Crohn's Disease and Ulcerative Colitis in Children and Adolescents

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Contents

1. Introduction

Martin Classen

IBD differs between adults and children

Inflammatory bowel disease (IBD) can present at any age, with a peak between the ages of 15 and 25. Nonetheless, the disease does not manifest in a strictly linear fashion, but rather in specific forms which vary based on the age of onset. As a result, disease activity and the course of IBD may differ between cases of early-onset IBD and adult-onset IBD.

Approximately 25% of IBD cases are diagnosed in patients ages 18 years old and younger [Benchimol et al. 2011], and approximately 25% of these cases are in turn diagnosed before the age of 10. The disease is typically more severe in children and adolescents than in adults in terms of its extent and inflammatory activity [Jakobsen et al. 2011]. The age cohort of children under the age of 2 represents a unique form of the disease, since many of these cases are actually monogenic immune disorders which present as IBD [Charbit-Henrion et al. 2018, Oliva-Hemker et al. 2015, Uhlig et al. 2014] (see Chapter 2: Unique aspects in the pathophysiology of pediatric IBD).

The impact of IBD on physical and mental development is particularly severe in children [Brooks et al. 2016]. Physicians must be familiar with the unique characteristics of each age group and take these characteristics into account when caring for patients. Pediatric gastroenterologists are specially trained on these topics, and accordingly they represent the group of providers specifically recommended in German guidelines [Kucharzik et al. 2018, Preiss et al. 2014]. Physicians must have expertise in education, psychology, and nutrition medicine when treating children and adolescents with IBD. The treatment approaches of pediatricians and internists differ greatly [Assa et al. 2016]. According to two recent publications based on data from the large CEDATA registry maintained by the GPGE (German Society for Pediatric Gastroenterology and Nutrition), there are major differences in the clinical presentation, course, and treatment between pediatric and adult IBD [Buderus et al. 2015, Daebritz et al. 2017].

Pediatric IBD patients are at an elevated risk of developing psychosocial issues and psychiatric disorders [Castaneda et al. 2013, Szigethy et al. 2009]. IBD can negatively impact academic performance, degree completion, vocational training, recreational activities, adherence to medication, and quality of life [Engelmann et al. 2015, Giannakopoulos

et al. 2016, Kilroy et al. 2011]. Depression is also a common psychiatric comorbidity of the disease [Clark et al. 2014, Szigethy et al. 2009].

The health provider structures also differ fundamentally between pediatric and adult patients. There are many fewer pediatric gastroenterologists than adult gastroenterologists in private practice in Germany. This is due to the lower number of patients and to the more stringent indications required for invasive procedures in children, but also due to the lack of a need for screening endoscopy in children. The vast majority of pediatricians who have completed a specialization in gastroenterology are employed at hospitals, although there is also a small yet steadily growing number of pediatric gastroenterologists in private practice. This group of pediatricians is often hampered by unfavorable insurance reimbursement policies. A list of contacts on this topic can be found on the GPGE website (www.gpge.de).

The goal for the authors of this booklet was to provide a concise, practice-oriented, scientific overview of the entire field of pediatric IBD. The booklet is intended to assist pediatricians, pediatric gastroenterologists, and internists at providing optimal care to this group of patients who are suffering under a tremendous burden.

Martin Classen, Stephan Buderus, Axel Enninger, Jan de Laffolie, Michael Melter, Carsten Posovszky, Burkhard Rodeck

Literature

Assa A, Avni I, Ben-Bassat O, Niv Y, Shamir R. Practice Variations in the Management of Inflammatory Bowel Disease Between Pediatric and Adult Gastroenterologists. J Pediatr Gastroenterol Nutr. 2016;62(3):372–7.

Benchimol EI, Fortinsky KJ, Gozdyra P, Van den Heuvel M, Van Limbergen J, Griffiths AM. Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. Inflamm Bowel Dis. 2011;17(1):423–39.

Brooks AJ, Rowse G, Ryder A, Peach EJ, Corfe BM, Lobo AJ. Systematic review: psychological morbidity in young people with inflammatory bowel disease – risk factors and impacts. Aliment Pharmacol Ther. 2016;44(1):3–15.

Buderus S, Scholz D, Behrens R, Classen M, De Laffolie J, Keller KM, et al. Inflammatory bowel disease in pediatric patients: Characteristics of newly diagnosed patients from the CEDATA-GPGE Registry. Dtsch Arztebl Int. 2015;112(8):121–7.

Castaneda AE, Tuulio-Henriksson A, Aronen ET, Marttunen M, Kolho KL. Cognitive functioning and depressive symptoms in adolescents with inflammatory bowel disease. World J Gastroenterol. 2013;19(10):1611–7.

Charbit-Henrion F, Parlato M, Hanein S, Duclaux-Loras R, Nowak J, Begue B, et al. Diagnostic Yield of Next-Generation Sequencing in Very Early-Onset Inflammatory Bowel Diseases: A Multicenter Study. J Crohns Colitis. 2018 May 18. doi: 10.1093/ecco-jcc/jjy068.

Clark JG, Srinath AI, Youk AO, Kirshner MA, McCarthy FN, Keljo DJ, et al. Predictors of depression in youth with Crohn disease. J Pediatr Gastroenterol Nutr. 2014;58(5):569–73.

Däbritz J, Gerner P, Enninger A, Claßen M, Radke M. Inflammatory Bowel Disease in Childhood and Adolescence. Dtsch Arztebl Int. 2017;114(19):331–8.

Engelmann G, Erhard D, Petersen M, Parzer P, Schlarb AA, Resch F, et al. Health-related quality of life in adolescents with inflammatory bowel disease depends on disease activity and psychiatric comorbidity. Child Psychiatry Hum Dev. 2015;46(2):300–7.

Giannakopoulos G, Chouliaras G, Margoni D, Korlou S, Hantzara V, Panayotou I, et al. Stressful life events and psychosocial correlates of pediatric inflammatory bowel disease activity. World J Psychiatry. 2016;6(3):322–8.

Jakobsen C, Bartek J Jr, Wewer V, Vind I, Munkholm P, Groen R, et al. Differences in phenotype and disease course in adult and paediatric inflammatory bowel disease – a population-based study. Aliment Pharmacol Ther. 2011;34(10):1217–24.

Kilroy S, Nolan E, Sarma KM. Quality of life and level of anxiety in youths with inflammatory bowel disease in Ireland. J Pediatr Gastroenterol Nutr. 2011;53(3):275–9.

Kucharzik T, Dignass AU, Atreya R, Bokemeyer B, Esters P, Herrlinger K, et al. [Updated S3-Guideline Colitis ulcerosa. German Society for Digestive and Metabolic Diseases (DGVS) - AWMF Registry 021/009]. Z Gastroenterol. 2018;56(9):1087–169.

Oliva-Hemker M, Hutfless S, Al Kazzi ES, Lerer T, Mack D, LeLeiko N, et al. Clinical Presentation and Five-Year Therapeutic Management of Very Early-Onset Inflammatory Bowel Disease in a Large North American Cohort. J Pediatr. 2015;167(3):527–32.e1–3.

Preiß JC, Bokemeyer B, Buhr HJ, Dignaß A, Häuser W, Hartmann F, et al. [Updated German clinical practice guideline on "Diagnosis and treatment of Crohn's disease" 2014]. Z Gastroenterol. 2014;52(12):1431–84.

Szigethy E, Craig AE, Iobst EA, Grand RJ, Keljo D, DeMaso D, et al. Profile of depression in adolescents with inflammatory bowel disease: implications for treatment. Inflamm Bowel Dis. 2009;15(1):69–74.

Uhlig HH, Schwerd T, Koletzko S, Shah N, Kammermeier J, Elkadri A, et al. The diagnostic approach to monogenic very early onset inflammatory bowel disease. Gastroenterology. 2014;147(5):990–1007.e3.

2. Unique aspects in the pathophysiology of pediatric IBD

Carsten Posovszky

Crohn's disease (CD) and ulcerative colitis (UC) are the two main components of inflammatory bowel disease (IBD). These two disorders were once thought to be autoimmune diseases, as they are both associated with extraintestinal autoimmune manifestations. For example, arthritis and uveitis may occur in patients with CD, while primary sclerosing cholangitis (PSC) is more common with UC. However, these diseases are in fact chronic inflammatory disorders of the gastrointestinal tract that are triggered by dysregulated immune responses to intestinal bacteria in genetically predisposed individuals [Xu et al. 2014].

The intestinal immune system – innate and adaptive immunity

The gut is the largest immune organ in the human body, with the intestinal mucosa forming an enormous boundary up to 40 m^2 in surface area [Helander & Fändriks 2014]. This mucosa confers protection from toxins, bacteria, and other harmful substances through both natural innate immune defenses and specific adaptive immune responses [Kurashima et al. 2013]. The mucosa provides a barrier to the contents of the bowel, including nutrients and gut microbiota as well as pathogenic viruses, bacteria, and parasites (Figure 2/1). The intestinal mucosa is comprised of a single layer of epithelial cells (the epithelium), a layer of connective tissue (lamina propria), and a muscular layer (muscularis mucosae) [Gracz & Magness 2014]. In addition to exerting a mechanical barrier function, the epithelium is also involved in numerous secretion and absorption processes which aid in both nutrient uptake and in protection from infection [DeSesso & Jacobson 2001]. The intestinal immune defenses begin in the lumen itself with "non-specific" factors in mucus and serous fluids.

Specific mucosal immunity is conferred by secretory immunoglobulin A (sIgA) on the mucosal surface and by lymphocytes in the epithelium, both of which are considered mucosa-associated lymphoid tissue (MALT) [Brandtzaeg 2010].

