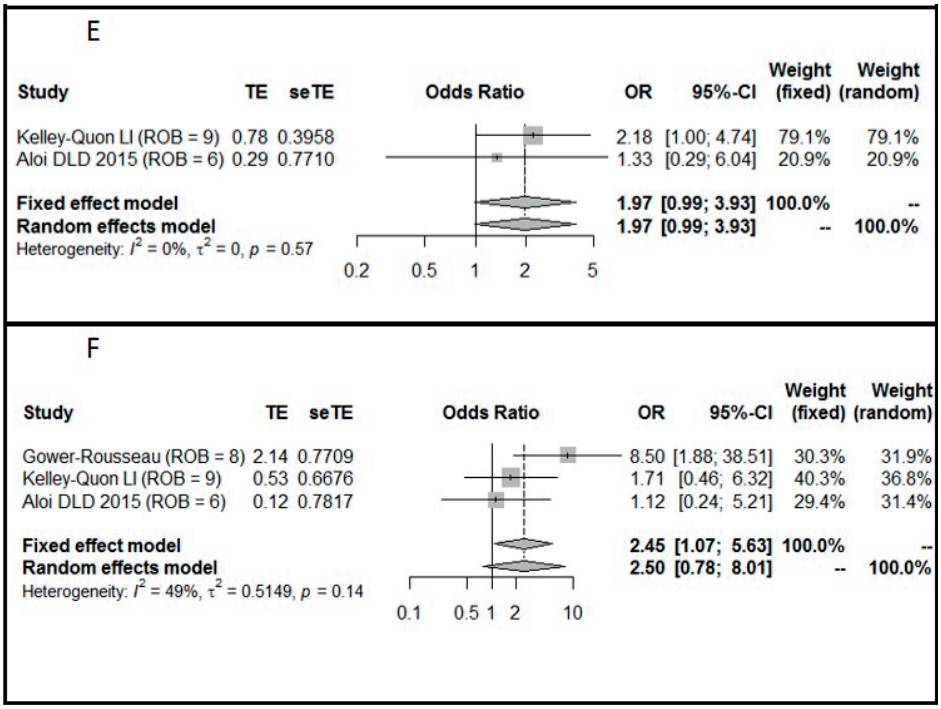

Figure 3. Forest plots for predictors that do not predict colectomy in pediatric ulcerative colitis: E – albumin; F – C-reactive protein.

DLD, Digestive and Liver Disease; JCC, Journal of Crohn's and Colitis; ROB, risk of bias; seTE, standard error of treatment estimate; TE, estimate of treatment effect.

C3425T variants[38] were not associated with colectomy. A genome-wide association study including 1,213 patients with UC (261 with childhood-onset UC) found an association between the minor allele of the NKX2-3 gene (s11190140) and the need for surgery (*P*=.038); however, this effect became trend-level among the childhood-onset patient subset.[37] Three studies found no association between ANCA status and colectomy.[9, 41, 42]

Statement 1.3. Primary sclerosing cholangitis (PSC) may be protective for colectomy (82% agreement).

Two studies found that PSC is protective against the need for colectomy for chronically active or medically refractory colitis, including a study of 8,688 children using the Pediatric Health Information System database.[22, 31]

Statement 1.4. Disease extension over time may predict the need for colectomy; neutrophilic infiltration of the stomach and duodenum (but not the esophagus) at diagnosis may predict the need for colectomy (86% agreement).

Statement 1.5. *Clostridium difficile* infection may be associated with increased risk of colectomy (85% agreement).

One[6] of 3[6, 9, 10] studies found an association between disease extension over time and colectomy (HR, 13.3; 95% CI, 1.72–102.87; n=113), but meta-analysis was possible only on OR and did not reach significance (pooled OR of 3 studies, 2.52; 95% CI,0.39–16.41; n=292; I^2=74%) (Figure 2F). One study identified a significant association between neutrophil infiltration of the stomach and duodenum (but not the esophagus), and greater likelihood of colectomy.[43]

C. difficile infection was associated with colectomy in the Pediatric Health Information System database of 8,688 children with UC (OR, 1.76; 95% CI, 1.5–3.25).[22]

Prognostic risk factors of acute severe colitis and related outcomes

Statement 2.1. Disease severity at onset, evaluated by PUCAI or endoscopic assessment, may predict future ASC (96% agreement).

Statement 2.2. Hypoalbuminemia at diagnosis may predict future ASC; no other blood tests (ie, hemoglobin, ESR, and CRP) during the first 3 months after diagnosis are predictors of ASC (92% agreement).

Statement 2.3. Age and disease extent at diagnosis do not predict development of ASC (88% agreement).

Effect of disease severity on ASC was investigated in a chart review of 115 children with new-onset UC.[13] Upon correction with the Bonferroni threshold for multiple testing, only endoscopic severity (*P*=.006) and hypoalbuminemia (*P*=.003) at diagnosis, and PUCAI at diagnosis and at 3 months (both *P*<.001), predicted ASC. Age at diagnosis did not predict ASC in 2 retrospective studies of children with UC.[27, 44] One of these studies also found no association between ASC and disease extent.[44]

Statement 2.4. PUCAI scores on days 3 and 5 of hospital admission predict the need for treatment escalation in the short- and long-term period following intravenous corticosteroid treatment (100% agreement).

Statement 2.5. Higher CRP at both days 3 and 5 of treatment predicts response to intravenous steroids; ESR and hemoglobin do not predict outcomes at any time (96% agreement).

Four studies examined PUCAI scores as predictors of steroid response in children hospitalized for ASC.[4, 9, 45, 46] In a prospective study of 128 children and a retrospective study of 99 children hospitalized for ASC, PUCAI >45 at day 3 and of >70 at day 5 pre-

dicted response to steroids and need for second-line therapy.[4, 45] Day 3 PUCAI score also predicted response up to 1 year after discharge (P<.001 for time to salvage therapy).[45] After the systematic review, this association was observed further in a small randomized controlled trial of children admitted for ASC[47] but not in another prospective study of 31 children.[9]

Two of 3 studies associated CRP determined at days 3 and 5 of admission for ASC with corticosteroid response.[4, 9, 45] ESR and hemoglobin did not predict response at any time during hospitalization.[9, 45] In a retrospective study of 56 children with ASC, ulcerations and megacolon on abdominal X-ray was associated with nonresponse to intravenous steroids.[48]

Statement 2.6. Shorter time from disease onset to ASC may predict nonresponse to intravenous steroids (94% agreement).

Three studies evaluated time-related parameters as predictors of response.[4, 9, 45] Two found no association between ASC at first presentation and corticosteroid response compared with those with a relapse.[4] On the other hand, in another prospective cohort, new-onset disease was associated with short-term corticosteroid failure on multivariate analysis with an OR of 0.27 (95% CI, 0.1–0.7).[45]

Statement 2.7. Genetic polymorphisms and cytokine status may predict the outcome in acute severe colitis (84% agreement).

In the prospective Outcome of Steroid therapy in Colitis Individuals (OSCI) study of 128 children with ASC, 41 genes were expressed differentially among children who were steroid-resistant; a cluster of 10 genes classified responders from nonresponders with 80% sensitivity and 80% specificity.[40] However, in a case-control study of 588 children with IBD (318 with UC), the 41 polymorphisms identified in the previous study were not associated with colectomy.[36]

Statement 2.8. Fecal inflammatory markers are weak predictors of steroid response and have limited value in addition to the PUCAI in ASC (80% agreement).

In an analysis from the prospective OSCI study including 101 children with ASC, levels of M2-pyrovate kinase and calprotectin on day 3 of hospitalization were higher among steroid-refractory children.[46] However, stool markers did not improve ability to predict steroid nonresponse above and beyond PUCAI.

Statement 2.9. Age, sex, disease extent, ANCA positivity, and family history of IBD do not predict outcomes of ASC (92% agreement).

Age at diagnosis did not predict response to corticosteroids in 2 pediatric studies of ASC.[4, 9] On the other hand, in the aforementioned OSCI study, younger age was associated with corticosteroid failure.[45] IBD family history did not predict corticosteroid response in 2 studies.[9, 45] Sex and disease extent did not predict response to intravenous steroids in these studies, as well as in an additional study.[4] Perinuclear antineutrophil cytoplasmic antibody positivity similarly did not predict response to corticosteroids.[8]

Prognostic factors for chronically active pediatric ulcerative colitis

Statement 3.1. Age at diagnosis and sex do not predict disease activity (96% agreement).

Studies suggested that age at diagnosis[27, 49] and sex[50] do not predict longitudinal disease activity. In another retrospective study of 8,120 patients with UC (210 of whom diagnosed younger than 16 years of age), younger age was associated with disease worsening.[51] However, childhood-onset disease was not analyzed separately.

Statement 3.2. Rectal sparing at diagnosis does not predict disease activity; no studies have evaluated the association between disease extent and disease activity in pediatrics (94% agreement).

In a single study published to date including 30 children with UC, rectal sparing was not associated with disease activity.[52] Of note, a higher proportion of children with proctitis achieved remission with initial medical treatment than those with rectal sparing.

Statement 3.3. ANCA positivity may not predict disease activity or endoscopic inflammatory grading (96% agreement).

One small retrospective study of 38 children with ulcerative proctitis found no association between ANCA and disease activity or endoscopic inflammatory grading.[41]

Statement 3.4. Family history of IBD may predict disease extension over time (91% agreement).

Three studies evaluated family history as a predictor of disease extension over time, of which only 1 found an association.[6, 10, 53] In that longitudinal study of 113 children, family history also predicted disease extension after controlling for follow-up duration and disease extent at diagnosis.[6]

Statement 3.5. At diagnosis, age, sex, weight, height, ethnicity, PUCAI, ANCA positivity, disease extent at diagnosis, and routine laboratory measures (CRP, ESR, hemoglobin/hematocrit, albumin, WBC, and ferritin level) do not predict disease extension (86% agreement).

Age at diagnosis and sex did not predict disease extension in 5 studies.[6, 10, 16, 54, 55] Similarly, weight, height, and BMI were not predictors in 2 studies.[53, 55] One retrospective study reported no association between ethnicity and disease extension in 723 patients with childhood-onset IBD.[53]

Disease activity at diagnosis (measured by the PUCAI) was evaluated as a predictor for disease extension in 4 pediatric studies,[10, 53-55] 1 of which (n=113) found an association with an adjusted HR of 8.77 (95% CI, 1.75–43.9).[53] The 3 others did not find any significant association.

Neither of 2 studies exploring disease extent at diagnosis as a predictor for disease extension over time reported a significant association.[6, 10] Four of the 5 studies reporting on differing laboratory values at diagnosis (ie, CRP, ESR, hemoglobin, hematocrit, albumin, WBC, and ferritin level) did not report an association with disease extension over time.[6, 10, 54, 55] One study, which included 134 UC patients with at least 5 years' follow-up, found an association between lower zinc levels at diagnosis and disease extension on multivariate analysis (HR, 0.94; 95% CI, 0.88–0.99; higher levels were protective).[53]

Statement 3.6. PUCAI score (≤10) at 3 months predicts sustained steroid-free remission; disease severity at diagnosis (assessed clinically or endoscopically) does not predict subsequent use of immunomodulators or biologics (81% agreement).

Disease severity (clinical or endoscopic) at diagnosis was not associated with subsequent use of immunomodulators or biologics in 4 studies.[13, 56-58] However, at 3 months, the probability of achieving 1-year sustained steroid-free remission was higher among children with PUCAI of ≤10, regardless of thiopurine or steroid use (probability of 48% in children with inactive disease vs 9%; $P<.0001$).[13] In the same study, PUCAI scores at diagnosis and at 3 months predicted the need for anti-TNF or calcineurin inhibitors during the first year. After completion of the systematic review, the PROTECT inception prospective cohort of pediatric UC was published, verifying that PUCAI at baseline and at 1 month after diagnosis independently predicted 1-year steroid-free remission.[20]

Statement 3.7. Genetic polymorphisms, particularly in genes associated with the treatment pathways, and ethnicity may predict response to medications (92% agreement).

Three of 5 studies found a positive association between genetic polymorphisms and response to medications in pediatrics.[37-39, 59, 60] The rs2395185 variant of the HLA gene was associated with response to steroids in a study of 1,213 children with UC, but this effect was lost after controlling for age at diagnosis.[37] In a study of 154 children with IBD, BclI polymorphism was associated with steroid response, and the NALP1 Leu55His mu-

tant variant was associated with steroid resistance.[59] Single-nucleotide polymorphisms of TNF-α and MDR1 genes were not associated with any clinical characteristics of UC, although a trend toward increased steroid resistance was noted in carriers of the TNF-α risk genotype.[38] In another study of patients with childhood-onset IBD, HLA-DRB101 was more common among patients who required anti-TNF treatment; no similar association was identified for other haplotypes.[60] No association was noted between the need for steroids and other genes, including CARD15, AA/AG genotypes of DLG5 variant, and presence of TC haplotype of OCTN1/2 variants.[39] In the prospective PROTECT cohort, 33 genes were differentially expressed in the rectum in patients with moderate/severe disease who achieved week 52 corticosteroid-free remission compared with those who did not.[20]

Ethnicity was found to predict treatment escalation in 2 studies. In 107 children with IBD (45 with UC), treatment with steroids, methotrexate, and adalimumab at 1 year was more common among South Asian children than White children.[61] In a 10-year review of 245 children with IBD (40 with UC: 33 White, 7 Black), a higher proportion of Black children were prescribed steroids and/or infliximab.[33] After the systematic review, the prospective PROTECT cohort did not find an association between race and sustained corticosteroid-free remission at 52 weeks.[20]

Statement 3.8. Serology (ANCA/anti-*Saccharomyces cerevisiae* antibodies [ASCA]) may predict anti-TNF use, but not immunomodulator use (91% agreement).
The utility of serology to predict the use of medications was inconsistent across 2 pediatric studies. Although 1 showed that perinuclear antineutrophil cytoplasmic anti-body+/ASCA– predicted use of biologics in UC,[42] the other showed no association between serologic markers and steroid or immunomodulator use.[41]

Statement 3.9. At diagnosis, age, sex, weight, height, family history of IBD, clinical/endoscopic disease severity, and laboratory blood tests (CRP, ESR, albumin, hemoglobin, platelets) do not predict medication intensification (90% agreement).
None of 6 relevant studies identified an association between age at diagnosis and response to medications, including steroids.[13, 27, 57, 59, 62, 63]

Two[26, 64] of 5 studies[26, 27, 49, 58, 64] reported a positive association between younger age and medication use. Data obtained from a prospective, multicenter observational study (n=1,928 children, 27% with UC) did not find a difference between age groups 1–5, 6–10, and 11–16 years and the use of antibiotics, mesalamine, corticosteroids, or immunomodulators at 1 year after diagnosis. At 5 years, however, those in the youngest group were more likely to receive mesalamine or thiopurine compared with the oldest age

group. As for the anti-TNF agents, treatment with infliximab and adalimumab did not differ significantly among the age groups,[49, 64] although in the study by Oliva-Hemker *et al.*[49], exposure to adalimumab was minimal in the younger age group, thus limiting the conclusions that could be drawn. Additionally, a retrospective chart review of children with IBD (20 of whom with UC were <6 years of age and 19 of whom with UC were between 6 and 17 years) showed a trend for a higher proportion of patients younger than 6 years at diagnosis requiring immunomodulatory therapy; no significant association was found for steroid treatment.[24]

Five of 6 studies identified no association between sex and medication use, treatment response, and sustained steroid-free remission.[50, 57, 58, 62, 63] One exception was a study of 154 children with IBD (74 with UC), in which boys were more likely to achieve better outcomes.[59] In retrospective study of 156 children with IBD (47 with UC), BMI and height *z*-scores were not associated with use of immunomodulators.[58] The PROTECT study, including 400 pediatric patients with UC, also did not find an association between age or sex and corticosteroid-free remission at 52 weeks.[20]

No association between family history of IBD and medication intensification was found in 2 studies.[24, 62] Disease severity at diagnosis, assessed clinically or endoscopically, did not predict medication use in 4 studies.[13, 56-58]

Findings exploring utility of laboratory tests (CRP, ESR, albumin, hemoglobin, and platelet level) for predicting medication use were inconsistent across 6 studies.[13, 56-58, 65, 66] In 124 children with UC, initial elevated CRP and abnormal iron levels were associated with subsequent use of azathioprine.[56] In a chart review of 115 children with new-onset UC, the need for salvage therapy during the first year was associated with ESR at 3 months.[13] Two other studies found no such association.[58, 65] In a retrospective study of 96 children with newly diagnosed UC, tissue and peripheral eosinophil counts correlated with short-term use of corticosteroids, immunomodulators, and biologics.[66] The aforementioned PROTECT study found an association between albumin, ESR, CRP, calprotectin, and bioavailable 25-hydroxyvitamin D and corticosteroid-free remission at 52 weeks, though only hemoglobin ≥10 g/dL at baseline was significant in 386 patients included in a multivariable model. Additionally, on microbiome analysis, decreased expression of Clostridiales was associated with escalation to anti-TNF therapy.[20]

Statement 3.10. Disease extent at diagnosis may predict medication use and response to treatment; it does not, however, predict relapse (87% agreement).

Statement 3.11. Duration of symptoms prior to diagnosis does not predict response to subsequent treatment (96% agreement).

Two of 6 studies identified an association between disease extent and medication use.[11, 13, 17, 58, 62, 63] Three evaluated response to medication[13, 62, 63] and 2, medication use.[11, 58] In 1 of the positive studies, cumulative probability of immunomodulator use was lower among children with isolated proctitis compared with all others, but anti-TNF therapy use was similar.[17] The other found that those with extensive disease (E3/E4) at

Table 4. Summary of outcomes and respective predictors in pediatric UC

Outcomes	Predictors	Possible predictors	No association
Colectomy		• At diagnosis: o Disease extent o PUCAI ≥65 o Hemoglobin, hematocrit, albumin o Neutrophilic infiltration in the upper gastrointestinal tract • At 3 months: o Family history of UC o Extraintestinal manifestations • PSC • Disease extension over time • *Clostridium difficile* infection	• At diagnosis: o Age o Sex o Endoscopic severity o ESR, CRP, ferritin o Ethnicity o Anthropometric measures o Duration of symptoms prior to diagnosis o Genetic polymorphisms o ANCA status
ASC		• Disease severity (PUCAI or endoscopic) at onset • Hypoalbuminemia at diagnosis	• Hemoglobin, ESR, CRP • Age • Disease extent
Outcomes of ASC	• PUCAI scores on days 3 and 5 of admission • CRP at days 3 and 5 of treatment • Shorter time from disease onset to ASC	• Ulcerations on X-ray and evidence of megacolon • Genetic polymorphisms • Cytokine status • Fecal inflammatory markers (but not in addition to PUCAI)	• ESR, hemoglobin • Radiological features other than ulcerations and megacolon • Age • Sex • Disease extent • ANCA (+) • Family history of IBD
Disease activity			• Age at diagnosis • Sex • Rectal sparing • ANCA (+)
Disease extension over time		• Family history of IBD	• Age • Sex • Weight, height • Ethnicity • PUCAI • ANCA (+) • Disease extent at diagnosis • CRP, ESR, hemoglobin, hematocrit, albumin, WBC, ferritin

Table 4. Summary of outcomes and respective predictors in pediatric UC (*continued*)

Outcomes	Predictors	Possible predictors	No association
Disease course	• Ethnicity • PUCAI (≤10) at 3 months (predicts steroid-free remission)	• Genetic polymorphisms • Serology may predict anti-TNF use • Disease extent at diagnosis may predict treatment response	• At diagnosis: o Disease severity o Age o Sex o Weight, height o Family history of IBD o Clinical/endoscopic disease o CRP, ESR, hemoglobin, albumin, platelets o Disease extent dose not predict relapse • Duration of symptoms prior to diagnosis
Cancer	• Concomitant diagnosis of PSC • Longstanding colitis • Male sex • Younger age at IBD diagnosis	• Having a first-degree relative with any cancer before 50 years of age	• Anti-TNF therapy alone

ANCA, antineutrophil cytoplasmic antibodies; ASC, acute severe colitis; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis; PUCAI, Pediatric Ulcerative Colitis Activity Index; TNF, tumor necrosis factor; UC, ulcerative colitis; WBC, white blood cells.

diagnosis increased the risk of receiving a biologic compared with patients with limited disease (E1/E2) (HR, 2.7; 95% CI, 1.2–6; *P*=0.015).[11]

Two studies evaluated disease extent as a predictor for relapse. In a 1-year prospective study of 37 children with newly diagnosed UC, histological upper gastrointestinal tract involvement did not differ among those who relapsed compared with those who did not, but children with more extensive disease trended toward a higher likelihood of relapse.[67] Rajwal *et al*.[52] assessed relapse index in 30 patients with newly diagnosed UC, 7 (23%) of whom had rectal sparing at endoscopy. The relapse index was slightly higher for children presenting with proctitis but did not reach statistical significance.[52] Similarly to prior adult data,[68] the PROTECT cohort found that patients with lower rectal eosinophil counts (<32 per high-power field) before treatment were more likely to escalate to anti-TNF therapy.[20]

None of the 3 studies exploring time to diagnosis as a predictor for treatment response reported a significant association.[58, 62, 63]

Prognostic risk factors for cancer and/or mortality in children with inflammatory bowel disease

Studies investigating cancer or mortality in PIBD are scarce and typically do not differentiate between UC and CD. Therefore, for these specific outcomes, prognostic factors were described for patients with PIBD in general.

Statement 4.1. Concomitant diagnosis of PSC, longstanding colitis (>10 years), male sex, and younger age at IBD diagnosis are risk factors for any cancer; having a first-degree relative with any cancer before 50 years of age may be a risk factor for cancer in UC (91% agreement).

In a study of 698 patients with childhood-onset IBD (median 15-year follow-up), 9 developed cancer (standardized incidence ratio [SIR] 3.0; 95% CI,1.3–5.9; *P*<.02).[69] In a cohort study comparing 9,405 pediatric patiens with with 92,870 age- and sex-matched control individuals, a higher risk for cancer was found in boys (HR, 4.6; 95% CI, 4.4–6.4) than in girls (HR, 1.5; 95% CI, 1.4–1.7), and in those with a younger age at first diagnosis (*P*=.006).[70] This study also found that longstanding colitis (≥ 10 years) was associated with increased risk of cancer. Having a first-degree relative with a cancer diagnosis before 50 years of age was associated with increased risk of cancer among patients with UC, but not with CD.[70]

PSC predicted colorectal cancer and cholangiocarcinoma.[70, 71] In the previously described study of 9,405 patients with childhood-onset IBD, patients with PSC IBD were at greater risk of developing cancer than those in the general population.[70] In addition, in a prospective case series from 20 European countries and Israel studying 60 patients with childhood-onset IBD who developed a malignancy or died, 56% of patients with fatal gastrointestinal cancer (cholangiocarcinoma or colorectal cancer) were also diagnosed with PSC.[71]

A pediatric study reported 15 malignancies among 5,766 patients with 24,543 years of follow-up, including 8 hematopoietic tumors.[32] The SIR for the development of a malignancy in patients exposed to a thiopurine with or without a biologic was significantly higher (SIR, 2.88; 95% CI, 1.44–5.14), whereas this was not the case in patients exposed to a biologic monotherapy. In a population-based study of 2,114 children who were ever treated with thiopurines, 15 cases of cancer were identified, of which 2 also received an anti-TNF agent at some point. Confidence intervals were wide and overlapping with no significant differences between groups of different drug exposures, which led the researchers to conclude that they cannot rule out thiopurines or anti-TNF agents as risk factors of cancer.[70]

In the aforementioned study, when compared with the Surveillance, Epidemiology, and End Results (SEER) reference population, no increased risk of malignancy was identified in a infliximab-treated cohort and biologics cohort.[32]

Statement 4.2. Malignancy and infection (sepsis and opportunistic infections) may be risk factors for mortality, but no population-based studies are currently available (83% agreement).

A survey of 21 pediatric gastroenterologists from 20 European countries and Israel identified 18 cases of cancer and 31 deaths in 44 children with IBD.[72] Infection was the most common cause of mortality, particularly among patients receiving 2 or more immunosuppressive agents. The second leading cause of mortality was cancer (5 cases, of which 3 were considered treatment related and 1 disease related [2 hepatosplenic T-cell lymphomas, 1 Epstein–Barr virus-positive lymphoma, and 1 colonic adenocarcinoma]).[72]

After the index date of systematic review, Olen *et al.*[73] reported 294 deaths among 138,690 patient-years of follow-up (n=9,442 individuals with pediatric IBD, 50 years of follow-up). This translated into 2.1/1,000 person-years compared with 0.7/1,000 person-years in matched control individuals. HRs for death were increased for UC (4.0; 95% CI, 3.4–4.7), CD (2.3; 95% CI, 1.8–3.0), and IBD unclassified (2.0; 95% CI, 1.2–3.4). Patients with IBD diagnosis at <6 years of age had higher HRs for death than children with later IBD onset. Apart from patients with very early onset IBD, the highest relative risk was observed in patients with UC with concomitant PSC (HR, 12.2; 95% CI, 8.4–17.8). Patients with UC undergoing bowel surgery or having a first-degree relative with UC were also at higher risk of death.

In the same aforementioned study, underlying causes for death in childhood-onset IBD included cancer (HR, 6.6; 95% CI, 6.3–8.2), infections (HR, 6.3; 95% CI, 2.1–16.9), and respiratory diseases (HR, 4.7; 95% CI, 1.8–11.3).[73]

IMPLICATIONS FOR PRACTICE

The PIBD-Ahead educational program reviewed clinical studies that sought to identify predictors of disease outcomes and treatment response in pediatric UC. Because treatments for IBD have advanced rapidly in recent years, it is important to explore predictors to guide management of the disease. Although this project is unprecedented in its systematic approach, with comprehensive involvement of many PIBD experts from dozens of countries and stringent consensus methodology, it is not without limitations. The

evidence was often limited, based on small retrospective cohorts, and with paucity of well-designed population-based studies. This has also led to heterogeneity in the methodology and results of the included studies. We have thus meta-analyzed only major outcomes and used soft language in statements when evidence was incomplete. The inability to separate CD and UC as exposures associated with future cancer or mortality is also a limitation. Nonetheless, the consensus statements presented here synthesize the current body of empirical evidence for predictors of pediatric UC outcome with the aim of supporting optimal, personalized treatments for children. This systematic review also serves to underscore the importance of continued multicenter efforts to further elucidate outcomes in pediatric UC.

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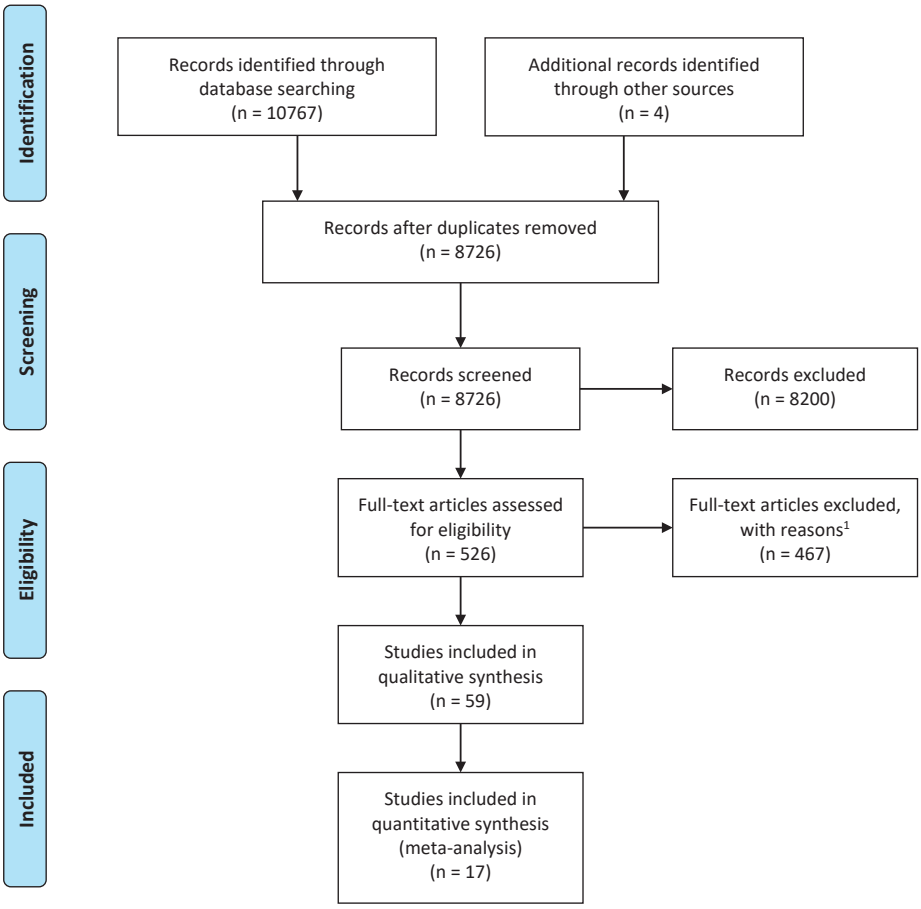
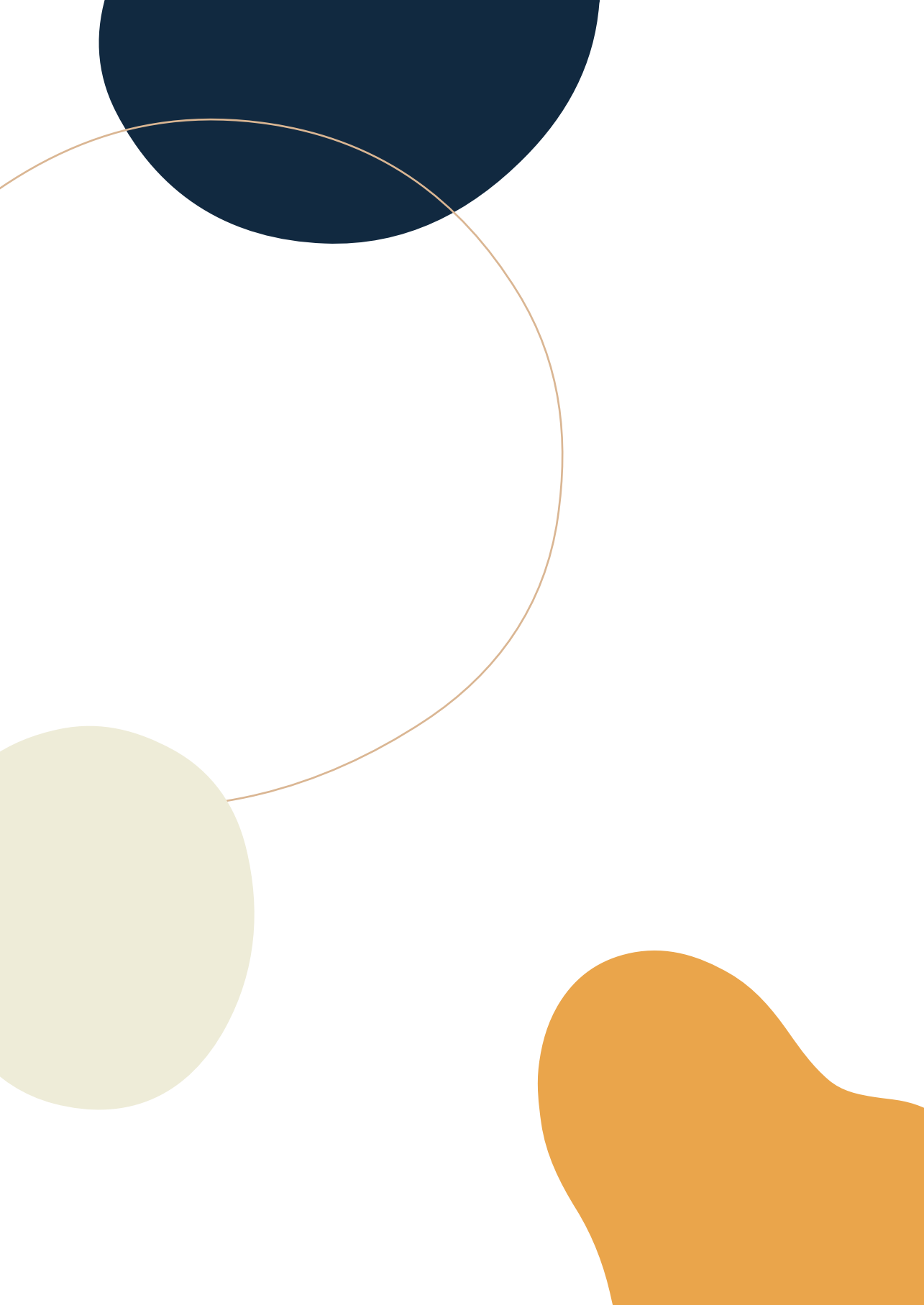