In the gut, lymphocytes are found both in secondary lymphoid tissues including the lymphoid follicles, the appendix, and the mesenteric lymph nodes, as well as diffusely localized in gut tissue as intraepithelial lymphocytes (IEL) between the epithelial cells and in the lami-

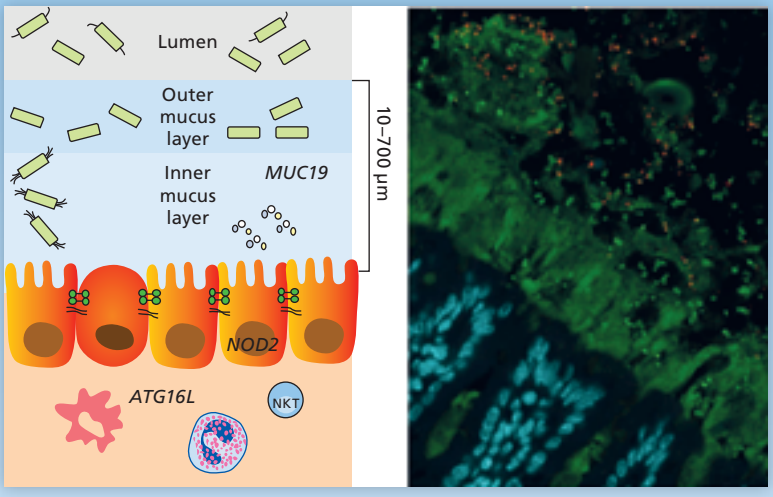


Figure 2/1: The intestinal barrier and the non-specific innate immune response. A single layer of epithelium comprised of enterocytes (yellow-brown) and goblet cells (red) forms a mechanical and chemical barrier in the bowel (schematic diagram in left panel). The tight junctions between the cells (green) prevent pathogens and other microbes from entering into the mucosa via the paracellular space. The mucus layers (turquoise) produced by the goblet cells (red) and the defensins and immunoglobulin A (small circles) produced by the enterocytes are both forms of chemical immune defenses. The inner mucus layer prevents non-flagellated bacteria from entering. The immunohistology image in the right panel shows bacteria (red) in the mucus layer (green) on the epithelial cell layer (blue) (source of right panel: Dirk Haller, TUM: https://www.tum.de/die-tum/aktuelles/pressemitteilungen/detail/article/31215/).

na propria. The MALT represents a gigantic reservoir of lymphocytes and is important for specific adaptive immunity in the gut.

The direct immune reaction which occurs between the contents of the bowel, the mucosa, and lymphoid tissues is key for the specific immune response. Peyer's patches, which are primarily located in the ileum and in the tonsils, contain specialized M cells that are in direct contact with the lumen and take up luminal antigens [Corr et al. 2008].

The immune system is constantly active in the gut. Activated T cells and memory T cells are found in the gut lymphoid tissues even in the absence of a stimulus (such as infection), and these tissues are the site of ongoing regulatory immune processes which inhibit immune responses and induce tolerance [Kurashima et al. 2013]. For example, regulatory T cells (Treg) prevent pro-inflammatory Th17 cells from inducing an inflammatory response. However, if anti-inflammatory bacteria become diminished – for example resulting from diet – or if proinflammatory bacteria dominate the gut flora, proinflammatory

cytokines will stimulate Th17 cells over Treg cells and it becomes impossible to contain the inflammatory response [Khor et al. 2011].

Intriguingly, germ-free mice have hypoplastic Peyer's patches and no solitary lymphoid follicles, suggesting that microbial stimulation is required for the formation of secondary lymphoid tissues in the gut [Hooper et al. 2012]. Moreover, the commensal microbiota also stimulates the non-specific antibacterial activity of enterocytes [Goto & Ivanov 2013]. Thus, the gut flora promotes the maturation and balance of the intestinal immune system.

The pathophysiology of IBD

Both the intestinal barrier but also non-specific and specific immune responses play major roles in the pathophysiology of IBD [Kurashima et al. 2013]. Several components of the intestinal barrier are dysfunctional in IBD, which are often associated with genetic risk factors [McCole 2014].

The microbiome of IBD patients differs from that of healthy persons, exhibiting for example less diversity of bacterial species and greater numbers of bacteria on the mucosal surface [Swidsinski et al. 2005]. This latter observation may be due to dysregulated or decreased production of mucus, as MUC knock-out mice (which do not produce mucin) develop IBD. Commensal bacteria upregulate the tight junctions connecting the epithelial cells, and thereby regulate diffusion and maintain epithelial polarity in the epithelium. Abnormal tight junction formation is observed in patients with *GNAI2* and *MAGI2* polymorphisms and is associated with the development of UC [McCole 2014]. Several different polymorphisms in *NOD2* are associated with CD, and expression of antimicrobial peptides by Paneth cells is reduced in patients with *NOD2* polymorphisms [Biswas et al. 2012, Kobayashi et al. 2005]. The numerous genetic mutations associated with IBD will be discussed below in the section on theories of the disease as part of the genetic hypothesis. The key point is that a stable and healthy microbiome may help maintain immune system equilibrium even in patients with an unfavorable genetic predisposition.

Epidemiological risk factors

Epidemiological studies have identified both protective factors and risk factors for UC and CD (Figure 2/2) (see also Chapter 3: Risk factors). The recent increase in the incidence of IBD has been attributed to environmental and socioeconomic factors [Guariso 2014, Ponder &

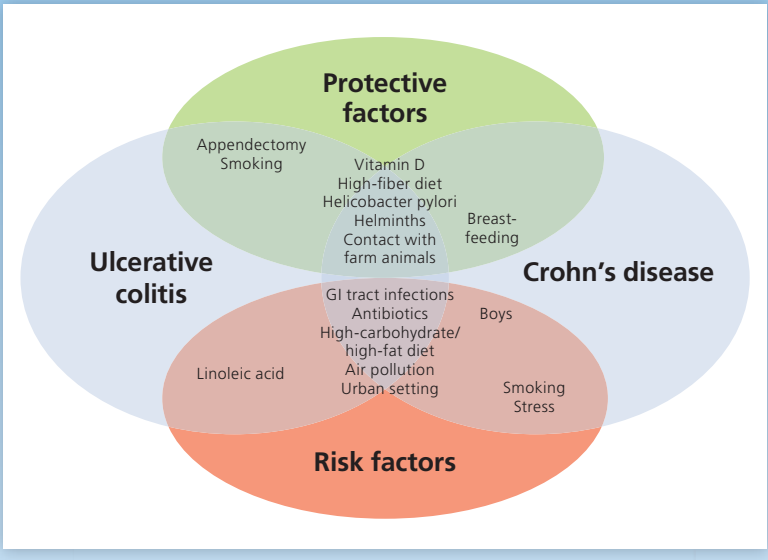


Figure 2/2: Environmental factors and the etiology of IBD. Epidemiological studies have identified risk factors (red circle) and protective factors (green circle) for CD and UC (adapted from Ponder & Long 2013).

Long 2013]. The uptick in IBD in Eastern Europe has been attributed in part to improved hygienic conditions, especially improvements in water quality *(hygiene hypothesis)*. However, the growing number of antibiotic prescriptions, and the concurrent decrease in beneficial bacteria (*Bifido*, *Lactobacillus*, *Bacteroides*, and *Firmicutes* spp.) and increase in pathogenic bacteria such as invasive *Escherichia coli* species, is also thought to be a cause. Indeed, epidemiological data have shown that antibiotic use is associated with an elevated risk of IBD [Hviid et al. 2011]. This risk is dose-dependent and increases with the number of cycles of antibiotics, and is particularly high in cases of early antibiotic treatment during the first year of life [Ponder & Long 2013].

The effects of smoking on the etiology of IBD have been studied in great detail. These studies have revealed an elevated risk of CD among active smokers and an elevated risk of UC among ex-smokers [Ponder & Long 2013].

However, these and other epidemiological studies have only been able to establish correlation, but not causation.

Theories on the pathogenesis of IBD

A number of theories on the etiology of IBD have been proposed in recent years (Figure 2/3), the most well-known of which is the *hygiene hypothesis*. This hypothesis postulates that fewer infections by helminths, *Helicobacter pylori*, or pathogenic mycobacteria, less contact with farm animals, improved water quality, and increasing antibiotic use may all elevate the risk of developing IBD, especially in small families with two children or fewer [Koletzko & Uhlig 2010, Ponder & Long 2013]. This theory may explain observations such as the increase in the incidence of IBD in Eastern Europe over the past two decades that has occurred in parallel with improvements in hygienic conditions in this region [Koletzko & Uhlig 2010].

In contrast, the *infection hypothesis* postulates that IBD may be triggered by infections of the gastrointestinal tract by agents such as *Helicobacter pylori* or *Salmonella* spp. However, there is still no scientific proof of this hypothesis despite exhaustive research efforts [Koletzko & Uhlig 2010].

The *barrier defect hypothesis* was postulated as a result of scientific insights into the crucial importance of the intestinal barrier and the microbiome in the etiology of IBD. The gut epithelium does indeed exhibit greater permeability in patients with IBD as well as in their healthy first-degree relatives. This phenomenon has been linked to genetic mutations or polymorphisms in protein tyrosine phosphatase N2 *(PTPN2)* or the transcription factor X-box binding protein 1 *(XBP1)*

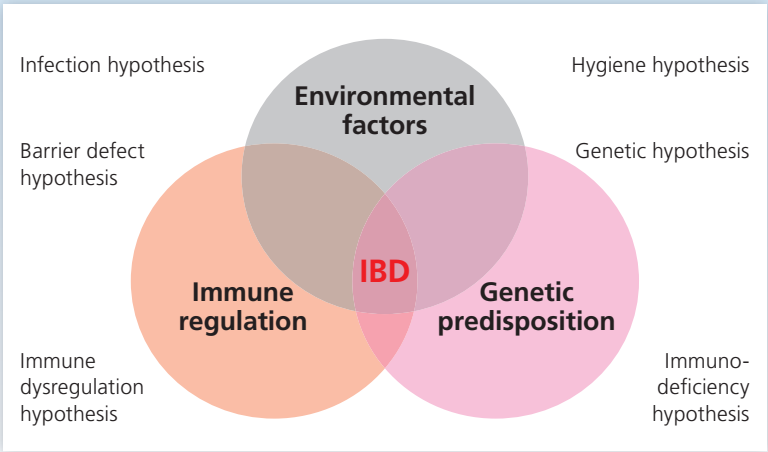


Figure 2/3: Hypotheses on the etiology of IBD

[Khor et al. 2011, Koletzko & Uhlig 2010]. CD patients also exhibit decreased mucosal antimicrobial activity resulting from reduced secretion of defensins [Nuding et al. 2007].

Scientific evidence has also established the importance of genetic predisposition in the development of IBD *(genetic hypothesis)*. The initial indications of genetic predisposition were provided by twin studies that showed a high level of familial risk (see also Chapter 3: Risk factors). First-degree relatives of IBD patients are themselves at a 10-fold greater risk of developing IBD [Orholm et al. 1991]. These studies suggested that genetic mutations may play a key role, and were followed by genetic linkage studies that initially identified nine independent susceptibility loci [Khor et al. 2011]. The genetic mutations linked to IBD were subsequently numbered IBD1, IBD2, IBD3, etc. up to IBD28 (www.omim.org). These genome-wide association studies (GWAS) were primarily conducted in adult IBD cohorts (see Figure 2/5). They reported a total of 169 susceptibility genes for IBD, of which 71 were CD-specific, 47 were UC-specific, and 28 were associated with an elevated risk of both disorders. Two pediatric studies identified similar genetic determinants as those found for adults, but also identified two new genetic loci: *TNFRS6B* (decoy receptor for the FasL pathway, DCR3) and *PSMG1* [Kugathasan et al. 2008, Scherr et al. 2009]. Next-generation sequencing has been used to identify genetic triggers in patients with severe forms of IBD or early-onset IBD [Christodoulou et al. 2013].

Molecular genetic studies in patients with very early-onset (VEO) disease have revealed more than 40 different monogenic mutations impacting the epithelial barrier, the stress response, and the immune response (Table 2/1) [Schwerd & Koletzko 2017, Uhlig 2013]. These mutations also frequently cause primary immunodeficiencies *(immunodeficiency hypothesis)*. General immunodeficiencies frequently impact the gut, as it is the largest immune organ in the body. Intriguingly, the disease phenotype differs by age group even among patients with the same genotype (Figure 2/4), strongly suggesting that the etiology of IBD also varies by age [Ruel et al. 2014].

In summary, environmental factors impact the microbiome through the mechanisms of increased hygiene, increased antibiotic use, and altered dietary patterns. These changes may trigger inflammatory responses through a reduction in anti-inflammatory bacteria or an increase in proinflammatory gut flora. When these factors occur in individuals who are also genetically predisposed to immune dysreg-

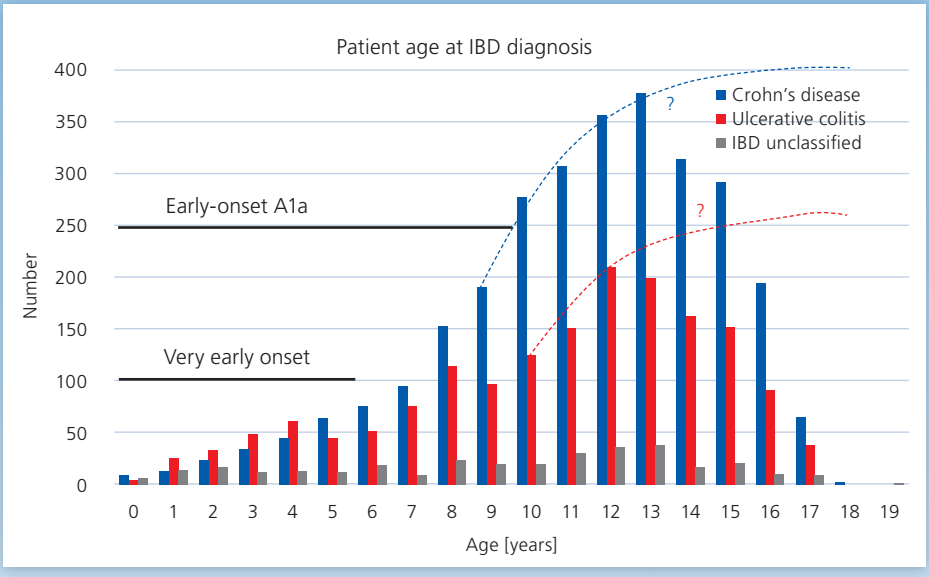


Figure 2/4: Disease onset and classification from the CEDATA-GPGE registry. The Paris classification defines pediatric disease as onset before the age of 17 (A1). Early onset of the disease before the age of 10 (A1a) is defined as a subgroup of this category, with very early-onset (VEO)-IBD defined as onset before the age of 6, and infantile IBD defined as onset before the age of 2. Approximately 15% of pediatric patients in the GPGE CEDATA registry had VEO-IBD. A high percentage of cases of VEO-IBD (up to 30%) are reported as "IBD unclassified" (source: CEDATA-GPGE/retrieved on: 7/2018) (see also Chapter 4: Epidemiology and the CEDATA-GPGE registry).

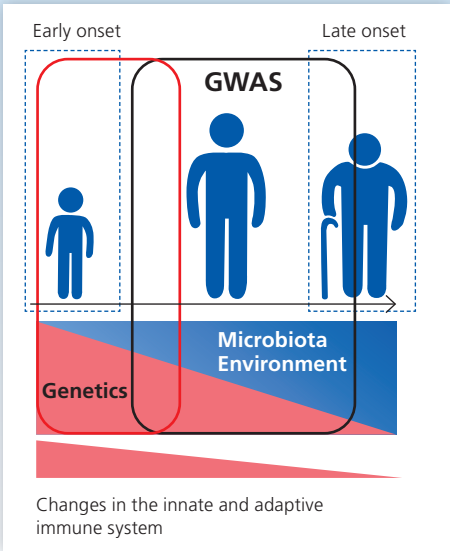


Figure 2/5: How genetics and environmental factors determine the pathogenesis of IBD depends on the age of onset. The changes to the immune system during the first few years of life are enormous, but diminish with increasing age. These first few years are also crucial for the development of an individual gut flora. Early-onset IBD is almost certainly genetically determined, as environmental factors are not yet of major relevance at this age. The majority of genome-wide association studies (GWAS) have been carried out in adult patients (black box). These studies have identified more than 169 susceptibility genes for IBD, genes which have also been confirmed for pediatric onset IBD by two other studies (red box). VEO-IBD prior to age 6 is also often due to monogenic causes (adapted from Uhlig 2013).

ulation, the result is IBD (see Figure 2/3). The influence of genetics is particularly relevant in cases of VEO-IBD. This is an age range during which the individual gut microbiome is still becoming established and the immune system is particularly active, all while environmental cues are continuously increasing (Figure 2/5) (see also Chapter 3: Risk factors).

Monogenic mutations with IBD phenotype in pediatric patients

A large number of rare monogenic disorders may present as IBD (see Table 2/1). These disorders are caused by genetic mutations that impact the epithelial barrier as well as the functions of lymphocytes, phagocytes, and other cell types. Several monogenic mutations are described below as examples together with their associated phenotypes.

CARD15 (NOD2) mutations, (IBD1) OMIM 266600

Genetic predisposition is a primary risk factor for developing IBD. *CARD15 (NOD2)* was the first IBD gene identified for CD [Hampe et al. 2001, Hugot et al. 1996, Hugot et al. 2001, Ogura et al. 2001]. NOD2 is primarily expressed by Paneth cells and regulates the secretion of antimicrobial peptides into the lumen. As a microbial sensor, NOD2 plays an important role in regulating the intestinal microbiota [Murray 2005]. The functional impairment triggered by certain polymorphisms in *NOD2* thus alters the microbial composition of the ileum, and is considered to be a predisposing factor for CD [Biswas et al. 2012]. The rare Blau syndrome (OMIM 186580) is caused by a mutation in *NOD2*. These patients suffer from CD with early-onset granulomatous arthritis accompanied by uveitis, granulomatous synovitis, camptodactyly, rash, and cranial neuropathies.

Defects in the IL10 signaling pathway

Interleukin (IL)10 is a pleiotropic cytokine that is highly conserved among higher eukaryotes [Pestka et al. 2004] and that exerts effects on innate and adaptive immune cells. It inhibits cell-mediated immune responses and promotes the humoral immune response [Moore et al. 2001]. The primary effect of IL10 is to suppress cellular immunity by inhibiting the synthesis of proinflammatory cytokines such as IL1, IL6, interferon-γ, and tumor necrosis factor (TNF)-α in T cells, monocytes, and macrophages. IL10 has been identified in GWAS as a risk allele for IBD. The biological function of IL10 is mediated by the IL10 receptor complex, which is a heterotetramer complex comprised of IL10 receptor 1 (IL10R1) and 2 (IL10R2) [Pestka et al.

2004]. IL10R1 is required for binding of the IL10 ligand, while IL10R2 is essential for signal transduction [Ding et al. 2001, Spencer et al. 1998].

The search for mutations in the IL10 signaling pathway initially revealed four single-nucleotide polymorphisms in IL10R1. One of these variants exhibited defective inhibition of TNF-α production by monocytes [Gasche et al. 2003].

Loss-of-function mutations in the *IL10* gene and in its receptors IL10R1 (IBD28) and IL10R2 (IBD25) were identified as being the cause of VEO-IBD in several patients [Kotlarz et al. 2012]. During the first few months of the disease, these children suffered from severe enterocolitis, perianal abscesses, enterocutaneous fistulas, and chronic folliculitis [Glocker et al. 2009]. These patients could be cured by bone marrow transplantation [Kotlarz et al. 2012].

IL10R1 mutation (IBD28) OMIM 613148

This form of IBD presents during infancy as severe hemorrhagic colitis together with perianal lesions. The cause was identified as homozygous and linked heterozygous mutations in the *IL10RA* gene that encodes IL10R1 [Glocker et al. 2009]. These mutations may impair binding of IL10 to IL10R1 and inhibit IL10R1 expression and STAT3 phosphorylation.