Supplemental Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram



09

International prospective observational study investigating the disease course and heterogeneity of pediatric-onset inflammatory bowel disease: the protocol of the PIBDSETQuality inception cohort study

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ABSTRACT

Introduction: Patients with paediatric-onset inflammatory bowel disease (PIBD) may develop a complicated disease course, including growth failure, bowel resection at young age and treatment-related adverse events, all of which can have significant and lasting effects on the patient's development and quality of life. Unfortunately, we are still not able to fully explain the heterogeneity between patients and their disease course and predict which patients will respond to certain therapies or are most at risk of developing a more complicated disease course. To investigate this, large prospective studies with long term follow-up are needed. Currently, no such European or Asian international cohorts exist. In this international cohort, we aim to evaluate disease course and which patients are most at risk of therapy non-response or development of complicated disease based on patient and disease characteristics, immune pathology and environmental and socioeconomic factors.

Methods and analysis: In this international prospective observational study, which is part of the PIBD Network for Safety, Efficacy, Treatment and Quality improvement of care (PIBD-SETQuality), children diagnosed with inflammatory bowel disease <18 years are included at diagnosis. The follow-up schedule is in line with standard PIBD care and is intended to continue up to 20 years. Patient and disease characteristics, as well as results of investigations, are collected at baseline and during follow-up. In addition, environmental factors are being assessed (eg, parent's smoking behaviour, dietary factors and antibiotic use). In specific centres with the ability to perform extensive immunological analyses, blood samples and intestinal biopsies are being collected and analysed (flow cytometry, plasma proteomics, mRNA expression and immunohistochemistry) in therapy-naïve patients and during follow-up.

Ethics and dissemination: Medical ethical approval has been obtained prior to patient recruitment for all sites. The results will be disseminated through peer-reviewed scientific publications.

Trial registration number: NCT03571373

INTRODUCTION

Background

Paediatric-onset inflammatory bowel disease (PIBD) is a chronic disease that often leads to disabling symptoms such as abdominal pain, diarrhoea and rectal bleeding. Inflammatory bowel disease (IBD) comprises Crohn's disease (CD), ulcerative colitis (UC) and IBD unclassified (IBD-U). Although IBD is most frequently known as an adult disease, in 5-25% of cases, it is diagnosed during childhood or adolescence.[1-3] The incidence of IBD in Western Europe and North America ranges from 1.85 to 23.82 per 100,000 for CD and 1.9 to 23.14 per 100,000 for UC.[4] Despite the fact that the incidence of IBD varies among different countries, a current concern is that the general trend shows increasing incidence rates over recent decades, especially among the patients <10 years of age.[1 3 5-7] Compared with adult-onset IBD, PIBD reflects a more severe disease.[8-10] Consequences of the disease, such as growth failure and bowel resection at a young age, may have a large impact on the patient's further development and quality of life (QoL). In addition, the early onset of this disease regularly leads to an early use of intensive therapies with a life-long risk of treatment-related adverse events.[8 11-13]

The pathogenesis of PIBD is currently partly explained by a combination of a genetic predisposition, microbial factors and susceptibility of the immune system leading to an aberrant inflammatory immune response.[14-16] Treatment strategies therefore focus on modulating or suppressing the immune response using immunosuppressive drugs or biologicals. Despite the known heterogeneity within paediatric patients with CD and UC at both disease diagnosis and during follow-up, we are still not able to predict which patients are at risk of developing a complicated disease course and which patients will respond to therapy.[17 18] Therefore, the majority of patients with PIBD have been treated following a step-up approach, a strategy in which patients start with a simpler, easily available therapy at the bottom of the therapeutic pyramid and medications at the top are often considered more efficacious but may present greater risk to the patient. This approach may lead to a delay in treatment response and increases the risk of ongoing inflammation risking penetrating and stricturing complications. The ability to predict complicated disease course and response or non-response to therapy would be of immense value. This is essential to develop strategies that balance, on an individual basis, therapeutic effectiveness with risks of treatment.

In studies including adult patients with IBD, several clinical risk factors have been identified for the development of a complicated disease course in CD and the need for colectomy in patients with UC.[19 20] Given the differences in disease phenotype, course of disease and benefits and risks of treatment between children and adults, findings

from studies in adult patients with IBD do not directly apply to PIBD. Few studies have assessed risk factors in patients with paediatric-onset CD and found that both stricturing disease behaviour[17 21 22] and older age at diagnosis [23-25] are associated with an increased risk for the need for surgery. In patients with paediatric-onset UC, the Paediatric Ulcerative Colitis Activity Index (PUCAI) at diagnosis and 3 months after diagnosis is found to be an essential predictor of colectomy.[26 27] Kugathasan *et al*. demonstrated that early anti-tumour necrosis factor (TNF) therapy in CD was associated with a decreased risk of penetrating but not stricturing complications.[28]

Due to the small number of available studies comprising a large variety of data on several different outcomes and predictors combined with a mainly retrospective set-up, to date most findings regarding predictors of disease course in PIBD are inconclusive. The majority of the identified predictors are demographic or associated with the disease phenotype and studies lack findings on the predictive value of biomarkers. Despite the known role of the immune system in PIBD, no immunological biomarkers have been identified to correlate with the disease phenotype or disease course. Therefore, there is an urgent need to generate a prospective long-term real-world cohort designed to analyse effectiveness and safety signals with the ability to correlate them to individual risk factors in well-phenotyped patients. To address this issue, the Paediatric Inflammatory Bowel Diseases Network for Safety, Efficacy, Treatment and Quality (PIBD-SETQuality) inception cohort was designed. Besides a few prospective PIBD cohorts, established in the USA and Canada, no international European cohorts currently exist to assess this.[28] Due to possible differences in genotype, environmental influences and treatment algorithms, European data are required. With this paper, we aim to inform the IBD research community about the existence of the PIBD-SETQuality inception cohort and provide insight into the establishment of this cohort.

Objectives

PIBD-SETQuality is an international project with the overall goal to develop and validate a treatment algorithm for PIBD based on high-risk or low-risk predictors for early complicated or relapsing disease. In this inception cohort, predictors of disease course are identified through prospective collection of longitudinal PIBD data in the first cohort that includes patients from several European and some Asian centres. Table 1 depicts the potentially relevant prognostic factors listed by the consortium, which formed the basis of parameters to investigate in this study.

The main objective of this study is to facilitate the discovery of predictors of disease course, treatment response or non-response and severe adverse events in patients with PIBD, by:

1) Collecting real-world longitudinal data with preferably a 20-year follow-up period.
2) Collecting biomaterials and linking this to the detailed clinical data.
3) Using standardised questionnaires to assess QoL.

Table 1. Potentially relevant prognostic factors in prediction of disease course and therapy responsiveness in PIBD.

Potentially relevant prognostic factors	
1	Family history
2	Medical history
3	Ethnicity
4	Severity of disease at diagnosis
5	Disease localisation
6	Course of disease
7	Level of inflammatory markers
8	Faecal calprotectin level
9	Endoscopic findings
10	Immunological biomarkers
11	Genetic polymorphisms
12	Environmental factors
13	Dietary factors
14	Health economic status
15	Psychosocial status

In addition, this cohort enables investigation of PIBD heterogeneity based on immunological biomarkers and racial or environmental factors. Patients of differing ethnicities in the European countries will be included along with patients from some non-European countries, which can allow comparison of different races in immigrant and non-immigrant subgroups.

METHODS AND ANALYSIS

Study design

The PIBD-SETQuality inception cohort is a multicentre prospective observational study in patients with PIBD. Participants are followed from the moment of diagnosis up to 20 years thereafter. During the first year after diagnosis, data collection is performed more frequently and reduced to annual visits after the second year of follow-up (Table 2).

Table 2. Visit schedule and included activities for PIBD-SETQuality inception cohort.

Visit number	**Visit 0**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Annual visits**	**Unscheduled visit**
Time point	**Prior to start of therapy**	**4 weeks after start of therapy**	**3 months after start of therapy**	**6 months after start of therapy**	**12 months after start of therapy**	**18 months after start of therapy**	**24, 36 months and so on**	
Activity								
Study explained, informed consent	X							
Collection of routine clinical and laboratory data, including faecal calprotectin	X	X	X	X	X	X	X	X
Extra blood sample taken at time of routine blood draw (maximum of 20 ml)*	O	O	O	O	O	O	O	O
Extra biopsies taken at time of clinically required colonoscopy (maximum of 8)*	O							O
Tissue sample in case of indication for surgical resection*		O	O	O	O	O	O	O
Environmental questionnaire	X							
IMPACT III & EQ-5D questionnaires	X (both)		X (EQ-5D)	X (EQ-5D)	X (both)	X (EQ-5D)	X (both)	
School attendance and WPAI questionnaires	X (both)		X (both)		X (both)		X (both)	

*This activity will only be performed in patients included in the subcohort. ''X'' is performed in all patients, ''O'' is only performed in patients included in the subcohort.
WPAI, Work Productivity and Activity Impairment.

At least 535 patients with PIBD need to be included in the inception cohort. However, since this is an observational study, depending on the feasibility, the study will aim to recruit 1000 patients. In specific centres with the capacity to perform immunological analyses, participants are included in a subcohort for additional collection of biological specimens. This allows in-depth characterisation of immunological pathways in 100 patients with CD and 50 patients with UC and provides the opportunity to relate predictive factors to underlying immune dysfunction during follow-up. The inception cohort is part of the PIBD-SETQuality project, which is funded by Horizon 2020.

Eligibility criteria

Children and adolescents <18 years with a likely or confirmed diagnosis of IBD are eligible. Diagnosis has to be made or confirmed within the first 2 months after inclusion. Diagnosis must be based on history, physical examination, laboratory, endoscopic, radiological and histological features according to the revised Porto criteria.[29] If a diagnosis of IBD is not confirmed after the investigations are complete, the patient will be excluded from follow-up. Other inclusion criteria comprise available data on all diagnostic procedures for inclusion in the database, informed consent of patient and parents according to the national guidelines, and, in case of inclusion in the subcohort for collection of biomaterial, the patient has not started therapy yet at the moment of diagnostic endoscopy. Patients are excluded from this study: (1) when they are on similar treatments as for IBD but for other conditions, defined as the use of any biological, immunosuppressant or systemic corticosteroid; (2) when they are known to have conditions directly affecting IBD (eg, immunodeficiency or major gastrointestinal resections); and (3) in case of inability to read or understand the patient and family information sheets.

Recruitment and data collection

All eligible patients are asked for informed consent to participate in the inception cohort. Within this study, clinical data and results of questionnaires will be collected in all patients. Biomaterial is collected as part of the subcohort in specific centres with the ability to perform immunological analyses.

Clinical data

At baseline, data on demographics, family history, diagnosis, disease activity, disease localisation and results of physical examination, endoscopy, radiographic imaging and laboratory results, including faecal calprotectin levels, are collected. Validated scores and classifications such as the weighted Paediatric Crohn's Disease Activity Index (wPCDAI), PUCAI, Simple Endoscopic Score for Crohn's Disease and Ulcerative Colitis Endoscopic Index of Severity are used.[30-33] During follow-up, the clinical disease activity

scores, results of additional investigations and detailed treatment information are collected at fixed time points and during hospitalisations.

Questionnaires

To assess the QoL, the validated IMPACT III questionnaire is being used. This questionnaire is a disease-specific health-related assessment of QoL, divided in the domains emotional functioning, social functioning, body image, and well-being.[34 35] Validated EQ-5D questionnaires are being used to assess the health status of the patient (EQ-5D-Y and EQ-5D-Y proxy) and the parents (EQ-5D-5L). The EQ-5D questionnaire consists of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.[36] Parent's work productivity is assessed by the Work Productivity and Activity Impairment questionnaire (WPAI) for caregivers. All validated questionnaires are used in accordance with their respective instructions regarding age limits. If validated translations of the IMPACT III, EQ-5D and WPAI are not available in a certain language, patients in the respective country will not complete these questionnaires. Due to the lack of validated questionnaires assessing the child's school attendance, a non-validated questionnaire is being used to address this subject. The frequency of the assessment of these questionnaires is shown in Table 2. At baseline, many environmental factors are being assessed comprising, for example, parent's smoking behaviour, antibiotic use, sun exposure, previous enteritis and appendectomy. Assessment of dietary factors is limited to assessing: (1) whether children are following a vegetarian or vegan diet and (2) if they are excluding specific items from their diet.

Biomaterial

In several centres biological specimens are collected in addition to the clinical data. When informed consent for the collection of biomaterial is obtained, blood samples and intestinal biopsies are collected prior to treatment initiation and during follow-up visits in concurrence with routine clinical diagnostics. At diagnosis, in all patients, biopsies are collected from affected and non-affected tissue in both ileum and colon according to the standard operating procedure written for this study (online supplementary Figure 1). During follow-up endoscopies, collection of ileum biopsies is optional and based on the clinician's decision in patients with UC. Analyses of biopsies include immunohistochemistry, targeted quantitative messenger RNA (mRNA) analyses and unbiased mRNA sequencing analyses. Peripheral blood samples are collected for plasma proteomics analyses, plasma antimicrobial reactivity, in-depth phenotypic and functional leukocyte analyses and screening for genetic polymorphisms (Figure 1). Immunological analyses will be related to the previously described clinical data that is being collected. Patients enrolled in the subcohort in whom the diagnosis of IBD is not confirmed after additional investigations will be analysed as non-IBD controls.