IL10R2 mutation (IBD25) OMIM 612567

This form of IBD also presents during infancy as severe hemorrhagic colitis, and is clinically indistinguishable from mutation of IL10R1. The cause was identified as homozygous and linked heterozygous mutations in the *IL10RB* gene that encodes IL10R2 [Glocker et al. 2009].

Immune dysregulation, polyendocrinopathy, and enteropathy, X-linked (IPEX) OMIM 304790

IPEX syndrome is an X-linked recessive immunodeficiency with an onset in early childhood that is clinically characterized by severe diarrhea, type 1 diabetes, and eczema. Patients may also present with hypothyroidism, autoimmune hemolytic anemia, thrombocytopenia, lymphadenopathy, hepatitis, arthritis, and nephritis [Goulet et al. 1998]. In 2001, IPEX was shown to be caused by mutations in the *FOXP3* gene, which belongs to the group of forkhead/winged helix transcription factors [Bennett et al. 2001, Wildin et al. 2001]. FOXP3 is primarily expressed by regulatory T cells. It is required for the maintenance of immune homeostasis and mediates tolerance to self [d'Hennezel et al. 2012, Gambineri et al. 2003].

Treatment of this disorder consists of immunosuppression of the autoimmune manifestations or bone marrow transplantation [d'Hennezel et al. 2012].

Chronic granulomatous disease (CGD) OMIM 233670, 233690, 233700, 233710, 306400, 613960

Chronic granulomatous disease can manifest in patients from infancy to adulthood and stems from an inability of granulocytes and macrophages to kill bacteria and fungi that have been ingested by phagocytosis. Five separate subtypes of this disorder have been identified which correlate with the five subtypes of NADPH oxidase. All subtypes result in deficient NADPH oxidase activity that can be detected by tests for reduced granulocyte function [Roos & de Boer 2014]. These subtypes are inherited in an autosomal recessive or X-linked manner and afflict 1–9/100,000 persons. Approximately 40% of patients with granulomatous disease present with discontinuous patterns of inflammation, some with perianal involvement and some with epithelioid granulomas on histology. This disorder should be ruled out as a potential important differential diagnosis for pediatric CD [Marks et al. 2009].

Diagnosis of rare monogenic IBD

Rare monogenic diseases with primary immunodeficiency (PID) or epithelial defects may potentially be missed in pediatric IBD patients, as the phenotype of these disorders does not differ from that of patients with CD or UC. For this reason, patients with early-onset or severe forms of these disorders should be examined for an immunodeficiency if other causes (e.g. celiac disease or allergic colitis) have been excluded.

IBD should always be diagnosed according to the applicable guidelines (Porto criteria) [Levine et al. 2014] (see Chapter 7: Diagnosis). Any additional findings which may be characteristic of immunodeficiency should be taken into consideration (Table 2/2). In patients with abnormal findings, standard immunology diagnostic procedures should be carried out (differential blood counts, immunoglobulins G, A, M, and E, complement activity CH50) with immunophenotyping (lymphocyte populations, leukocyte adhesion molecules CD18/CD11), and HIV infection should also be excluded. Moreover, a specialized laboratory can be contracted to exclude specific functional disorders: for example, granulocyte function using an oxidative burst assay (for granulomatous disease), XIAP expression (XIAP deficiency), detection of FOXP3+ regulatory T cells (IPEX syndrome), STAT3 phosphorylation or IL10 suppression test (IL10R mutation), MHC class II ex-

pression (MHC class II mutation). Any suspected diagnoses can then be genetically confirmed using Sanger sequencing. Unfortunately, functional tests are not available for all forms of PID-IBD. Alternatively, genetic screening using genome and exome sequencing or multigene panel sequencing may also be performed. Whole-exome sequencing (WES) and targeted next-generation sequencing (TNGS) are especially recommended for VEO-IBD and for severe forms of IBD requiring treatment decisions with wide-reaching consequences (e.g. colectomy, stem cell transplantation) [Charbit-Henrion et al. 2018, Christodoulou et al. 2013, Schwerd & Uhlig 2017, Uhlig et al. 2014]. These techniques can also be used to identify rare monogenic diseases that were not detected by special functional diagnostic tests [Charbit-Henrion et al. 2018]. These molecular techniques allowed a genetic diagnosis to be made for 32% of the 207 patients with severe VEO-IBD in the ESPGHAN-GENIUS cohort [Charbit-Henrion et al. 2018]. Whenever a patient is diagnosed using genetic techniques, functional tests should be performed to validate the diagnosis if possible.

Rare monogenic disorders with an IBD phenotype	
Disease or deficiency	**Gene**
1. Epithelial defects	
Dystrophic epidermolysis bullosa	*COL7A1*
Kindler syndrome	*FERMT1*
X-linked ectodermal dysplasia with immunodeficiency	*IKBKG*
TTC7A deficiency	*TTC7A*
ADAM17 deficiency	*ADAM17*
Familial diarrhea syndrome	*GUCY2C, SLC9A3*
Chronic enteropathy associated with *SLCO2A1* gene (CEAS)	*SLCO2A1*
NADPH oxidase-1 mutation	*NOX1*
Congenital Tufting enteropathy	*EPCAM*
Microvillus inclusion disease (MVID)	*MYO5B*
2. Phagocyte defects	
Granulomatous disease	*CYBB, CYBA, NCF1, NCF2, NCF4*
Glycogen storage disease type Ib	*SLC37A4*
Congenital neutropenia	*G6PC3*
Leukocyte adhesion deficiency 1	*ITGB2*
3. Hyper- and autoinflammatory syndromes	
Mevalonate kinase deficiency	*MVK*
Phospholipase Cγ2 mutation	*PLCG2*

NLRC4 mutation	*NLRC4*
Familial Mediterranean fever	*MEFV*
Familial hemophagocytic lymphohistiocytosis type 5	*STXBP2*
X-linked lymphoproliferative disease type 2 (XLP-2), XIAP deficiency	*XIAP*
X-linked lymphoproliferative disease type 1 (XLP-1)	*SH2D1A*
Hermansky-Pudlak syndrome	*HPS1, HPS4, HPS6*
TRIM22 deficiency	*TRIM22*
Niemann-Pick syndrome type C1	*NPC1*
Blau syndrome	*NOD2*
4. T- and B-cell defects	
Common variable immunodeficiency	*ICOS, LRBA*
IL21 deficiency	*IL21*
CTLA4 deficiency	*CTLA4*
Agammaglobulinemia	*BTK, PIK3R1*
Hyper IgM syndrome	*CD40LG, AICDA*
Wiskott-Aldrich syndrome (WAS)	*WAS* gene
WAS-like syndrome	*ARPC1B*
Atypical SCID/Omenn syndrome	*DCLRE1C, ZAP70, RAG1, RAG2, IL2RG, LIG4, ADA, CD3G*
Høyeraal-Hreidarsson syndrome	*DKC1, RTEL1*
Loeys-Dietz syndrome	*TGFBR1, TGFBR2*
PI3K signaling pathway hyperactivation	*PIK3R1, PTEN, PIK3CD*
5. Immune dysregulation, polyendocrinopathy, enteropathy, and autoimmunity	
IPEX syndrome	*FOXP3*
IPEX-like syndrome	*IL2RA, STAT1, STAT3, MALT1*
6. IL10 signaling defects	
IL10 and IL10 receptor defects	*IL10RA, IL10RB, IL10*
7. Miscellaneous	
MASP2 deficiency	*MASP2*
Trichohepatoenteric syndrome	*SKIV2L, TTC37*
POLA1 deficiency	*POLA1*
TGFβ1 deficiency	*TGFB1*
Enteric anendocrinosis	*NEUROG3*

Table 2/1: IL = Interleukin; IPEX = Immune dysregulation, polyendocrinopathy, and enteropathy, X-linked; SCID = Severe combined immunodeficiency (mod. from Schwerd & Uhlig 2017, Uhlig et al. 2014, Uhlig et al. 2016). Genes are named according to the Human Genome Organisation (HUGO) classification.

Findings indicative of primary immunodeficiency (mod. from Schwerd & Uhlig 2017)	
Very early-onset of IBD up to age 6	An onset of disease at ages up to 6, especially infantile IBD, are more likely to be monogenic IBD
Positive family history or consanguinity	Multiple family members or primarily male family members afflicted (X-linked heredity)
Very severe phenotype of IBD, particularly with perianal involvement or fistulizing disease	Severe perianal involvement with fistulas/abscesses
Unusual findings by endoscopy and histology	For example Behçet's disease-like ulcers, high percentage of apoptotic epithelial cells, no evidence of reactive lymphoid follicles, villous atrophy in the absence of positive celiac serology, infection, or allergic origin Extensive granuloma formation
Does not respond to conventional IBD treatments	No remission despite adequate therapy: nutritional therapy, immunomodulators, corticosteroids, biologics, etc.
Severe, invasive, or frequent infections (gastrointestinal tract and other organs), atypical localization, or atypical pathogens	Particularly in the lungs, skin, or ENT region; liver abscess, infections with atypical pathogens (*Pneumocystis jirovecii*, CMV, BCG, mycobacteria)
Recurrent fever	In the absence of pathogens, polyserositis
Abnormal lymphoid organs	For example splenomegaly, lymph node abscesses
Autoimmune disorders	Including arthritis, serositis, autoimmune hemolytic anemia, endocrine dysfunction such as diabetes, thyroiditis
Hemophagocytic lympho-histiocytosis or macrophage activation syndrome	Hemophagocytic lymphohistiocytosis triggered by viral infections such as Epstein-Barr virus (EBV) or cytomegalovirus (CMV)
Skin, hair, and nail lesions	For example eczema, blistering, thrombo-cytopenic purpura, onychodystrophy, trichorrhexis nodosa, folliculitis, pyoderma, gray hair, split hairs
Cancer	Early cancers such as non-Hodgkin lymphoma, skin cancer, thyroid cancer

Table 2/2: Findings associated with primary immunodeficiency

Literature

Bennett CL, Christie J, Ramsdell F, Brunkow ME, Ferguson PJ, Whitesell L, et al. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. Nat Genet. 2001;27(1):20–1.