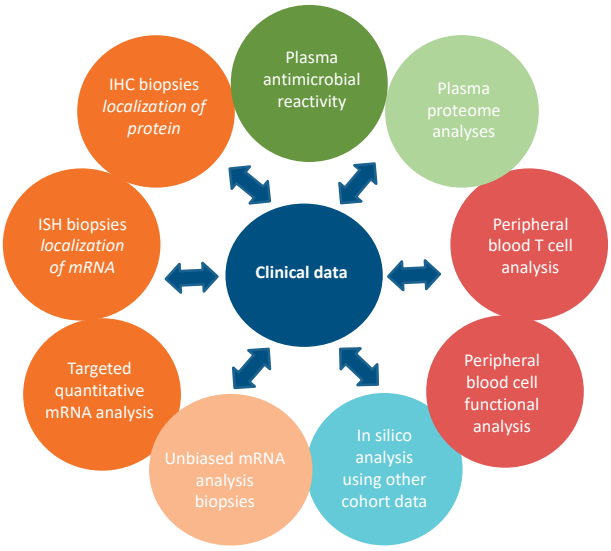

Figure 1. Different immunological analyses that will be performed. Data will be correlated to the clinical data. IHC, immunohistochemistry; ISH, in situ hybridisation.

Outcome measures

This study design and statistical analysis plan are based on one primary and several secondary and exploratory outcomes. At baseline, prior to the start of therapy, the clinical characteristics of patients with PIBD will be reviewed and compared by country, as well as racial background. In patients participating in the subcohort, immunological biomarkers are reviewed in order to classify disease heterogeneity based on underlying immune pathology. Thereto, immunological parameters will be related to clinical and morphological disease features at this time point.

The primary outcome is clinical remission at 1 year, which reflects our aim to study therapy response and non-response. Clinical remission is defined as a wPCDAI <12.5 in patients with CD and a PUCAI <10 in patients with UC or IBD-U. According to the set hypothesis, the disease localisation, extension, behaviour and type of induction therapy are important factors that influence the primary outcome, while age at diagnosis and the initial disease activity score are expected to be important covariates. In addition, biochemical and immunological parameters at baseline will be evaluated to predict clinical remission. In a subanalysis, the effect of early use of immunomodulators and biologicals (less than 3 months from diagnosis) on remission rates will be investigated by comparing groups with early and later use.

One of the secondary outcomes of this study is to assess clinical remission over a period of 3 and 6 months since the start of treatment to evaluate short-term response. In addition, the need for treatment intensification within 1 year will be assessed. The longitudinal follow-up analyses of individual immunological biomarkers will reveal which immune parameters change when patients are in clinical remission. Clinical, biochemical and immunological findings at baseline and 12 weeks after the start of therapy will be assessed for their predictive value on the disease course after 1, 3, 5, 10, 15 and 20 years of follow-up. Lastly, as a longer term secondary outcome, we will assess: (1) moderate or severe disease over the last 6-12 months, (2) the development of complications such as fibrostricturing disease, penetrating disease, active perianal fistula or an abscess, (3) the need for IBD-related luminal surgery and (4) the need for biologic use or need for treatment intensification, after 1, 3, 5, 10, 15 and 20 years.

As an exploratory outcome, the initial management of newly diagnosed patients with PIBD will be evaluated. The type of induction therapy and proportion of patients started on early immunomodulators or anti-TNF agents will be assessed and compared by country or region. Several environmental factors will be evaluated to assess their possible role in the heterogeneity of the presenting phenotype as well as disease course. Lastly, longitudinal findings on QoL, health status, parents' work productivity and child's school attendance will be evaluated, compared by country or region and correlated to disease activity and disease course.

Sample size calculation

To ensure that the study is adequately powered for the primary outcome, we have calculated the minimum required sample size, which we have also adjusted for a 10% expected information loss and multiple comparisons. To maintain the global significance level alpha at 0.05, for the sample size calculations, we decreased the significance level for the univariate analyses to 0.01 per Bonferroni correction. As we aim to capture predictors with significant influence on clinical remission, we set the effect size of the primary outcome at 25%. In order to detect a 25% or higher difference between the compared groups, as defined by disease characteristics and therapy induction types and considering the variable sampling ratio (2:1 to 1:2 depending on the factor), we will need 203 patients with CD and 214 patients with UC/IBD-U. Considering approximately 40% of PIBD diagnoses comprises UC/IBD-U, we will need 535 patients with PIBD. Subsequently, the CD group will have slightly increased power than the originally planned 80%.

Data collection and management

Data are collected in REDCap, a secured database, by using online case report forms (CRFs). CRFs are based on the dataset of the Canadian inception cohort by the Canadian

Children Inflammatory Bowel Disease Network (CIDsCaNN) and adjusted to the needs of this study. A monitor performs remote (digital) monitoring for each participating centre yearly after inclusion. The coordinating investigator runs consistency checks on a monthly basis and produces queries to be resolved by the local investigators. To secure accurate comparison of biomarkers in tissue specimens obtained from different centres, highly reproducible sample preparation is required across all centres participating in this study. Therefore, all aspects of sample acquisition and all reagents will be strictly regulated and sample quality will be tightly monitored.

Analysis and statistical methods

Data analysis will be performed with SPSS V.26 or higher for Windows and R version 3.6 or higher (R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics will be computed overall and per disease (CD and UC). Phenotypic grouping will be performed according to specific disease characteristics (eg, age of onset, disease localisation and disease behaviour). Next to this, patients will be categorised according to treatment categories. The appropriate descriptive statistics will be used to summarise the demographic characteristics. The primary outcome will be analysed using a 2-proportion Z test for the comparison of the different groups in our sample, using a stricter confidence level of 0.01 per Bonferroni correction. All proportions will be summarised per group and 95% CIs will be provided. The important factors from the univariate analyses will be used to build a generalised linear model with a logit link function. This will be a multiple analysis of the effects that the selected factors and covariates have on the outcome of clinical remission. The final model will also include interaction terms, if necessary, and will be optimised based on fit diagnostics and residual analysis. The same approach will be used for the secondary outcomes of clinical remission. We will use a mixed-effects linear model to study the effects of the predictors on the disease activity index over time, taking into account the non-independence between the observations due to the repeated measurements from each patient. For the additional long-term secondary outcomes that have a time-to-event nature, we will use Kaplan-Meier curves to summarise the effects of the categorical factors on the outcome. This will be used to build a Cox regression model with the important factors and covariates that have a significant effect on the time and frequency of the events as defined in the outcomes section.

Similar methods will be used for the analysis of the exploratory outcomes. For these outcomes, propensity scores and multivariate methods are required, in particular for the immunological data, including principal component, factor and cluster analysis. Incidences of serious adverse events (SAE) and the SAE rate per 100 patient-years will be calculated. Missing data analysis will be performed based on the missing at random

or missing completely at random mechanisms. Emerging patterns will be thoroughly examined.

Study status

The first study participant was recruited in 2017. The number of included patients up until February 2020 is 400. Enrolment is expected to be completed by the end of 2021.

Patient and public involvement

Patients and/or the public were not involved in the initial development, or conduct, or reporting or dissemination plans of this research. However, the French patient charity AFA Crohn, RCH, France, was involved in the final study design and critically reviewed and commented upon main aspects of the trial.

DISCUSSION

The PIBD-SETQuality inception cohort is a unique study, being the first cohort in its size including patients with PIBD from European and Asian countries. The homogeneous collection of data from several different countries in one cohort enables comparison of disease phenotype and treatment paradigms between countries and continents. The hypothesised role of environmental factors in the pathogenesis of PIBD might thus be assessed within this cohort. In addition, being a cohort with real-world data, this study will complement data derived from clinical trials and provide insight in drug use in everyday practice and the related international differences.

The main outcome of this study will be the prediction of a complicated disease course and response or non-response to therapy. One of the important strengths of this study is the collection of biomaterial in therapy-naïve patients. Studies assessing immunological biomarkers in patients with PIBD are scarce and even lacking in therapy-naïve patients. The prospective set-up of this study will reveal whether immunological biomarkers in PIBD change overtime and in response to therapy. In addition, these biomarkers can be correlated to the clinical data. Besides finding predictive factors of a complicated disease course and response to therapy within this real-world cohort, we will also use this cohort to examine and possibly validate previously reported findings from other studies such as the GROWTH CD study.[37 38]

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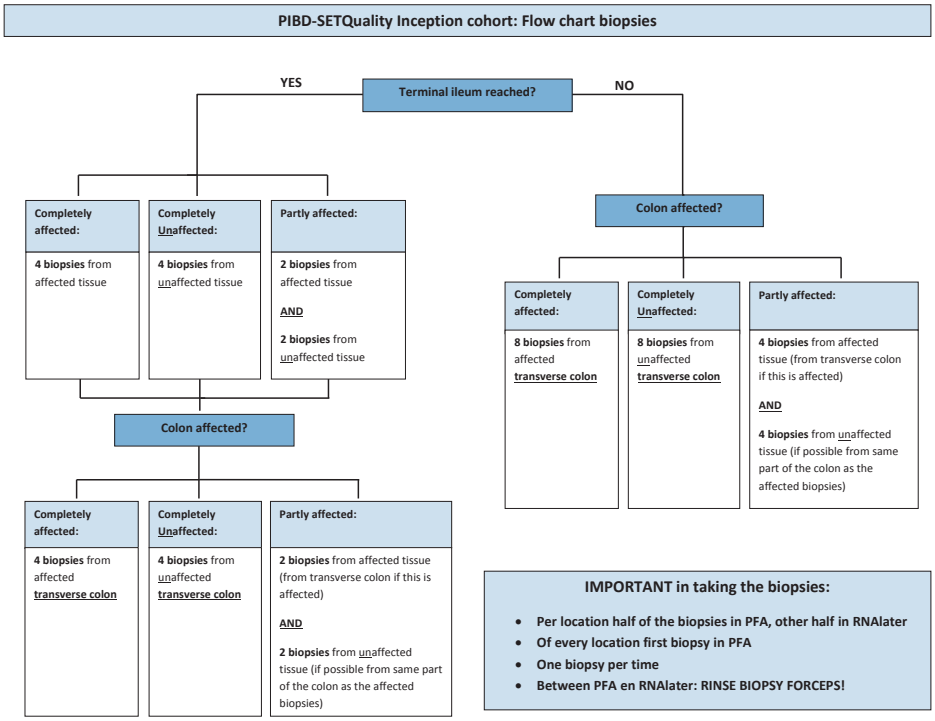
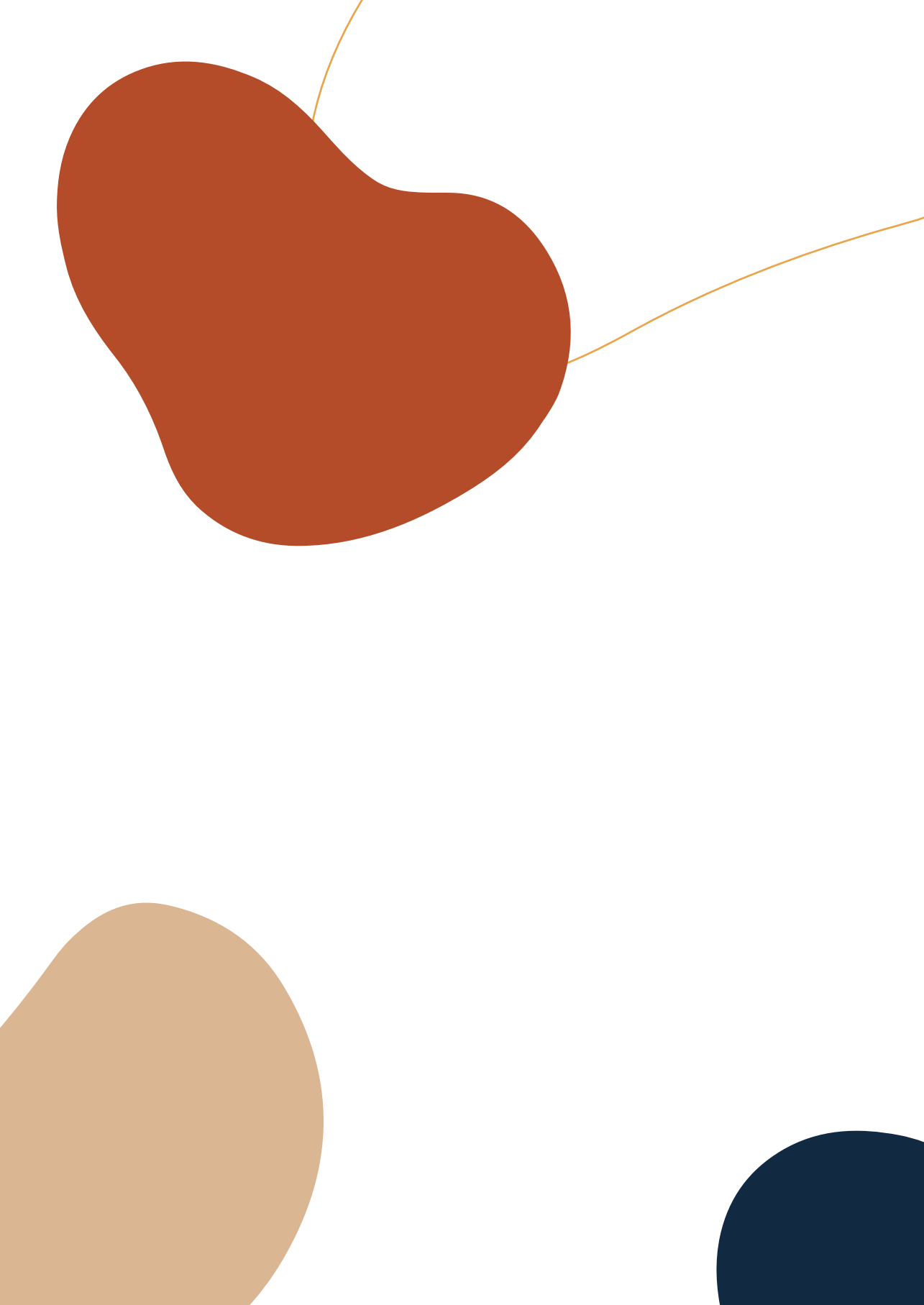


Supplemental Figure 1. Flow chart depicting the standardized approach for collection of biopsies during the endoscopy.



10

General Discussion

GENERAL DISCUSSION

The aim of this thesis was to gain knowledge on predictors of disease course in patients with pediatric-onset inflammatory bowel disease (PIBD), including identification of children with inflammatory bowel disease (IBD) who are at-risk of developing complications. Additionally, new treatment strategies, guided towards precision medicine in IBD, were investigated and optimized. In this chapter, the findings described in this thesis are discussed in view of the current knowledge, clinical practice and future perspective.

Disease heterogeneity

IBD is a chronic disease with a multifactorial cause that has a heterogeneous disease presentation and disease course. This heterogeneity leads to a wish to adjust treatment strategies according to the individual needs. The path towards personalized or precision medicine starts with knowing which children are at risk of a complicated disease course. Disease course is often described by the number of disease flares, the need for second-line therapy and the need for surgery. A strict definition of complicated disease does not exist, as is reflected by the several outcome measures used in **Chapter 7 and 8.**

Severe outcomes

Malignancy and mortality

Having a chronic disease, children are life-long exposed to the risk of developing severe complications that are a consequence of the disease itself or medication that is being used to control the inflammation. Risk benefit strategies in managing IBD are dependent upon understanding the risks of uncontrolled inflammation versus those of treatments. On one hand, ongoing inflammation has been associated with the risk of developing colon cancer, but on the other hand the use of azathioprine may result in a higher risk of developing lymphomas.[1,2] The existing literature on those outcomes in children with IBD is scarce. In **Chapter 2 and 3** we have summarized the existing literature and described the findings of our own prospective study, reflecting the largest number of cases describing malignancy and mortality in children with PIBD. In **Chapter 3** we show that in some countries, especially the ones with the highest data quantity and quality, such as the Netherlands, the incidence of malignancies is increased. This is in line with findings in other studies that investigated the incidence of malignancies in children with IBD in a population-based cohort and found this to be up to 2-fold higher compared to the general population.[3,4]

Both **Chapter 2 and 3** show that lymphomas are the most frequently reported malignancies in PIBD. The long term DEVELOP registry reported on lymphomas in particular in a large cohort of 5766 PIBD patients and found that the incidence of malignancy was

significantly higher in children exposed to anti-TNF and thiopurine combination therapy compared to monotherapy with anti-TNF or thiopurines.[5] The data in this thesis show that the increased incidence of malignancy in the PIBD population is mainly caused by other types of cancer than those occurring in the general pediatric population. Hepatosplenic T-cell lymphoma, cholangiocarcinoma and colon carcinoma are the most frequently reported types of cancer in the PIBD population in our studies, whereas these types of cancer are very uncommon in the general pediatric population.[6] An important finding in this thesis is the high ratio (56%) of PIBD patients with concomitant primary sclerosing cholangitis (PSC) in the described cancer and mortality cases. The increased risk of cholangiocarcinoma and colon carcinoma in patients with PSC-IBD has also been described in studies with adult patients.[7-11] Still, this finding in children is notable, given the generally shorter disease duration which these complications have developed. Findings from a retrospective cohort study by Deneau et al., including 781 children with PSC, showed that cholangiocarcinoma occurs in 1% of children with PSC.[12] As PSC occurs more frequently in UC than CD the current pediatric UC guideline includes recommendations to detect colorectal carcinoma and cholangiocarcinoma at an early stage. The findings in our study contributed to the definition of statements in the recently updated pediatric UC guideline.[13] Annual or biannual surveillance colonoscopy in prepubertal children, preferably by chromo-colonoscopy with targeted biopsies, is recommended to screen for colorectal cancer or dysplasia.[13,14] Careful screening according to these guidelines in children with PSC-IBD is important. For cholangiocarcinoma, the available surveillance modalities (blood tumor marker and ultrasound or magnetic resonance cholangiopancreatography) are low-risk and not very invasive for the patient and surveillance could thus be performed relatively easy. However, once cholangiocarcinoma is detected the treatment options are limited and the survival benefit of surveillance is largely unknown.[15] To date, available medication for PSC such as ursodeoxycholic acid has not shown to reduce time to development of cholangiocarcinoma or death.[16] New treatment strategies for PSC are under investigation[17] and urgently needed to prevent severe outcomes. As PSC itself often presents asymptomatically in patients with IBD,[18] regular liver enzyme monitoring is important in IBD patients to make sure a PSC diagnosis and the accompanying increased risk of malignancy and fatal outcome are not overlooked.

Association with IBD treatment

Most population-based studies in children have thus far been underpowered with regard to drug exposure in patients who develop malignancy.[3,19] **Chapter 3** describes a prospective case series and is thus not designed to truly determine the causality between drug use and development of a malignancy. However, our observations are in line with other studies regarding the association between thiopurine exposure and the risk

of development of lymphomas.[5,20] In the past decades, thiopurines and anti-TNF have been increasingly prescribed, alone or concomitantly. The largest study investigating risk of lymphoma in any of these treatment strategies in children with IBD, the DEVELOP registry, shows a significantly increased risk in those who receive combination therapy, but not in those who receive thiopurines or anti-TNF treatment alone.[5] More data is available from adult IBD patients, as several studies have described an increased risk of lymphomas in IBD patients that use thiopurines.[20,21] There is also evidence that anti-TNF monotherapy is associated with an increased lymphoma risk[22], but in a meta-analysis with short term follow-up no increased risk was found.[23] In addition, two population based studies of children showed that treatment with thiopurines and biologics did not influence cancer risk.[3,4] The currently available data in adult and pediatric literature has led to international differences in clinical practice regarding thiopurine use in PIBD treatment.[24-26] In all, it seems that the risk of lymphomas in IBD patients is largely driven by a combination of anti-TNF and immunomodulators, particularly thiopurines.[20,27] Male patients require special consideration because, similar to the findings in **Chapter 3**, almost all cases of the often fatal hepatosplenic T-cell lymphomas have been reported in males.[28] Another reason for limiting the use of combination therapy may be the risk of severe infectious complications, the second leading cause of fatal outcome described in **Chapter 3**. The use of an anti-TNF agent, thiopurine or steroid was individually associated with a 2.9 (CI; 95% CI 1.5-5.3) times increased risk of infection in adult patients with IBD, which increased to 14.5 (95% CI 4.9-43) when two or three of these drugs were used in combination.[29] All together these findings led to the recommendation to start combination therapy to prevent immunogenicity, but stop combination therapy after 6-12 months to minimize the risk of complications.[30]

Possible association with disease burden

Another striking finding in **Chapter 3** was suicide being the third leading cause of mortality. These children all had complicated disease, which highlights the need of precision medicine. Moreover, it stresses the importance of psychological support in addition to medical treatment in children and adolescents with IBD. Butwicka et al. assessed the risk of suicide and psychiatric disorders in a study of 6464 individuals with childhood-onset IBD and compared this with 323,000 matched reference individuals. They found that IBD was significantly associated with suicide attempt (HR 1.4, 95% CI 1.2-1.7) and several psychiatric disorders.[31] Anxiety and depression are known to be prevalent among children with IBD.[32]. Physicians should be aware of the impact of (complicated) IBD in children and pay attention to the mental health of their patients.

Venous thromboembolisms

Several studies including adult patients with IBD have reported on the increased incidence of venous thromboembolisms.[33,34] In children, few retrospective studies based on billing or insurance databases have reported significantly increased incidences of VTE when compared to non-IBD patients.[35,36] In **Chapter 4** we show a 14-fold increased incidence of venous thromboembolisms in children with PIBD compared to the general population. In line with our findings, the increased incidence of VTE was recently demonstrated in a Canadian population-based study. Our study has a different design than previous studies which enabled us to collect data prospectively and in a homogenous manner. The most frequently reported type of VTE was a cerebral sinus venous thrombosis (CSVT), which is in line with findings in a systematic literature review by Lazzerini et al. showing 50 out 92 VTEs occurring in children were CSVTs.[37] We showed that the incidence of CSVT in children with PIBD is much higher than in the general pediatric population (1.86 vs. 0.045 per 10,000 patient years; $p<0.001$). Two children in our cohort died due to the consequences of the CSVT and one needed a craniotomy. Although the absolute number of collected cases is relatively low it shows the devastating impact this complication can have. In adult patients with IBD, guidelines recommend to start thromboembolic prophylaxis in every hospitalized patient and to consider prophylaxis after hospital discharge, after recent surgery and in outpatients with active disease.[14] International guidelines for children with IBD are more conservative and only recommend to consider thromboembolic prophylaxis since 2018 in children with acute severe colitis.[38] Prophylaxis is recommended in hospitalized patients with a pediatric ulcerative colitis activity index ≥60 and at least one additional risk factor. In a pre-pubertal child with UC, the guideline states that prophylaxis should be considered when two or more additional risk factors are present. In our cohort 40% of children with IBD who developed VTE was <12 years of age and 30% of the patients had CD. Those children would thus not have been considered for thromboembolic prophylaxis according the current guidelines. Our study is limited because of the inability to obtain a number of children with IBD needed to treat in order to prevent one VTE case in this population. The most important reason not to provide thromboembolic prophylaxis is safety and bleeding risk.[39] Pediatric studies and extrapolation of data from adult IBD studies show however that administration of thromboembolic prophylaxis is safe.[40,41] Therefore, recommendations to consider thromboembolic prophylaxis in children should be extended to a broader pediatric IBD population.

Future perspective of rare but severe events in pediatric-onset IBD

In all above-described studies, one of the goals is to cause awareness of the possible occurrence of these events in children with IBD. Although **Chapters 2, 3 and 4** show an increased incidence of VTE, mortality and malignancies in patients with PIBD compared

to the general pediatric population, it is important to stress that the absolute numbers are fortunately low. Despite their rarity, better phenotyping is required to prevent future severe outcomes. This results in a challenge to gain information on these outcomes. Data is often retrospective and based on insurance or billing databases, resulting in limited validity of these studies.[42] To improve data collection on this topic, we established the PIBD Safety Registry, which is described in the methods section of **Chapter 4**. In this registry detailed information on rare but severe complications in PIBD is prospectively collected and the incidence of these complications in this patient population is investigated. Via this registry more information on other rare but debilitating complications that may present in PIBD patients, such as haemophagocytic lymphohistiocytosis, severe opportunistic infections and neurological complications, can be obtained in the future.

Treatment strategies in pediatric-onset IBD

First-line infliximab treatment in high-risk patients

A complicated disease course can be caused by ineffective treatment strategies that lead to ongoing active inflammatory bowel disease, resulting in possible growth delay, slow pubertal development and school absence in children.[43] In children with CD, clinical and endoscopic remission is frequently not achieved with conventional treatment strategies.[44] In **Chapter 5** we show that a subgroup of patients, children with moderate-to-severe CD, benefits more from first-line infliximab treatment compared to conventional treatment. The need for treatment escalation within the first year is significantly lower if children are treated with first-line infliximab. One comparable RCT was available, in which adult IBD patients received three infliximab infusions as primary induction treatment.[45] In line with findings from this study in adults, in the group of children treated with first-line infliximab a significantly higher proportion was in clinical and endoscopic remission at week 10 than in the conventionally treated group. Previously, studies had shown that anti-TNF treatment was effective in achieving mucosal healing in refractory pediatric patients with CD[46,47], but the mucosal healing rate of 59% ten weeks after start of induction treatment in children treated with first-line infliximab in our cohort is superior to previously reported mucosal healing rates. At one year, no significant difference in clinical and biochemical remission rate was found between the two treatment groups. However, at that time point, a significantly higher proportion of patients in the conventional treatment group than the first-line infliximab treatment group had received treatment escalation. Disadvantages of corticosteroid use such as growth failure are well-described in literature.[48] The median SDS height-for-age significantly improved in the first-line infliximab group whereas it significantly decreased in the conventional treatment group, which indicates insufficient control of inflammation in the conventional treatment group. Unfortunately, the number of patients with

endoscopic evaluation at 52 weeks limits the comparison of mucosal healing rates at that time point between the two groups. Based on this thesis, the differences between first-line infliximab and conventional treatment after longer duration of follow-up cannot be evaluated. The ongoing follow-up of patients in this study will show how often restarting infliximab will be necessary and if immunogenicity and consecutive loss of response will become an issue. **In Chapter 5** azathioprine monotherapy is continued after five infliximab infusions. Considering the previously described potential association with the development of malignancies, one might suggest to continue using infliximab monotherapy instead of azathioprine monotherapy. Cyclic treatment with biologics is currently being investigated in adult IBD patients and shows promising results regarding re-treatment with infliximab.[49] However, concerns are the risk of relapse, the risk of infusion reactions and loss of efficacy when infliximab has to be restarted and consequently, being left with limited medical treatment options.[50,51] The findings in this thesis support the use of first-line infliximab treatment in children with moderate-to-severe CD. We experienced how children and their parents well accepted this treatment strategy. In **Chapter 5** a cost-effectiveness evaluation is not described, but this is currently being investigated. Looking further ahead, if cyclic infliximab treatment would become a safe and effective treatment strategy, this may also benefit cost reduction.[52]

Targeted conventional treatment

In **Chapter 5**, 15% of patients with moderate-to-severe disease in the conventional treatment group achieved clinical remission at one year without needing treatment escalation. Borrelli et al. randomized 37 therapy-naïve children with moderate-to-severe CD to exclusive enteral nutrition (EEN) or corticosteroid treatment and found endoscopic mucosal healing rates of 74% for 10-week-EEN treatment and 33% for corticosteroid treatment at week 10. The mucosal healing rates, particularly considering EEN treatment, are higher than in our RCT. This may be explained by the longer duration of EEN treatment in the study by Borrelli et al. Although studies show a significant increase of fecal calprotectin levels and a decline in sustained corticosteroid-free remission rates in the weeks after EEN is stopped,[53] these findings show that there may be a group of CD patients that does well after induction treatment with EEN.[54] Preventing overtreatment by identifying those who do well on these conventional treatment strategies is a challenge that still needs to be overcome. While the use of biological agents for treatment of IBD is increasing, there is also a rising interest in adjusted forms of dietary treatments, so-called anti-inflammatory diets. Several studies have been investigating modification of conventional treatment strategies. Given that EEN treatment is not an easy treatment to adhere to, the results of dietary therapies such as Crohn's disease exclusion diet or CD-TREAT diet are promising.[55,56] However, at present, we cannot identify the subgroup

of patients that will achieve and maintain mucosal healing with dietary treatment. In **Chapter 9** we describe how we aim to phenotype patients for future targeted therapy.

New drugs and treatment optimization

Vedolizumab, an agent directed against α4β7-integrin, is a relatively new agent in the treatment of PIBD and has not been studied in large pediatric cohorts. Although it is effective in a significant proportion of patients,[57] a systematic review and meta-analysis shows that 54% of patients may benefit from dose optimization.[58] Prior to our study, data on vedolizumab trough levels was practically non-existent. In **Chapter 6** we show that trough levels in children with IBD are comparable to those in adult patients with IBD. We identified a lower baseline albumin, higher fecal calprotectin and CRP and longer time between infusions to be associated with lower vedolizumab trough levels. Although due to the small cohort we did not stratify for UC and CD in in our statistical analysis, trough levels were lower in CD patient than UC patients. The data in our cohort was not sufficient to find a certain trough level to predict treatment response. Based on adult studies higher trough levels during induction are associated with sustained clinical benefit over the first year,[59] but even in adult IBD patients, there is insufficient evidence for an optimization strategy that is based on therapeutic drug monitoring yet. However, assessment of trough levels at an early stage could be considered to help distinguish those who might need a dose increase or shortened time between infusions.[60] The prospective VEDOKIDS study, which is currently being conducted [NCT02862132], might in future result in a prediction model for treatment success based on vedolizumab trough levels in children with IBD.

Therapeutic advances in the field of adult IBD are being adopted by pediatric gastroenterologists. Although only infliximab and vedolizumab have been investigated in this thesis, more agents with similar or alternative acting mechanisms are being explored in the pediatric IBD field. Like vedolizumab, other anti-adhesion molecules like natalizumab which act by blocking the trafficking of T-lymphocytes to the inflammation site in the gut are being investigated.[61,62] Moreover, ustekinumab, which prevents the interaction of pro-inflammatory cytokines IL-12 and IL-23 on naïve T cells and thus blocks the pro-inflammatory cascade, has shown to be safe and effective in few pediatric studies.[63-65] Recently, few studies investigating the use of tofacitinib, an agent that interferes with the JAK/STAT inhibitor pathway, are emerging in children with IBD.[66] These agents all affect a different part of the immunological system, which increases the opportunities of targeted therapy. But in order to provide therapy targeted on specific immunological pathways we must first be able to recognize PIBD patients with a certain immunological profile. In **Chapter 9** we have described how we are obtaining blood samples and biopsies of the intestinal mucosa of therapy-naïve PIBD patients around the time of disease

diagnosis and during follow-up. Dysregulation of effector T-cell response is an important driver of IBD pathology.[67] The methods in **Chapter 9** describe how changes in regulatory and inflammatory $CD4^+$ T-cell responses are being investigated to enable patient stratification. Protein profiling combined with immune phenotyping of peripheral blood cells and in depth analysis of intestinal immune responses are being used to categorize patients. The combination of the immunological data and detailed clinical characteristics, both collected according to a strict protocol, is key in the set-up of this study. Current clinical decision making does not involve immune parameters reflecting the patient's individual disease. However, accumulating evidence is occurring to support the role of immunological biomarkers in prediction of the disease course.[68] By the investigation of immune profiles in correspondence with clinical disease parameters we are aiming to change this. With this data, in future, the effect of current treatment strategies on an immunological level can be investigated.