Biswas A, Petnicki-Ocwieja T, Kobayashi KS. Nod2: a key regulator linking microbiota to intestinal mucosal immunity. J Mol Med (Berl). 2012;90(1):15–24.

Brandtzaeg P. Update on mucosal immunoglobulin A in gastrointestinal disease. Curr Opin Gastroenterol. 2010;26(6):554–63.

Charbit-Henrion F, Parlato M, Hanein S, Duclaux-Loras R, Nowak J, Begue B, et al. Diagnostic Yield of Next-Generation Sequencing in Very Early-Onset Inflammatory Bowel Diseases: A Multicenter Study. J Crohns Colitis. 2018 May 18. doi: 10.1093/ecco-jcc/jjy068.

Christodoulou K, Wiskin AE, Gibson J, Tapper W, Willis C, Afzal NA, et al. Next generation exome sequencing of paediatric inflammatory bowel disease patients identifies rare and novel variants in candidate genes. Gut. 2013;62(7):977–84.

Corr SC, Gahan CC, Hill C. M-cells: origin, morphology and role in mucosal immunity and microbial pathogenesis. FEMS Immunol Med Microbiol. 2008;52(1):2–12.

d'Hennezel E, Bin Dhuban K, Torgerson T, Piccirillo CA. The immunogenetics of immune dysregulation, polyendocrinopathy, enteropathy, X linked (IPEX) syndrome. J Med Genet. 2012;49(5):291–302.

DeSesso JM, Jacobson CF. Anatomical and physiological parameters affecting gastrointestinal absorption in humans and rats. Food Chem Toxicol. 2001;39(3):209–28.

Ding Y, Qin L, Zamarin D, Kotenko SV, Pestka S, Moore KW, et al. Differential IL-10R1 expression plays a critical role in IL-10-mediated immune regulation. J Immunol. 2001;167(12):6884–92.

Gambineri E, Torgerson TR, Ochs HD. Immune dysregulation, polyendocrinopathy, enteropathy, and X-linked inheritance (IPEX), a syndrome of systemic autoimmunity caused by mutations of FOXP3, a critical regulator of T-cell homeostasis. Curr Opin Rheumatol. 2003;15(4):430–5.

Gasche C, Grundtner P, Zwirn P, Reinisch W, Shaw SH, Zdanov A, et al. Novel variants of the IL-10 receptor 1 affect inhibition of monocyte TNF-alpha production. J Immunol. 2003;170(11):5578–82.

Glocker EO, Kotlarz D, Boztug K, Gertz EM, Schäffer AA, Noyan F, et al. Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. N Engl J Med. 2009;361(21):2033–45.

Goto Y, Ivanov II. Intestinal epithelial cells as mediators of the commensal-host immune crosstalk. Immunol Cell Biol. 2013;91(3):204–14.

Goulet OJ, Brousse N, Canioni D, Walker-Smith JA, Schmitz J, Phillips AD. Syndrome of intractable diarrhoea with persistent villous atrophy in early childhood: a clinicopathological survey of 47 cases. J Pediatr Gastroenterol Nutr. 1998;26(2):151–61.

Gracz AD, Magness ST. Defining hierarchies of stemness in the intestine: evidence from biomarkers and regulatory pathways. Am J Physiol Gastrointest Liver Physiol. 2014;307(3):G260–73.

Guariso G, Gasparetto M, Day AS, Henderson P. Epidemiology and Natural History of IBD in the Paediatric Age. Gastroenterol Res Pract. 2014;2014:432807.

Hampe J, Cuthbert A, Croucher PJ, Mirza MM, Mascheretti S, Fisher S, et al. Association between insertion mutation in NOD2 gene and Crohn's disease in German and British populations. Lancet. 2001;357(9272):1925–8.

Helander HF, Fändriks L. Surface area of the digestive tract – revisited. Scand J Gastroenterol. 2014;49(6):681–9.

Hooper LV, Littman DR, Macpherson AJ. Interactions between the microbiota and the immune system. Science. 2012;336(6086):1268–73.

Hugot JP, Laurent-Puig P, Gower-Rousseau C, Olson JM, Lee JC, Beaugerie L, et al. Mapping of a susceptibility locus for Crohn's disease on chromosome 16. Nature. 1996;379(6568):821–3.

Hugot JP, Chamaillard M, Zouali H, Lesage S, Cézard JP, Belaiche J, et al. Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. Nature. 2001;411(6837):599–603.

Hviid A, Svanström H, Frisch M. Antibiotic use and inflammatory bowel diseases in childhood. Gut. 2011;60(1):49–54.

Khor B, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. Nature. 2011;474(7351):307–17.

Kobayashi KS, Chamaillard M, Ogura Y, Henegariu O, Inohara N, Nuñez G, et al. Nod2-dependent regulation of innate and adaptive immunity in the intestinal tract. Science. 2005;307(5710):731–4.

Koletzko S, Uhlig HH. Hygienehypothese: Schlüssel zur Ätiologie und Pathogenese von CED? Monatsschr Kinderheilkd. 2010;158(8):759–65.

Kotlarz D, Beier R, Murugan D, Diestelhorst J, Jensen O, Boztug K, et al. Loss of interleukin-10 signaling and infantile inflammatory bowel disease: implications for diagnosis and therapy. Gastroenterology. 2012;143(2):347–55.

Kugathasan S, Baldassano RN, Bradfield JP, Sleiman PM, Imielinski M, Guthery SL, et al. Loci on 20q13 and 21q22 are associated with pediatric-onset inflammatory bowel disease. Nat Genet. 2008;40(10):1211–5.

Kurashima Y, Goto Y, Kiyono H. Mucosal innate immune cells regulate both gut homeostasis and intestinal inflammation. Eur J Immunol. 2013;43(12):3108–15.

Levine A, Koletzko S, Turner D, Escher JC, Cucchiara S, de Ridder L, et al. ESPGHAN revised porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. J Pediatr Gastroenterol Nutr. 2014;58(6):795–806.

Marks DJ, Miyagi K, Rahman FZ, Novelli M, Bloom SL, Segal AW. Inflammatory bowel disease in CGD reproduces the clinicopathological features of Crohn's disease. Am J Gastroenterol. 2009;104(1):117–24.

McCole DF. IBD candidate genes and intestinal barrier regulation. Inflamm Bowel Dis. 2014;20(10):1829–49.

Moore KW, de Waal Malefyt R, Coffman RL, O'Garra A. Interleukin-10 and the interleukin-10 receptor. Annu Rev Immunol. 2001;19:683–765.

Murray PJ. NOD proteins: an intracellular pathogen-recognition system or signal transduction modifiers? Curr Opin Immunol. 2005;17(4):352–8.

Nuding S, Fellermann K, Wehkamp J, Stange EF. Reduced mucosal antimicrobial activity in Crohn's disease of the colon. Gut. 2007;56(9):1240–7.

Ogura Y, Bonen DK, Inohara N, Nicolae DL, Chen FF, Ramos R, et al. A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. Nature. 2001;411(6837):603–6.

Orholm M, Munkholm P, Langholz E, Nielsen OH, Sørensen TI, Binder V. Familial occurrence of inflammatory bowel disease. N Engl J Med. 1991;324(2):84–8.

Pestka S, Krause CD, Sarkar D, Walter MR, Shi Y, Fisher PB. Interleukin-10 and related cytokines and receptors. Annu Rev Immunol. 2004;22:929–79.

Ponder A, Long MD. A clinical review of recent findings in the epidemiology of inflammatory bowel disease. Clin Epidemiol. 2013;5:237–47.

Roos D, de Boer M. Molecular diagnosis of chronic granulomatous disease. Clin Exp Immunol. 2014;175(2):139–49.

Ruel J, Ruane D, Mehandru S, Gower-Rousseau C, Colombel JF. IBD across the age spectrum: is it the same disease? Nat Rev Gastroenterol Hepatol. 2014;11(2):88–98.

Scherr R, Essers J, Hakonarson H, Kugathasan S. Genetic determinants of pediatric inflammatory bowel disease: is age of onset genetically determined? Dig Dis. 2009;27(3):236–9.

Schwerd T, Koletzko S. Chronisch entzündliche Darmerkrankungen. Monatsschr Kinderheilkd. 2017;165(3):257–70.

Schwerd T, Uhlig HH. Chronisch-entzündliche Darmerkrankung und Immundefekte. Monatsschr Kinderheilkd. 2017;165(12):1092–101.

Spencer SD, Di Marco F, Hooley J, Pitts-Meek S, Bauer M, Ryan AM, et al. The orphan receptor CRF2-4 is an essential subunit of the interleukin 10 receptor. J Exp Med. 1998;187(4):571–8.

Swidsinski A, Weber J, Loening-Baucke V, Hale LP, Lochs H. Spatial organization and composition of the mucosal flora in patients with inflammatory bowel disease. J Clin Microbiol. 2005;43(7):3380–9.

Uhlig HH. Monogenic diseases associated with intestinal inflammation: implications for the understanding of inflammatory bowel disease. Gut. 2013;62(12):1795–805.

Uhlig HH, Schwerd T, Koletzko S, Shah N, Kammermeier J, Elkadri A, et al. The diagnostic approach to monogenic very early onset inflammatory bowel disease. Gastroenterology. 2014;147(5):990–1007.e3.

Uhlig HH, Schwerd T. From Genes to Mechanisms: The Expanding Spectrum of Monogenic Disorders Associated with Inflammatory Bowel Disease. Inflamm Bowel Dis. 2016;22(1):202–12.

Wildin RS, Ramsdell F, Peake J, Faravelli F, Casanova JL, Buist N, et al. X-linked neonatal diabetes mellitus, enteropathy and endocrinopathy syndrome is the human equivalent of mouse scurfy. Nat Genet. 2001;27(1):18–20.