Prediction of disease course

Reduction of the development of complications may be established by the use of intensified treatment.[69] Prognostic factors at disease diagnosis in children with inflammatory bowel disease are therefore highly needed. Due to the more severe disease phenotype and age-related considerations such as pubertal development and psychosocial needs findings in adult studies cannot be directly applied on children.[70,71] The systematic review we undertook in **Chapter 7 and 8** describes clinical characteristics and biomarkers that predict poor outcomes during the disease course. A meta-analysis could be performed for some outcomes, resulting in evidence-based guidance for clinical decision making. In children with Crohn's disease, poor growth, stricturing and/or penetrating disease, the presence of NOD2/CARD15 variants and positive anti-Saccharomyces cerevisiae antibodies are predictive of surgery, whereas isolated colonic disease is associated with fewer surgeries. Factors that predict the development of stricturing and/or penetrating disease during the course of Crohn's disease are the presence of small bowel disease, antimicrobial seropositivity, NOD2 polymorphisms and perianal disease. Additionally, ASCA positivity and non-white ethnicity predict penetrating disease (**Chapter 7**). In children with ulcerative colitis a more severe disease extent and disease activity, a positive family history of UC and the presence of extra-intestinal manifestations may predict the need for a colectomy (**Chapter 8**). The meta-analysis in both studies included a fairly small number of studies, which should be taken into account when interpreting these findings. For several outcomes, insufficient data was available to perform a meta-analysis. The mainly retrospective design of the included studies and the heterogeneity in definition of outcome measures limited us from making strong statements. However, these two chapters do provide the most comprehensive review of the available literature on predictors in PIBD to date. It shows the importance of well-designed population

based studies and multi-center efforts to gain evidence on this topic. With the study described in **Chapter 9** we aim to contribute to this. The prospective observational design of this study enables validation of findings from previous studies such as the PROTECT study and GROWTH study.[72,73] Ideally, this will lead to prognostic factors that are readily available in clinical practice.

The starting point of improving management of children with IBD, reducing complications and eventually precision medicine, is a better understanding of prognostic factors. This thesis adds to this understanding by showing the impact of complications in PIBD, describing the current knowledge on prognostic factors and providing suggestions to improve current treatment strategies based on patient stratification.

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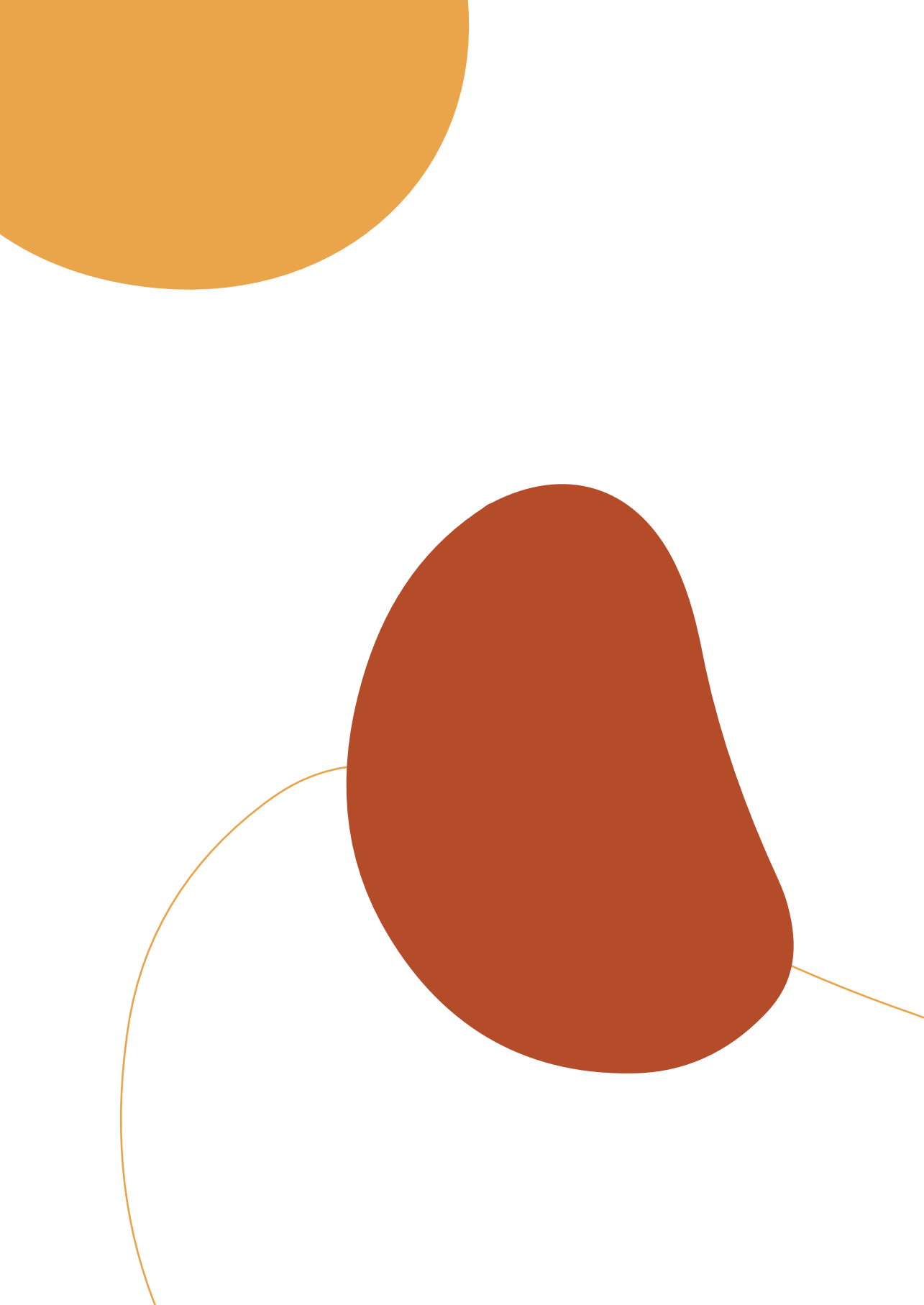

APPENDICES

ENGLISH SUMMARY

Inflammatory bowel disease (IBD) is a chronic inflammation of the gastrointestinal tract that is generally classified as Crohn's disease (CD) or ulcerative colitis (UC). If the diagnosis is made during childhood or adolescence (paediatric-onset IBD), approximately two third has CD. Given it is a life-long disease, the disease may have consequences on the child's physical and mental development. Paediatric-onset IBD (PIBD) has a relapsing and remitting pattern and is very heterogeneous. The disease course of an individual child with IBD can currently not be predicted. Therefore, in general, there are two treatment strategies; one for children with CD and one for children with UC. Ineffective treatment strategies negatively affect the disease course of children with IBD. The aim of this thesis was to gain knowledge on predictors of disease course in children with IBD, and to identify children who are at-risk of developing complications. Additionally, new treatment strategies, guided towards a more individualized treatment strategy were investigated and optimized. In **Chapter 1**, the background and aims of the studies presented in this thesis are provided.

Severe outcomes

Risk-benefit strategies in managing IBD are dependent upon understanding the risks of uncontrolled inflammation versus the risks of IBD treatment. The disease course of children with IBD can be impacted by severe complications such as cancer, venous thromboembolism or even death. Due to the rarity of these events, studies investigating the incidence and characteristics of these events are scarce. As these events have a major impact, it is important to know when we need to be aware of this risk while treating a very heterogeneous group of children and adolescents with IBD. Therefore, characterization of patients who are at risk to develop these complications is needed. In **Chapter 2**, we summarized the existing literature on children with IBD that developed cancer. We found that there is an increased risk for cancer in children and adolescents with IBD, but absolute numbers are fortunately low. Types of cancer that are usually uncommon in the general paediatric population, such as cholangiocarcinoma, colorectal carcinoma and a specific and often fatal type of lymphoma, hepatosplenic T-cell lymphoma, show a predominance in our systematic review of the literature. The most frequently reported type of fatal cancer was colorectal carcinoma, which occurred at a strikingly young median age of 25 years. In this review, we also collected information on other causes that led to a fatal outcome in patients with PIBD and found that next to malignancy, infectious complications were a frequent cause. Details regarding medication used prior to and at the time of cancer diagnosis or occurrence of the fatal outcome were often lacking in literature. This, and other knowledge gaps identified in this literature review, led to the set-up of the prospective study described in **Chapter 3.** In **Chapter**

3 the largest number of PIBD patients that developed cancer or had a fatal outcome to date is described, including data on IBD treatment strategies in these patients. The most frequently reported malignancies in this cohort were in line with findings described in **Chapter 2**. Although the case series described in this study cannot determine causality between drug exposure and the development of a malignancy, our findings added to the existing knowledge. We found that the majority of patients with a hematopoietic malignancy had been exposed to thiopurines, of whom most were exposed in the three months prior to their diagnosis. The main causes of fatal outcome were malignancies, IBD or IBD-therapy related non-malignant causes (including infections) and suicide. The latter highlights the importance of mental health surveillance in children with IBD. Both **Chapter 2** and **Chapter 3** showed that a concomitant diagnosis of primary sclerosing cholangitis, a disease involving severe destruction of the bile ducts in the liver, was associated with a higher risk for cancer-associated mortality.

In 2018, the first recommendations regarding thrombotic prophylaxis were included in the treatment guidelines for children with UC. In **Chapter 4** we describe how we investigated the incidence and characteristics of venous thromboembolisms in children and adolescents (aged <19 years) with IBD since 2016. We found that the incidence of venous thromboembolisms in children <19 years with IBD is 14-fold higher than in the general paediatric population. However, the absolute number of cases is low, which makes the occurrence of a venous thromboembolism in a PIBD patients still a rare event. Although the ratio CD:UC within the PIBD population is roughly 3:1, more children with UC than with CD presented with a VTE. Children are most at risk when the disease is moderately or severely active and one or more risk factors are present. Half of the described VTE cases concerned a cerebral sinus venous thrombosis, resulting in a 46-fold higher incidence than in the general population. Of the 20 children described in this study, only four would have fulfilled the criteria for thromboprophylaxis based on the 2018 treatment guideline. With this study the importance of awareness among physicians of VTE symptoms in children with IBD and those with suspicion of IBD is underlined. In addition, it shows that thromboprophylaxis should not only be considered in hospitalized children with UC, but also in those with CD and additional risk factors.

The studies described in **Chapter 2, 3 and 4** all aim to increase awareness and recognition of rare but severe outcomes in children with IBD. In 2016 we set up the international PIBD Safety Registry, which is described in more detail in the methods section of **Chapter 4**. Via this ongoing registry detailed information on rare but severe complications in PIBD is prospectively collected and the incidence of these complications in this patient population is investigated. Information on other severe complications such as hae-

mophagocytic lymphohistiocytosis, severe opportunistic infections and neurological complications is currently being obtained.

Optimizing treatment strategies

In **Chapter 5** the results of a randomized controlled trial that compares conventional treatment with first line infliximab treatment in children with moderate-to-severe CD are described. Infliximab is a biological that is currently being used as second-line treatment in children with CD after failing conventional treatment. We investigated whether directly starting infliximab after diagnosis is more effective in achieve and maintain remission than the conventional treatment with oral corticosteroids or exclusive enteral nutrition. We evaluated the effect on clinical symptoms (clinical remission) and healing of the intestinal mucosa (endoscopic remission). Moreover, we investigated the proportion of patients that needed treatment escalation one year after starting any of the two treatment strategies. We found that ten weeks after the start of treatment the proportion of children in clinical and endoscopic remission is significantly higher in the group of children treated with first-line infliximab treatment. After 1 year a significantly greater proportion of children in the conventional treatment group than in the first-line infliximab treatment group received an additional course of corticosteroids, and thus needed treatment escalation (15% versus 41%). Our results show a negative effect of conventional treatment on growth compared to first-line infliximab treatment, suggesting that conventional treatment provides insufficient disease control. Given that ineffective induction treatment strategies in children and adolescents may put them at risk of developing complications that lead to more symptoms, a decrease in quality of life and poorer growth, we argue that children and adolescents with moderate-to-severe CD would benefit from first-line infliximab treatment. In this study, children treated with first-line infliximab received five infliximab infusion and then continued with an immunomodulator as maintenance therapy. As longer-term follow-up of the patients in this study is still ongoing, future findings will reveal how often re-treatment with infliximab is necessary during the disease course and how effective re-treatment is. Future research needs to evaluate the cost-effectiveness and role of cyclic treatment with biologicals.

Chapter 6 focusses on a relatively new biological in the treatment of PIBD; vedolizumab. This agent is being used as second-line agent in the treatment of children with UC and CD. For other agents, such as the previously discussed agent infliximab, the treatment is optimized by adjusting dose or dosing intervals based on trough levels. Due to the scarcity of data on the use of vedolizumab in children with IBD, no studies have yet described the role of trough levels in children with IBD. In **Chapter 6** we show that trough levels in children are comparable to those in adults with IBD. We identified several factors that are associated with lower vedolizumab trough levels. Vedolizumab trough

levels in CD patients were lower than in UC patients. In adult IBD patients more evidence is emerging that higher trough levels during induction treatment are associated with sustained clinical benefit over the first year. Although our study provides the first insight in vedolizumab trough levels, the small cohort limits us from correlating vedolizumab trough levels to the clinical effectiveness. Prospective studies in children using vedolizumab should be performed to evaluate a dose-response correlation.

Prediction of outcomes

Chapter 7 and 8 describe the findings of a systematic literature review on predictors of several outcomes in pediatric CD and UC, respectively. It describes de current evidence on prognostic factors of surgery, complications, hospitalization and chronically active disease in pediatric CD and prognostic factors of colectomy, acute severe colitis and chronically active UC in pediatric UC. A meta-analysis was performed for some outcomes, showing that, in children with CD, the presence of poor growth, stricturing and/or penetrating disease, the genetic NOD2/CARD15 variant and antimicrobial seropositivity are associated with the need for surgery. In pediatric UC patients, the meta-analysis showed that disease extent, disease severity, family history of UC and the presence of extra intestinal manifestations significantly associated with the need for a colectomy, whereas PSC may be protective. The study was limited by the heterogeneity in the data, mainly due to the paucity of available large prospective cohort studies in children with IBD. Meta-analysis therefore included only a small number of studies and could not be performed for all outcome measures. However, **Chapter 7 and Chapter 8** do provide an overview of the available literature on predictors in PIBD to date. These chapters include consensus statements that were voted on by a team of PIBD experts to provide evidence –based guidance for clinical decision making.

As concluded in **Chapter 7 and 8**, prospective large cohorts are needed to better evaluate prognostic factors of the disease course in children with IBD. **Chapter 9** describes the prospective international observational cohort study, the so-called PIBD-SETQuality study, we set up. In this study we describe how we collect clinical and immunological data for immunological profiling in therapy-naïve patients. Linking the immunological data to detailed clinical characteristics is key in the set-up of this study. The follow-up of patients in this study after start of treatment will enable investigation of treatment effect in relation to these immunological profiles. With regards to the clinical data, findings described in **Chapter 7 and 8** and previous prospective cohorts can be validated in this study. Additionally, it includes the large scale collection of quality of life measures in order to correlate this to clinical findings.

Chapter 10, the last chapter of this thesis, describes the findings of this thesis in view of the current knowledge and clinical practice. In addition, the future perspective on the topics included in this thesis is discussed in more detail.

NEDERLANDSE SAMENVATTING

Inflammatoire darmziekten, afgekort als IBD, afkomstig van de Engelse term ‘’inflammatory bowel disease’’, zijn chronische ontstekingsziekten van het maagdarmstelsel. Binnen IBD wordt grofweg onderscheid gemaakt tussen de ziekte van Crohn en colitis ulcerosa. Het ziektebeloop van zowel de ziekte van Crohn als colitis ulcerosa wordt gekenmerkt door periodes van opvlamming van de ontsteking, afgewisseld met periodes waarin de ontsteking rustig is, wat ook wel remissie wordt genoemd. Het onderscheid tussen deze twee ziekten wordt onder andere gemaakt op basis van de locatie van de ontsteking. De diagnose IBD wordt in 8-25% van de gevallen op de kinderleeftijd gesteld, waardoor het gevolgen kan hebben voor de fysieke en mentale ontwikkeling van een kind. Binnen de groep kinderen met IBD heeft ongeveer twee derde de ziekte van Crohn. Per individu met IBD zijn er echter grote verschillen in de manier waarop de ziekte zich presenteert en gedurende de daaropvolgende jaren verloopt. Ondanks deze grote verschillen per individu worden alle kinderen met IBD momenteel volgens een van de twee standaardmethoden behandeld; één voor kinderen met de ziekte van Crohn en één voor kinderen met colitis ulcerosa. Het doel van de behandeling van IBD bestaat uit het in remissie brengen van de ontsteking (inductietherapie) en vervolgens voorkomen van opvlammingen (onderhoudstherapie). Wanneer de therapie niet voldoende effectief is, zal dit het ziektebeloop negatief beïnvloeden.

Het doel van dit proefschrift is het verkrijgen van meer kennis over factoren die het beloop van de ziekte bij kinderen met IBD kunnen voorspellen en het identificeren van kinderen die risico lopen op het ontwikkelen van complicaties. Daarnaast zijn in dit proefschrift nieuwe behandelmethoden onderzocht met als uiteindelijk doel een meer gepersonaliseerde behandeling te bewerkstelligen. In **hoofdstuk 1** wordt achtergrondinformatie gegeven over IBD en de onderwerpen die in dit proefschrift worden beschreven. Tevens wordt het doel van dit proefschrift verder toegelicht.

Ernstige complicaties

De wetenschappelijke onderzoeken beschreven in **hoofdstuk 2, 3 en 4** zijn allen bedoeld om de bewustwording en mate van herkenning van zeldzame maar ernstige complicaties bij kinderen met IBD te vergroten. Bij de behandeling van IBD op de kinderleeftijd is het van belang de mogelijke gevolgen van de ongecontroleerde ontsteking in het maagdarmstelsel af te wegen tegen de risico’s van de behandeling. Tijdens het ziektebeloop kunnen ernstige complicaties optreden zoals kanker, veneuze tromboembolieën (bloedstolsels) of zelfs overlijden. Doordat deze complicaties zeldzaam zijn is wetenschappelijk onderzoek naar de frequentie waarin ze voorkomen en details over de presentatie van deze complicaties bij kinderen met IBD schaars. Aangezien

deze complicaties wel een grote impact hebben, is het van belang om te weten wie, binnen de groep van kinderen met IBD, risico loopt op het ontwikkelen van een ernstige complicatie. In **hoofdstuk 2** van dit proefschrift is de bestaande literatuur over kinderen met IBD die kanker ontwikkelden samengevat. Op basis van deze literatuur vonden wij een verhoogd risico op het ontwikkelen van kanker bij kinderen met IBD. De absolute aantallen hiervan zijn gelukkig laag. Binnen de populatie van kinderen met IBD worden naar verhouding vaker typen kanker gerapporteerd die over het algemeen weinig voorkomen op de kinderleeftijd. Het betreft onder andere cholangiocarcinoom, colorectaal carcinoom en een specifiek type lymfoom, namelijk het hepatosplenisch T-cel lymfoom. Het colorectaal carcinoom werd het meest gerapporteerd en werd vastgesteld op een opvallend jonge gemiddelde leeftijd van 25 jaar. In dit systematische literatuuroverzicht werd daarnaast ook informatie verzameld over oorzaken die leidden tot een overlijden. Naast kanker werden ook infectieuze complicaties gerapporteerd als oorzaak van overlijden. In de meeste studies die geïncludeerd werden in ons onderzoek ontbrak gedetailleerde informatie over medicatie die gebruikt werd voorafgaand aan en tijdens het vaststellen van de diagnose kanker of overlijden. De kennishiaten die geïdentificeerd werden in **hoofdstuk 2** waren aanleiding voor het opzetten van de studie omschreven in het hierop volgende hoofdstuk. In **hoofdstuk 3** wordt een cohort met prospectief verzamelde casus van kinderen met IBD beschreven die kanker ontwikkelden of overleden, inclusief beschrijving van medicatie die werd gebruikt voorafgaand aan het optreden van de complicatie. De meest gerapporteerde typen kanker die in deze studie werden gerapporteerd komen overeen met de bevindingen in zoals beschreven in **hoofdstuk 2**. Hoewel de opzet van het onderzoek omschreven in **hoofdstuk 3** niet volstaat om een causaal verband te kunnen leggen tussen blootstelling aan bepaalde medicatie en het optreden van een complicatie, geeft het hier wel een beter inzicht in. Wij vonden dat het merendeel van de kinderen met IBD die een vorm van bloed- of lymfeklierkanker ontwikkelden blootgesteld waren aan azathioprine, een geneesmiddel dat de afweer onderdrukt. In deze groep kinderen waren de belangrijkste oorzaken van overlijden kanker, de ontstekingsziekte van de darm zelf, infecties en zelfmoord. Deze laatstgenoemde oorzaak benadrukt het belang van psychische begeleiding voor kinderen met IBD. Zowel in **hoofdstuk 2** als in **hoofdstuk 3** werd de diagnose primaire scleroserende cholangitis (een ziekte die schade aan de galwegen in de lever veroorzaakt) geassocieerd met een hoger risico op overlijden door kanker binnen de groep kinderen met IBD.

In 2018 werden voor het eerst aanbevelingen met betrekking tot het voorkomen van bloedstolsels, ook wel trombose profylaxe genoemd, opgenomen in de behandelrichtlijnen van kinderen met colitis ulcerosa. In **hoofdstuk 4** wordt beschreven hoe wij vanaf 2016 de incidentie en kenmerken van veneuze trombo-embolieën (bloedstolsels) bij kinderen met IBD (< 19 jaar) onderzochten. In ons onderzoek werd ontdekt dat veneuze

trombo-embolieën 14 keer vaker voorkomen bij kinderen met IBD dan bij kinderen uit de algemene populatie. Omdat het absolute aantal trombo-embolieën ook binnen de groep kinderen met IBD zeldzaam is betreft het nog steeds een zeldzame complicatie. Hoewel er binnen de groep kinderen met IBD meer kinderen zijn met de ziekte van Crohn dan met colitis ulcerosa, zijn de meeste gerapporteerde veneuze trombo-embolieën echter opgetreden bij kinderen met colitis ulcerosa. Het merendeel van de kinderen had een hoge ziekteactiviteitsscore op het moment dat de veneuze trombo-embolie werd vastgesteld. In deze studie werden 20 casus beschreven. In de helft van de omschreven casus was sprake van een cerebrale veneuze sinus trombose, een bloedstolsel in de bloedvaten van de hersenen. Hieruit kon worden opgemaakt dat dit type veneuze trombo-embolie 46 keer vaker voorkomt binnen de populatie kinderen met IBD dan binnen de algemene kinderpopulatie. Theoretisch gezien kwamen op basis van de op dat moment geldende behandelrichtlijnen maar 4 van deze 20 casus in aanmerking voor tromboseprofylaxe. Deze studie toont het belang van bewustwording van de symptomen van veneuze trombo-embolieën bij kinderen met IBD en kinderen met verdenking op IBD. Daarnaast is het belangrijk om tromboseprofylaxe niet alleen te overwegen bij kinderen met colitis ulcerosa die opgenomen zijn in het ziekenhuis, maar ook bij kinderen met de ziekte van Crohn en bijkomende risicofactoren.

In 2016 hebben wij een internationale veiligheidsregistratie opgezet genaamd de ‘’PIBD Safety Registry’’, welke in meer detail wordt omschreven onder het kopje ‘’methode’’ van **hoofdstuk 4**. Middels deze veiligheidsregistratie wordt op prospectieve wijze gedetailleerde informatie verzameld over zeldzame maar ernstige complicaties bij kinderen met IBD en de frequentie waarin deze complicaties optreden. Naast kanker, overlijden en veneuze trombo-embolieën worden ook andere complicaties binnen deze veiligheidsregistratie onderzocht zoals hemofagocytaire lymfohistiocytose, ernstige opportunistische infecties en neurologische complicaties.

Het optimaliseren van behandelmethoden

In **hoofdstuk 5** worden de resultaten beschreven van een gerandomiseerd gecontroleerd onderzoek binnen een groep kinderen met matig tot ernstige ziekteactiviteit van de ziekte van Crohn. De standaard behandelmethode wordt vergeleken met het starten van infliximab. Infliximab is een biological die momenteel wordt gebruikt als tweedelijnstherapie wanneer de standaardbehandeling onvoldoende effect heeft. Wij onderzochten of het direct starten van infliximab direct na de diagnose effectiever is in het bereiken en behouden van remissie dan de standaardbehandeling, bestaande uit oraal prednison of voedingstherapie. We evalueerden het effect op de klinische symptomen (klinische remissie) en het effect op herstel van het slijmvlies in de darm (endoscopische remissie). Bovenal werd vergeleken bij hoeveel kinderen in elke groep

een noodzaak was tot het intensiveren van de behandelmethode binnen één jaar na het starten van de behandeling. Wij toonden aan dat het percentage kinderen dat tien weken na het starten van de behandeling in klinische remissie was, significant hoger was in de groep behandeld met infliximab dan in de groep behandeld met de standaard behandelmethode. Ditzelfde gold voor endoscopische remissie na tien weken. Eén jaar na het starten van de behandeling had een significant groter deel van de kinderen in de groep behandeld met de standaard behandelmethode intensivering nodig van de therapie middels een extra corticosteroïden kuur. Dat kwam neer op intensivering van de therapie bij 45% van de kinderen behandeld met de standaard behandelmethode in vergelijking met 15% bij de kinderen behandeld met infliximab. Uit onze bevindingen blijkt tevens een negatief effect op de groei in de groep kinderen behandeld met de standaard behandelmethode. Dit suggereert dat de standaard behandelmethode de ziekte onvoldoende in remissie brengt. Ineffectieve behandelstrategieën aan het begin van het ziektebeloop kunnen leiden tot een hoger risico op het ontwikkelen van complicaties die leiden tot meer klachten, een verminderde kwaliteit van leven en slechte groei. Op basis van onze bevindingen stellen wij dat kinderen met de ziekte van Crohn die zich bij diagnose presenteren met matig tot ernstige ziekteactiviteit profijt hebben van primaire behandeling met infliximab. In dit onderzoek werden kinderen behandeld met 5 infusen infliximab in combinatie met azathioprine. Na deze 5 infusen werd alleen de azathioprine gecontinueerd als onderhoudsbehandeling. De patiënten die geïncludeerd werden in deze studie zullen gedurende langere tijd worden gevolgd. Resultaten uit deze langere follow-up zullen ons meer informatie kunnen geven over de noodzaak voor herstarten van infliximab gedurende het ziektebeloop. Toekomstig onderzoek is noodzakelijk voor het in kaart brengen van de kosteneffectiviteit van primaire behandeling met infliximab en de plaats van herhaaldelijk (cyclisch) geven van biologicals.

In **Hoofdstuk 6** wordt ingegaan op een relatief nieuwe biological binnen de behandeling van kinderen met IBD; vedolizumab. Dit middel wordt ingezet als tweedelijnstherapie bij kinderen met de ziekte van Crohn en colitis ulcerosa. Tijdens de behandeling met andere biologicals, zoals infliximab, worden medicatiespiegels in het bloed gecontroleerd om de dosis en doseringsintervallen te optimaliseren. Door de beperkte literatuur over het gebruik van vedolizumab bij kinderen met IBD zijn er vooralsnog geen gegevens beschikbaar over het gebruik van vedolizumab spiegels binnen deze groep. In **hoofdstuk 6** tonen wij aan dat de vedolizumab spiegels bij kinderen met IBD vergelijkbaar zijn met die van volwassenen. We stelden verschillende factoren vast die geassocieerd zijn met lagere vedolizumab spiegels. Zo beschrijven wij in dit hoofdstuk dat de vedolizumab spiegels bij kinderen met de ziekte van Crohn lager zijn dan die van kinderen met colitis ulcerosa. Op basis van studies die verricht werden binnen een populatie volwassenen met IBD, is er steeds meer bewijs dat hogere vedolizumab spiegels tijdens inductiethe-

rapie geassocieerd zijn met aanhoudend klinische remissie gedurende het eerste jaar. Het door ons verrichte onderzoek geeft een eerste inzicht in de hoogte en betekenis van vedolizumab spiegels bij kinderen met IBD. Door het kleine cohort is het echter niet mogelijk de vedolizumab spiegels te correleren aan de klinische effectiviteit. Het is daarom van belang dat dit onderzocht wordt in toekomstige prospectieve studies.

Voorspellen van het beloop van de ziekte

In **hoofdstuk 7** en **hoofdstuk 8** worden de resultaten beschreven van een systematisch verzameld literatuuroverzicht wat samenvat welke factoren, voor zover nu bekend, een ernstige uitkomst voorspellen bij kinderen met IBD. Ernstige uitkomsten zijn onder andere noodzaak tot operatief ingrijpen, chronische actieve ziekte, stenose, fistelende ziekte en ziekenhuisopnames. Bij kinderen met de ziekte van Crohn, zoals beschreven in **hoofdstuk 7**, bleek dat de aanwezigheid van slechte groei, stenoserende of fistelende ziekte, bepaalde genetische varianten (NOD2/CARD15 variant) en anti-microbiële antilichamen geassocieerd is met de noodzaak tot een chirurgische ingreep. In de groep kinderen met colitis ulcerosa, beschreven in **hoofdstuk 8**, was de uitgebreidheid van de locatie van de darmontsteking, de ernst van de ontsteking, het hebben van een familielid met colitis ulcerosa en de aanwezigheid van extra-intestinale manifestaties geassocieerd is met de noodzaak tot operatief ingrijpen in de vorm van een colectomie. De aanwezigheid van primaire scleroserende cholangitis is hierin juist een beschermende factor. Dit systematische literatuuronderzoek werd beperkt door de grote verschillen in de manier van verzamelen en rapporteren van gegevens in de beschikbare wetenschappelijke onderzoeken. Deze grote verschillen zijn het gevolg van het beperkte aantal grote prospectieve cohortstudies dat verricht is binnen de populatie van kinderen met IBD. In de door ons verrichte meta-analyse werden om die reden maar een klein aantal studies geïncludeerd. Ook was het niet mogelijk een meta-analyse te verrichten voor alle onderzochte uitkomstmaten. Ondanks deze beperkingen geven **hoofdstuk 7** en **hoofdstuk 8** voor het eerst een overzicht van de huidige stand van zaken betreffende voorspellende factoren van het beloop van IBD bij kinderen. Beide hoofdstukken bevatten standpunten die richting kunnen geven aan het gebruik van prognostische factoren in de klinische zorg. Deze standpunten werden opgesteld op basis van de wetenschappelijke literatuur en werden vervolgens gevalideerd op basis van consensus tussen internationale experts op het gebied van IBD bij kinderen.