Xu XR, Liu CQ, Feng BS, Liu ZJ. Dysregulation of mucosal immune response in pathogenesis of inflammatory bowel disease. World J Gastroenterol. 2014;20(12):3255–64.

3. Risk factors

Martin Classen

Genetics, diet, deficiencies

The incidence and prevalence of inflammatory bowel disease (IBD), and especially of Crohn's disease (CD), are much greater in developed Western countries than in the developing world. At the same time, the incidence of IBD in developing countries rises when lifestyles in those countries approach those of developed nations [Prideaux et al. 2012]. However, the incidence of IBD has also risen dramatically in Europe over the past few decades, with the number of IBD patients doubling over the last 20 years in France and Germany [Ghione et al. 2018].

Numerous potential explanations exist for this correlation. There is evidence for the hypothesis that some dietary factors may have pathogenic relevance (especially high consumption of meat, animal protein, fat, and sugary foods) as these foods affect the composition of the gut microbiome [Dolan & Chang 2017, Khalili et al. 2018, Statovci et al 2017]. It has also been postulated that some ingredients in processed foods, such as emulsifiers, preservatives, dyes, and nanoparticles may be triggers [Roberts et al. 2013, Rogler et al. 2016].

Other dietary factors also affect the risk of IBD, with fiber, vegetarian diet, and omega-3 fatty acids all reducing the risk of the disease (Figure 3/1).

A lower incidence of infections (particularly helminths and gastroenteritis), less exposure to bacterial antigens and toxins, and alterations to the microbiome resulting from antibiotics and the method of childbirth may also all play a role [Cholapranee & Ananthakrishnan 2016, Shouval & Rufo 2017]. Antibiotic treatment during childhood increases the risk of developing CD, but not ulcerative colitis (UC) [Ungaro et al. 2014].

Micronutrient deficiency

In recent years, a great deal of attention has been focused on the role of vitamin D in IBD. The known north-south gradient in the prevalence of IBD within Europe and North America can be considered as an epidemiological indication of this phenomenon [Holmes et al. 2015]. Furthermore, vitamin D influences NOD2 function [White 2018], enhances the epithelial barrier function, and affects adaptive

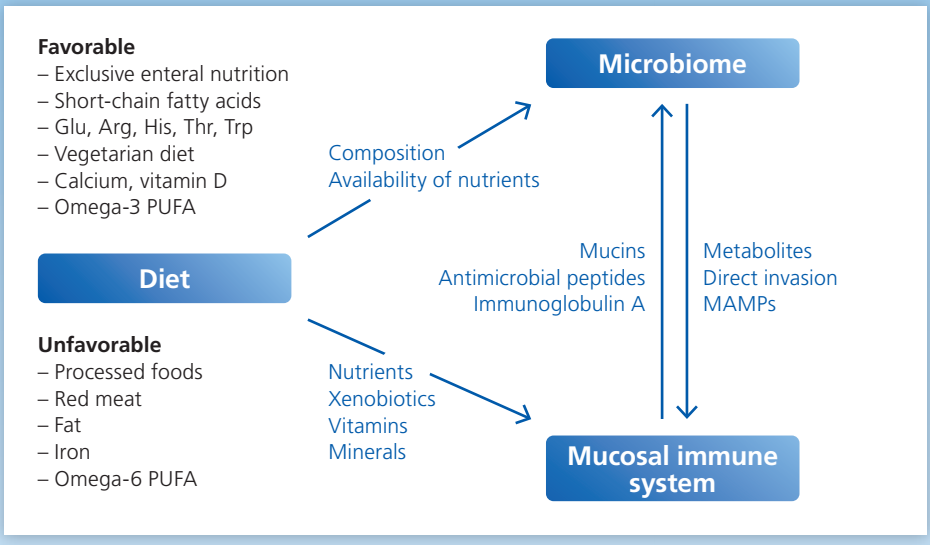


Figure 3/1: Effects of diet (source: mod. from Lee et al. 2015). PUFA = Polyunsaturated fatty acids; MAMP = Mucosa-associated molecular patterns.

immune responses. While IBD patients do have a higher prevalence of vitamin D deficiency, this may also be a consequence of the disease itself [Lu et al. 2015]. Polymorphisms in the vitamin D receptor may explain the inconsistent data on this topic [Ananthakrishnan et al. 2015a].

Vitamin D deficiency is associated with greater morbidity and disease severity over the course of IBD [Kabbani et al. 2016]. Higher levels of vitamin D are correlated with better quality of life and an increased likelihood of response to anti-tumor necrosis factor (TNF)-α antibody therapy [Gubatan et al. 2017, Hlavaty et al. 2014, Limketkai et al. 2016], while lower levels of vitamin D are associated with a higher rate of flares in UC patients.

No association is known between selenium or other micronutrients and the pathogenesis of IBD. High levels of zinc intake by adult women reduce the risk of CD but not of UC [Ananthakrishnan et al. 2015b]. Although zinc deficiency may occur as a consequence of chronic diarrhea [Griffin et al. 2004], zinc intake does not appear to affect the incidence of IBD in adults. Patients may need to be tested for zinc deficiency over the course of the disease, as this condition may negatively impact disease severity [Siva et al. 2017].

Smoking

Although the data on the effects of smoking on IBD comes solely from studies in adults, cigarette smoking is also relevant in children and especially adolescents. Smoking increases the risk of both developing CD as well as having a more severe form of CD with greater complications [Abegunde et al. 2016].

Genetics

Familial clustering of IBD has been known for some time. The genetic risk depends on the familial proximity to a patient, with the risk being highest for familial forms of CD, and twins at highest risk within these families (Figure 3/2).

Genome-wide association studies have identified 163 genetic loci associated with an elevated risk of IBD (see also Chapter 2: Unique aspects in the pathophysiology of pediatric IBD). Some of these loci are found only in patients with CD while others are found only in patients with UC; only a small fraction of the loci are linked to both disorders. Although the genes involved typically encode factors associated with immune pathologies, the majority of the mutations identified do not alter the actual function of the corresponding protein. A high percentage of the hits are found in non-coding regions

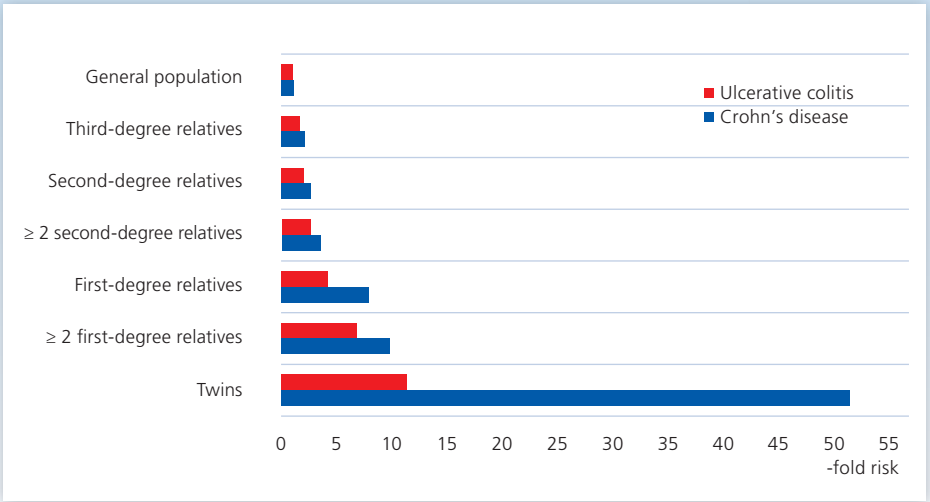


Figure 3/2: Familial risk of IBD (source: Moller et al. 2015)

of genes and drive altered gene expression. No single genetic polymorphism alone can explain the etiology of IBD, rather, epigenetic alterations and microbiome factors must also be involved. For these reasons, genetic testing cannot contribute to the diagnosis of IBD at present [Liu & Stappenbeck 2016, Ye & McGovern 2016].

A major exception to this rule is children with an infantile onset of IBD (VEO-IBD), for whom monogenic disorders are highly relevant [Charbit-Henrion et al. 2018] (see Chapter 2: Unique aspects in the pathophysiology of pediatric IBD). Because targeted therapeutic options are available for some of these monogenic disorders (e.g. stem cell transplantation), and because immunosuppressants may exacerbate some of these disorders, patients in this age cohort must be tested for individual immune system functions and must undergo genetic screening for known mutations [Uhlig et al. 2014] (see Chapter 2: Unique aspects in the pathophysiology of pediatric IBD, and Chapter 7: Diagnosis). This also holds true for severe forms of the disease and for families with a high degree of disease penetrance.

Literature

Abegunde AT, Muhammad BH, Bhatti O, Ali T. Environmental risk factors for inflammatory bowel diseases: Evidence based literature review. World J Gastroenterol. 2016;22(27):6296–317.

Ananthakrishnan AN, Cagan A, Cai T, Gainer VS, Shaw SY, Churchill S, et al. Common Genetic Variants Influence Circulating Vitamin D Levels in Inflammatory Bowel Diseases. Inflamm Bowel Dis. 2015a;21(11):2507–14.

Ananthakrishnan AN, Khalili H, Song M, Higuchi LM, Richter JM, Chan AT. Zinc intake and risk of Crohn's disease and ulcerative colitis: a prospective cohort study. Int J Epidemiol. 2015b;44(6):1995–2005.

Charbit-Henrion F, Parlato M, Hanein S, Duclaux-Loras R, Nowak J, Begue B, et al. Diagnostic Yield of Next-Generation Sequencing in Very Early-Onset Inflammatory Bowel Diseases: A Multicenter Study. J Crohns Colitis. 2018 May 18. doi: 10.1093/ecco-jcc/jjy068.

Cholapranee A, Ananthakrishnan AN. Environmental Hygiene and Risk of Inflammatory Bowel Diseases: A Systematic Review and Meta-analysis. Inflamm Bowel Dis. 2016;22(9):2191–9.

Dolan KT, Chang EB. Diet, gut microbes, and the pathogenesis of inflammatory bowel diseases. Mol Nutr Food Res. 2017;61(1):1600129.

Ghione S, Sarter H, Fumery M, Armengol-Debeir L, Savoye G, Ley D, et al. Dramatic Increase in Incidence of Ulcerative Colitis and Crohn's Disease (1988–2011): A Population-Based Study of French Adolescents. Am J Gastroenterol. 2018;113(2):265–72.

Griffin IJ, Kim SC, Hicks PD, Liang LK, Abrams SA. Zinc metabolism in adolescents with Crohn's disease. Pediatr Res. 2004;56(2):235–9.

Gubatan J, Mitsuhashi S, Zenlea T, Rosenberg L, Robson S, Moss AC. Low Serum Vitamin D During Remission Increases Risk of Clinical Relapse in Patients With Ulcerative Colitis. Clin Gastroenterol Hepatol. 2017;15(2):240–6.e1.

Hlavaty T, Krajcovicova A, Koller T, Toth J, Nevidanska M, Huorka M, et al. Higher vitamin D serum concentration increases health related quality of life in patients with inflammatory bowel diseases. World J Gastroenterol. 2014;20(42):15787–96.

Holmes EA, Xiang F, Lucas RM. Variation in incidence of pediatric Crohn's disease in relation to latitude and ambient ultraviolet radiation: a systematic review and analysis. Inflamm Bowel Dis. 2015;21(4):809–17.

Kabbani TA, Koutroubakis IE, Schoen RE, Ramos-Rivers C, Shah N, Swoger J. Association of Vitamin D Level With Clinical Status in Inflammatory Bowel Disease: A 5-Year Longitudinal Study. Am J Gastroenterol. 2016;111(5):712–9.

Khalili H, Chan SSM, Lochhead P, Ananthakrishnan AN, Hart AR, Chan AT. The role of diet in the aetiopathogenesis of inflammatory bowel disease. Nat Rev Gastroenterol Hepatol. 2018;15(9):525–35.

Lee D, Albenberg L, Compher C, Baldassano R, Piccoli D, Lewis JD, et al. Diet in the pathogenesis and treatment of inflammatory bowel diseases. Gastroenterology. 2015;148(6):1087–106.

Limketkai BN, Bechtold ML, Nguyen DL. Vitamin D and the Pathogenesis of Inflammatory Bowel Disease. Curr Gastroenterol Rep. 2016;18(10):52.

Liu TC, Stappenbeck TS. Genetics and Pathogenesis of Inflammatory Bowel Disease. Annu Rev Pathol. 2016;11:127–48.

Lu C, Yang J, Yu W, Li D, Xiang Z, Lin Y, et al. Association between 25(OH)D Level, Ultraviolet Exposure, Geographical Location, and Inflammatory Bowel Disease Activity: A Systematic Review and Meta-Analysis. PLoS One. 2015;10(7):e0132036.

Moller FT, Andersen V, Wohlfahrt J, Jess T. Familial risk of inflammatory bowel disease: a population-based cohort study 1977–2011. Am J Gastroenterol. 2015;110(4):564–71.

Prideaux L, Kamm MA, De Cruz PP, Chan FK, Ng SC. Inflammatory bowel disease in Asia: a systematic review. J Gastroenterol Hepatol. 2012;27(8):1266–80.

Roberts CL, Rushworth SL, Richman E, Rhodes JM. Hypothesis: Increased consumption of emulsifiers as an explanation for the rising incidence of Crohn's disease. J Crohns Colitis. 2013;7(4):338–41.

Rogler G, Zeitz J, Biedermann L. The Search for Causative Environmental Factors in Inflammatory Bowel Disease. Dig Dis. 2016;34 Suppl 1:48–55.

Shouval DS, Rufo PA. The Role of Environmental Factors in the Pathogenesis of Inflammatory Bowel Diseases: A Review. JAMA Pediatr. 2017;171(10):999–1005.

Siva S, Rubin DT, Gulotta G, Wroblewski K, Pekow J. Zinc Deficiency is Associated with Poor Clinical Outcomes in Patients with Inflammatory Bowel Disease. Inflamm Bowel Dis. 2017;23(1):152–7.

Statovci D, Aguilera M, MacSharry J, Melgar S. The Impact of Western Diet and Nutrients on the Microbiota and Immune Response at Mucosal Interfaces. Front Immunol. 2017;8:838.

Uhlig HH, Schwerd T, Koletzko S, Shah N, Kammermeier J, Elkadri A, et al. The diagnostic approach to monogenic very early onset inflammatory bowel disease. Gastroenterology. 2014;147(5):990–1007.e3.

Ungaro R, Bernstein CN, Gearry R, Hviid A, Kolho KL, Kronman MP. Antibiotics associated with increased risk of new-onset Crohn's disease but not ulcerative colitis: a meta-analysis. Am J Gastroenterol. 2014;109(11):1728–38.

White JH. Vitamin D deficiency and the pathogenesis of Crohn's disease. J Steroid Biochem Mol Biol. 2018;175:23–8.

Ye BD, McGovern DP. Genetic variation in IBD: progress, clues to pathogenesis and possible clinical utility. Expert Rev Clin Immunol. 2016;12(10):1091–107.

4. Epidemiology and the CEDATA-GPGE registry

Jan de Laffolie

Epidemiology

Currently, about 20% of the adults afflicted by the two primary components of IBD, Crohn's disease (CD) and ulcerative colitis (UC), are diagnosed before the age of 20. This shift towards onset at younger ages can also be observed within the pediatric population [Benchimol et al. 2011, Kelsen & Baldassano 2008]. Although current estimates calculate approximately 5–12 new cases per 100,000 children and adolescents under the age of 18, recent analyses suggest that the real figures are actually much higher. There are thought to currently be at least 800–1,500 new cases of IBD per year among the approximately 13.5 million children and adolescents in Germany [Buderus et al. 2015].

The overall epidemiology of inflammatory bowel disease (IBD) is especially characterized by an increasing incidence and prevalence in developed countries and in recently developed countries with a large urban segment [Benchimol et al. 2011].

The highest global prevalence rates among children, adolescents, and adults have been reported in Western Europe and North America. Between 28.2 (Bosnia and Herzegovina) and 322 (Hesse, Germany)/100,000 residents are afflicted with CD, and between 43.1 and 412/100,000 residents with UC. In other words, the prevalence in Hesse (as an example) has now exceeded 0.3%, meaning nearly 1 in 300 persons has the disease [Ng et al. 2018].

The incidence rates in Western Europe are reported to be between 1.85–10.5/100,000 residents for CD, and between 1.9–17.2/100,000 residents for UC. The North American figures are much higher at 6.3–23.82 for CD and 8.8–23.14 for UC. Increasing incidence (from an initially low baseline) has also been reported in Asia and South America, with increases of 10–14% per year over the prior incidence [Hein et al. 2014, Molodecky et al. 2012, Ng et al. 2018, Salkic et al. 2010].

The rate and the extent of the epidemiological changes vary greatly [Lopez et al. 2018]. For example, Benchimol et al. reported increases in the incidence rates of CD in Canada (Ontario province) from 9.5 to 11.4 per 100,000 per year over a period of 11 years (up to 2005) [Benchimol et al. 2009]. However, the incidence of UC in this region remained unchanged over the same time frame (4.1 to 4.2 per 100,000

per year). An increase of up to 10-fold in the incidence of IBD was reported for several regions of Australia over a 30-year period. An 11-fold increase in pediatric UC was also reported, with the increase being the steepest during the previous two decades [Phavichitr et al. 2003].

The increased incidence observed across nearly the entire world has also provided new impetus to the discussions about the pathogenesis of these disorders and the opportunities for improving care [Abramson et al. 2010, Benchimol et al. 2009, Benchimol et al. 2011, Buderus et al. 2015].

While it is well-known that the incidence of IBD is greater among urban populations, a recent study from Canada demonstrated that this correlation with residential density is strongest among toddlers < 5 years old, followed by children < 10 years old and then adolescents, with no significant correlation to urban setting among adults [Benchimol et al. 2017]. There was no difference in this study between CD and UC.

Nonetheless, there are limitations to the relevance of these effects at the population level. Even the authors of the Canadian paper speculated that the strong differences in incidence among young children may be a reflection of differences in access to and utilization of health care services in different settings.

Models of the etiology of IBD consistently define categories of genetic factors, environmental factors (diet, nicotine for CD, etc.), and gut microbiome factors, all of which interact to elicit a dysregulated immune response.

Genetic factors are of greater importance in children whose symptoms emerge prior to the age of 6. These patients should be tested specifically for genetic causes of their disease, with crucial differential diagnoses being undertaken to exclude other disorders whose presentation may mimic that of IBD (see also Chapter 2: Unique aspects in the pathophysiology of pediatric IBD).

In contrast to the increasing incidence of IBD with ever-younger ages of onset, epidemiological studies on VEO-IBD (very early-onset inflammatory bowel disease = IBD with onset prior to age 6) have demonstrated that the percentage of children who present at a very early age has remained low yet constant, while the incidence of symptomatic IBD among older children and adolescents is increasing [Bequet et al. 2017].

For example, data on immigrants from developing countries who move to countries with urban, western lifestyles argues particularly strongly in favor of a major environmental factor, whether it be diet, lifestyle, air pollution, or antibiotic use [Ahuja & Tandon 2010, Malaty et al. 2010, Pinsk et al. 2007, Schildkraut et al. 2013] (see also Chapter 2: Unique aspects in the pathophysiology of pediatric IBD, and Chapter 3: Risk factors). Studies have previously shown that contact with farm animals and a rural lifestyle are protective factors [Radon et al. 2007].

CEDATA-GPGE

In 2004, the German Society for Pediatric Gastroenterology and Nutrition (GPGE) initiated the CEDATA-GPGE® patient registry with the objective of improving the quality of care for children and adolescents with IBD. The registry fulfills this objective by systematically collecting and evaluating treatment data.