Hoofdstuk 7 en **hoofdstuk 8**, en de kennishiaten die hieruit naar voren komen, tonen het belang van het verrichten van grote prospectieve cohortonderzoeken om factoren die het beloop van IBD bij kinderen kunnen voorspellen beter te kunnen evalueren. In **Hoofdstuk 9** wordt de methode van een door ons opgerichte internationale prospectieve studie beschreven; de zogenaamde ‘’PIBD-SETQuality study’’. In dit hoofdstuk

omschrijven we hoe we klinische en immunologische gegevens verzamelen met als doel het immunologische profiel van kinderen met IBD voor het starten van therapie in kaart te brengen. Het relateren van de klinische gegevens aan de immunologische bevindingen speelt hierin een belangrijke rol. Door de patiënten na het starten van de therapie te blijven volgen hopen we in de toekomst het effect van therapie op de vastgestelde immunologische profielen te kunnen beoordelen. De klinische gegevens die verzameld worden binnen dit cohort bieden de mogelijkheid de bevindingen omschreven in **hoofdstuk 7, hoofdstuk 8** en eerdere prospectieve studies te valideren. Aanvullend hierop worden binnen dit cohort ook verschillende uitkomstmaten onderzocht met betrekking tot de kwaliteit van leven van kinderen met IBD.

In **hoofdstuk 10**, het laatste hoofdstuk, worden de bevindingen uit dit proefschrift in perspectief van de wetenschappelijke literatuur en klinische praktijk geplaatst. Tevens worden suggesties gedaan voor toekomstig onderzoek betreffende de onderwerpen die besproken werden in dit proefschrift.

ABBREVIATIONS:

aHR	adjusted hazard ratio
ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
ANCA	antineutrophil cytoplasmic antibody
ASC	acute severe colitis
ASCA	anti-*Saccharomyces cerevisiae* antibody
AZA	azathioprine
B2	stricturing behavior
B3	internal penetrating behavior
B2/B3	stricturing and/or internal penetrating behavior
BMD	bone mineral density
BMI	body mass index
CCA	cholangiocarcinoma
CD	Crohn's disease
CI	confidence interval
CRC	colorectal carcinoma
CRP	C-reactive protein
CSVT	cerebral sinus venous thrombosis
CVC	central venous catheter
DVT	deep venous thrombosis
EEN	exclusive enteral nutrition
ESPGHAN	European Society of Paediatric Gastroenterology, Hepatology and nutrition
ESR	erythrocyte sedimentation rate
Fcal	faecal calprotectin
FL-IFX	first-line infliximab
GI	gastrointestinal
HCC	hepatocellular carcinoma
HLA	human leukocyte antigen
HR	hazard ratio
IBD	inflammatory bowel disease
IBD-U	inflammatory bowel disease unclassified
IFX	Infliximab
Ig	immunoglobulin
IQR	interquartile range
LMWH	low molecular weight heparin
MOF	multi organ failure
NHL	non-Hodgkin lymphoma
NR	not relevant
OR	odds ratio

OSCI	outcome of steroid therapy in colitis individuals
pANCA	perinuclear antineutrophil cytoplasmic antibody
PCDAI	pediatric CD activity index
PE	pulmonary embolism
PedilBDC	pediatric inflammatory bowel disease consortium
PGA	physician global assessment
PIBD	pediatric-onset inflammatory bowel disease
PSC	primary sclerosing cholangitis
PUCAI	pediatric ulcerative colitis activity index
QOL	quality of life
RCT	randomized controlled trial
SC	steering committee
SD	standard deviation
SDS	standard deviation scores
SES-CD	simple endoscopic score for Crohn's disease
SIR	standardized incidence ratio
TDM	therapeutic drug monitoring
TNF	tumor necrosis factor
TNF-α	tumor necrosis factor alpha
TPMT	thiopurine methyltransferase
UC	ulcerative colitis
UNK	unknown
VTE	venous thromboembolism
WBC	white blood cells
wPCDAI	weighted paediatric Crohn's disease activity index

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Jasja Wolthoorn	Department of Bioanalysis, Sanquin Diagnostic Services, Amsterdam, the Netherlands

LIST OF PUBLICATIONS

Included in this thesis

Aardoom MA, Klomberg RCW, Kemos P, Ruemmele FM, van Ommen H, de Ridder L, Croft NM. The incidence and characteristics of venous thromboembolisms in paediatric-onset inflammatory bowel disease; a prospective international cohort study based on the PIBD-SETQuality Safety Registry. J Crohns Colitis. 2021 Oct 2:jjab171. Epub ahead of print.

Ricciuto A*, **Aardoom M***, Orlanski-Meyer E*, Navon D, Carman N, Aloi M, Bronsky J, Däbritz J, Dubinsky M, Hussey S, Lewindon P, Martín De Carpi J, Navas-López VM, Orsi M, Ruemmele FM, Russell RK, Veres G, Walters TD, Wilson DC, Kaiser T, de Ridder L, Turner D, Griffiths AM; Pediatric Inflammatory Bowel Disease–Ahead Steering Committee. Predicting Outcomes in Pediatric Crohn's Disease for Management Optimization: Systematic Review and Consensus Statements From the Pediatric Inflammatory Bowel Disease-Ahead Program. Gastroenterology. 2021 Jan;160(1):403-436.e26.

Orlanski-Meyer E*, **Aardoom M***, Ricciuto A*, Navon D, Carman N, Aloi M, Bronsky J, Däbritz J, Dubinsky M, Hussey S, Lewindon P, Martin De Carpi J, Navas-López VM, Orsi M, Ruemmele FM, Russell RK, Veres G, Walters TD, Wilson DC, Kaiser T, de Ridder L, Griffiths A, Turner D. Predicting Outcomes in Pediatric Ulcerative Colitis for Management Optimization: Systematic Review and Consensus Statements From the Pediatric Inflammatory Bowel Disease-Ahead Program. Gastroenterology. 2021 Jan;160(1):378-402.e22.

Jongsma MME, **Aardoom MA**, Cozijnsen MA, van Pieterson M, de Meij T, Groeneweg M, Norbruis OF, Wolters VM, van Wering HM, Hojsak I, Kolho KL, Hummel T, Stapelbroek J, van der Feen C, van Rheenen PF, van Wijk MP, Teklenburg-Roord STA, Schreurs MWJ, Rizopoulos D, Doukas M, Escher JC, Samsom JN, de Ridder L. First-line treatment with infliximab versus conventional treatment in children with newly diagnosed moderate-to-severe Crohn's disease: an open-label multicentre randomised controlled trial. Gut. 2022 Jan;71(1):34-42.

Aardoom MA*, Jongsma MME*, de Vries A, Wolthoorn J, de Ridder L, Escher JC. Vedolizumab Trough Levels in Children With Anti-Tumor Necrosis Factor Refractory Inflammatory Bowel Disease. J Pediatr Gastroenterol Nutr. 2020 Oct;71(4):501-507.

Aardoom MA, Kemos P, Tindemans I, Aloi M, Koletzko S, Levine A, Turner D, Veereman G, Neyt M, Russell RK, Walters TD, Ruemmele FM, Samsom JN, Croft NM, de Ridder L; PIBD-

SETQuality consortium and PIBD-NET. International prospective observational study investigating the disease course and heterogeneity of paediatric-onset inflammatory bowel disease: the protocol of the PIBD-SETQuality inception cohort study. BMJ Open. 2020 Jul 1;10(7):e035538.

Aardoom MA, Veereman G, de Ridder L. A Review on the Use of Anti-TNF in Children and Adolescents with Inflammatory Bowel Disease. Int J Mol Sci. 2019 May 23;20(10):2529.

Joosse ME*, **Aardoom MA***, Kemos P, Turner D, Wilson DC, Koletzko S, Martin-de-Carpi J, Fagerberg UL, Spray C, Tzivinikos C, Sladek M, Shaoul R, Roma-Giannikou E, Bronsky J, Serban DE, Ruemmele FM, Garnier-Lengline H, Veres G, Hojsak I, Kolho KL, Davies IH, Aloi M, Lionetti P, Hussey S, Veereman G, Braegger CP, Trindade E, Wewer AV, Hauer AC, de Vries ACH, Sigall Boneh R, Sarbagili Shabat C, Levine A, de Ridder L; Paediatric IBD Porto group of ESPGHAN. Malignancy and mortality in paediatric-onset inflammatory bowel disease: a 3-year prospective, multinational study from the paediatric IBD Porto group of ESPGHAN. Aliment Pharmacol Ther. 2018 Sep;48(5):523-537.

Aardoom MA*, Joosse ME*, de Vries ACH, Levine A, de Ridder L. Malignancy and Mortality in Pediatric-onset Inflammatory Bowel Disease: A Systematic Review. Inflamm Bowel Dis. 2018 Mar 19;24(4):732-741.

Not included in this thesis

Klomberg RCW, **Aardoom MA**, Kemos P, Rizopoulos D, Ruemmele FM, Croft NM, de Ridder L, Neyt M; on behalf of the PIBD-SETQuality consortium. High impact of pediatric inflammatory bowel disease on caregivers' work productivity and daily activities: an international prospective study. *Manuscript submitted for publication.*

Roozeboom MH*, **Aardoom MA***, Nelemans PJ, Thissen MR, Kelleners-Smeets NW, Kuijpers DI, Mosterd K. Fractionated 5-aminolevulinic acid photodynamic therapy after partial debulking versus surgical excision for nodular basal cell carcinoma: a randomized controlled trial with at least 5-year follow-up. J Am Acad Dermatol. 2013 Aug;69(2):280-7.

**shared first authorship*

PHD PORTFOLIO

Erasmus MC Department:	Pediatric Gastroenterology
PhD period:	June 2016 – June 2020
Promotors:	Prof. dr. J.C. Escher, Prof. dr. J.N. Samsom
Copromotor:	Dr. L. de Ridder

PhD training

	Year	Workload (ECTS)
General courses		
Biostatistical Methods I: Basic Principles	2017	5.7
BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2016	1.0
Research Integrity	2018	0.3
Biomedical English Writing and Communication	2019	3.0
Photoshop and Illustrator CC 2019 Workshop	2019	0.3
Specific courses (e.g. Research school, Medical Training)		
The basic introduction course on SPSS	2016	1.0
Endnote & Pubmed courses	2016	
PIBD ESPGHAN Masterclass, Rotterdam	2016	0.6
Evidence Based Guideline Development (EBRO course)	2017	0.3
Immunology ESPGHAN Masterclass, Leiden	2017	0.6
NVK SLAM presentation course	2019	0.3
Attended seminars and workshops		
Young Investigator Forum, ESPGHAN	2016	1.5
Symposia Young Initiative on Crohn's and Colitis (biannual, 6x)	2016 - 2019	1.0
Sophia Research Days (annual, 3x)	2017 - 2019	1.0
Symposia Initiative on Crohn's and Colitis (annual, 2x)	2017 - 2018	1.0
National presentations		
Adult-Pediatric IBD meetings	2016 - 2020	1.5
Lab & Clinic meetings Pediatric Gastroenterology	2016 - 2020	2.0
Research meetings Kids Initiative on Crohn's and Colitis (KICC)	2016 - 2020	0.6
Regional symposium pediatric gastroenterology, Rotterdam	2018	0.3
ACE Inflammunity meeting, Rotterdam	2018	0.3
Paediatric gastroenterologists meeting on new NVK guideline PIBD, Amsterdam	2019	0.3
International presentations		
Investigators meeting C&M project IBD Porto Group, Barcelona	2017	0.3
PIBDSETQuality consortium meetings, Paris	2017-2019	1.5
PIBD Ahead project meeting, Vienna	2018	0.3
Grant applications		
Stichting Autoimmuun Onderzoek (SAIO); granted 96.666 euro	2019	0.6
National conferences		
Sophia Research Day, Rotterdam, *oral presentation*	2017	0.3
NVK congress, Papendal, *oral presentation*	2019	0.3

International conferences		
ESPGHAN congress, Prague, *oral presentation*	2017	1.0
PIBD congress, Barcelona, *poster presentation*	2017	1.0
ECCO congress, Vienna, *poster presentation*	2018	1.0
ESPGHAN congress, Geneva, *oral presentation & two E-posters*	2018	2.0
ECCO congress, Copenhagen, *two posters*	2019	2.0
ESPGHAN congress, Glasgow, *two oral presentations*	2019	2.0
PBD congress, Barcelona, *two poster presentations*	2019	2.0
Organisational activities		
Board member Young Initiative on Crohn's and Colitis	2016 – 2018	3.0
Member of working group NVK guideline PIBD	2016 – 2018	0.3
Treasurer of organizing committee of Sophia Research Day 2018	2017 – 2018	2.0
Member of international PIBD Ahead working group	2017 – 2018	0.3
Chairman of organizing committee of Sophia Research Day 2019	2018 – 2019	2.0
Board member Sophia Researchers Association	2018 – 2019	1.0
Teaching activities		
National pediatric surgery nurses symposium, Rotterdam	2018	0.3
Lecturing on ''PIBD'', EMC, nurse education	2018	0.3
Lecturing on ''paediatric gastroenterology'', EMC, nurse education	2018-2019	1.0
Supervising Master thesis of two medical students	2018-2019	2.0
Awards and grants		
Young Investigators Award, ESPGHAN, *three times*	2017 – 2019	
Poster of distinction, PIBD congress, Barcelona	2017	
One of 100 best scored posters, ESPGHAN, *two times*	2018 – 2019	
EUR Trust fund conference participation grant	2019	
KNAW Ter Meulen Grant, 4400 euro	2019	
Grant Stichting Autoimmuun Onderzoek, 96.666 euro	2019	
Total		**49.1 ECTS**

ECTS = European Credit Transfer and Accumulation System (1 ECTS represents 28 hours)

ABOUT THE AUTHOR

Martine Adriënne Aardoom was born on the 30th of July 1989 in Bemmel, the Netherlands.

After graduating in 2007 from Stedelijk Gymnasium Nijmegen, she studied Psychology at Maastricht University and obtained her first year's degree. In 2008 she began her study Medicine at the same university. In 2011 she conducted research in the field of Dermatology at Maastricht University Medical Center. She obtained her medical degree in December 2014 and started working as a pediatric resident (ANIOS) at Bronovo Hospital in the Hague.

In 2016 she started her PhD study under the supervision of Prof. dr. J.C. Escher, Dr. L. de Ridder and Prof. dr. J.N. Samsom at the Department of Pediatric Gastroenterology of Erasmus MC-Sophia Children's Hospital in Rotterdam. Between 2016 and 2018 she was a board member of the Young Initiative on Crohn's and Colitis and organized several symposia for young researchers in the field of inflammatory bowel disease. She was a board member of the Sophia Researchers Association and organized the Sophia Research Days in 2018 and 2019. In 2020 she received a research grant from the Stichting Autoimmuun Onderzoek to enable the financing of a new researcher to continue the ongoing research projects she was working on. In October 2020 she started her residency (AIOS) in Pediatrics at Rijnstate Hospital in Arnhem. She is looking forward to soon continue this residency at Radboud University Medical Center in Nijmegen.

De omgeving van de mens is de medemens

Jules Deelder