Three institutions were involved in the establishment of this registry: the Institute for Medical Informatics and Biometry at the Technical University of Dresden, the Institute for Epidemiology at the Ludwig Maximilian University of Munich, and the Department of General Pediatrics and Neonatology at the Justus Liebig University of Giessen.

The database and the reporting procedures were reviewed and approved by all relevant ethics committees and data protection officers, and the participating institutes and hospitals in Austria were granted approval by their local ethics committee.

Data is now being collected in anonymous form in a platform-independent manner using a web-based system and the data is concurrently reviewed for medical plausibility. Feedback is also provided to the reporting institutions on the quality and outcomes of treatment. The registry has helped improve outcome parameters relevant to patients at the institutions participating in the registry. More information and options for contacting and participating in the registry can be found at the GPGE website (www.gpge.de).

Literature

Abramson O, Durant M, Mow W, Finley A, Kodali P, Wong A, et al. Incidence, prevalence, and time trends of pediatric inflammatory bowel disease in Northern California, 1996 to 2006. J Pediatr. 2010;157(2):233–9 e1.

Ahuja V, Tandon RK. Inflammatory bowel disease in the Asia-Pacific area: a comparison with developed countries and regional differences. J Dig Dis. 2010;11(3):134–47.

Benchimol EI, Guttmann A, Griffiths AM, Rabeneck L, Mack DR, Brill H, et al. Increasing incidence of paediatric inflammatory bowel disease in Ontario, Canada: evidence from health administrative data. Gut. 2009;58(11):1490–7.

Benchimol EI, Fortinsky KJ, Gozdyra P, Van den Heuvel M, Van Limbergen J, Griffiths AM. Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. Inflamm Bowel Dis. 2011;17(1):423–39.

Benchimol EI, Bernstein CN, Bitton A, Carroll MW, Singh H, Otley AR, et al. Trends in Epidemiology of Pediatric Inflammatory Bowel Disease in Canada: Distributed Network Analysis of Multiple Population-Based Provincial Health Administrative Databases. Am J Gastroenterol. 2017;112(7):1120–34.

Bequet E, Sarter H, Fumery M, Vasseur F, Armengol-Debeir L, Pariente B, et al. Incidence and Phenotype at Diagnosis of Very-early-onset Compared with Later-onset Paediatric Inflammatory Bowel Disease: A Population-based Study (1988–2011). J Crohns Colitis. 2017;11(5):519–26.

Buderus S, Scholz D, Behrens R, Classen M, De Laffolie J, Keller KM, et al. Inflammatory bowel disease in pediatric patients: Characteristics of newly diagnosed patients from the CEDATA-GPGE Registry. Dtsch Arztebl Int. 2015;112(8):121–7.

Hein R, Koster I, Bollschweiler E, Schubert I. Prevalence of inflammatory bowel disease: estimates for 2010 and trends in Germany from a large insurance-based regional cohort. Scand J Gastroenterol. 2014;49(11):1325–35.

Kelsen J, Baldassano RN. Inflammatory bowel disease: the difference between children and adults. Inflamm Bowel Dis. 2008;14 Suppl 2:S9–11.

Lopez RN, Evans HM, Appleton L, Bishop J, Chin S, Mouat S, et al. Prospective Incidence of Paediatric Inflammatory Bowel Disease in New Zealand in 2015: Results From the Paediatric Inflammatory Bowel Disease in New Zealand (PINZ) Study. J Pediatr Gastroenterol Nutr. 2018;66(5):e122–6.

Malaty HM, Fan X, Opekun AR, Thibodeaux C, Ferry GD. Rising incidence of inflammatory bowel disease among children: a 12-year study. J Pediatr Gastroenterol Nutr. 2010;50(1):27–31.

Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012;142(1):46–54.e42.

Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 2018;390(10114):2769–78.

Phavichitr N, Cameron DJ, Catto-Smith AG. Increasing incidence of Crohn's disease in Victorian children. J Gastroenterol Hepatol. 2003;18(3):329–32.

Pinsk V, Lemberg DA, Grewal K, Barker CC, Schreiber RA, Jacobson K. Inflammatory bowel disease in the South Asian pediatric population of British Columbia. Am J Gastroenterol. 2007;102(5):1077–83.

Radon K, Windstetter D, Poluda AL, Mueller B, von Mutius E, Koletzko S, et al. Contact with farm animals in early life and juvenile inflammatory bowel disease: a case-control study. Pediatrics. 2007;120(2):354–61.

Salkic NN, Pavlovic-Calic N, Gegic A, Jovanovic P, Basic M. Ulcerative colitis in the Tuzla region of Bosnia and Herzegovina between 1995 and 2006: epidemiological and clinical characteristics. Eur J Gastroenterol Hepatol. 2010;22(3):346–53.

Schildkraut V, Alex G, Cameron DJ, Hardikar W, Lipschitz B, Oliver MR, et al. Sixty-year study of incidence of childhood ulcerative colitis finds eleven-fold increase beginning in 1990s. Inflamm Bowel Dis. 2013;19(1):1–6.

5. Symptoms and differential diagnoses

Stephan Buderus

Clinical symptoms

The most important and prominent gastrointestinal symptoms that point to a diagnosis of inflammatory bowel disease (IBD) in children and adolescents are **abdominal pain and diarrhea** as well as **blood in stool** or bloody diarrhea. These symptoms may obviously also be due to intestinal infections, but such infections should not persist longer than 2–3 weeks, after which the patient should show clear signs of improvement or be completely healed. In addition to abdominal pain and diarrhea, the third classical clinical symptom of Crohn's disease is **impaired weight gain** or even **weight loss**. However, the critical challenge for pediatricians (and other primary care physicians with pediatric patients) is to identify patients who very likely have IBD from among the high number of patients suffering from similar symptoms of other causes, and to do so in a rapid and precise manner without the need for invasive procedures. Once identified, such patients then require more specific and, indeed, invasive diagnostic testing. A recent analysis of the German-language pediatric IBD registry CEDATA-GPGE [Buderus et al. 2015] showed that 58–79% of patients report abdominal pain at the time of diagnosis regardless of whether they are diagnosed with ulcerative colitis (UC), Crohn's disease (CD), or inflammatory bowel disease unclassified (IBDU). Between 66% and 90% of all patients suffer from diarrhea, with the highest rates among children < 10 years old with UC, and the relatively lowest rates among children in this age group with CD. There is a marked difference in the frequency of the symptom "blood in stool" between the two disorders: Whereas the vast majority (85–95%) of all patients with colitis (both UC and IBDU) has blood in stool, for CD only 47% of children < 10 years old and 33% of older children report this symptom. In contrast, while a large percentage of CD patients suffer from impaired weight gain or weight loss (64% of patients > 10 years old, 46% of younger patients); this is the case for only 35–40% of UC patients. Approximately one-quarter of CD patients report the related symptom of loss of appetite compared with nearly 15% of UC patients. Several other international studies have reported similar frequencies of symptoms and correlations with specific IBD diagnoses, which have also remained "stable" over time [Bequet et al. 2017, Kughathasan et al. 2003, Langholz et al. 1997, Sawczenko & Sandhu 2003]. In addition to

gastrointestinal symptoms, IBD also involves extraintestinal symptoms and extraintestinal manifestations (EIM) [Timmer et al. 2011]. These symptoms may occur before (up to 30% of all EIMs!; Greuter et al. 2017) or at diagnosis of IBD, or over the course of the disease. These manifestations include quite non-specific symptoms such as **fever, fatigue**, and/or **reduced performance**. All pediatricians must thoroughly record and evaluate their patients' developments in height and weight using percentiles. IBD may present in pediatric patients as a **disorder of height and weight growth**, and may be observed as a **rapid change in percentile** or a **drop in percentile**. The chronic inflammation may also lead to **delayed puberty** (see Chapter 15: Growth and puberty).

Key elements in clinical gastroenterological examinations

Even a "basic" impression (by physician global assessment) of the patient may help steer a physician toward the diagnosis of IBD. A child with abdominal pain who "really looks sick" will elicit a different diagnostic approach and consultation than another child (or adolescent) with the same symptoms who appears at first glance to be rather healthy. Naturally, a basic global impression is never sufficient. The specific examination must cover the entire body, particularly including an inspection of the anogenital region. The **oral mucosa** must be examined for possible **mouth ulcers** (patients should also be asked about this while collecting their history). **Swollen lips** with marked inflammation (with or without aphthae) may be due to CD or to another rare form of IBD known as orofacial granulomatosis. Abdominal palpation may reveal **local pain on palpation** and **palpable guarding** in the lower right abdomen caused by Crohn's ileitis or Crohn's ileocolitis. Painful palpation or guarding over affected sections of the gut is also typical of an UC flare. If the anal inspection reveals **perianal fistulas**, these indicate a diagnosis of CD. **Abscesses** may also be observed in this region, and are a consequence of penetrating Crohn's inflammation that may present clinically as redness, overheating, and local pain on pressure. Small **anal skin tags and anal fissures** may be observed with both CD and UC. Large and obviously inflamed anal skin tags which are often smeared with stool are typical of CD [Levine et al. 2014]. Whenever IBD is suspected, the patient's **Tanner puberty stage** should be measured and recorded (age-appropriate? see above and Chapter 15: Growth and puberty). The patient's puberty stage should continue to be recorded at regular intervals over the course of IBD treatment

until the completion of puberty. IBD patients often appear pale during examinations, a reflection of the fact that 30–75% of pediatric IBD patients are also diagnosed with **anemia** [de Laffolie et al. 2017, Sjöberg et al. 2014, Wiskin et al. 2012]. This common finding, which is relevant for both diagnosis and treatment, is classified as an EIM of IBD.

Other organ-specific symptoms or findings during the diagnosis of IBD which may represent EIMs

According to various studies, either **arthralgia** (approximately 15–20%) and/or **arthritis** (4–15%) are the most common EIMs. Both can affect peripheral joints as well as the spinal cord, especially the sacroiliac joint. The most common **skin** manifestation of IBD is **erythema nodosum**, which may also present as a dermal symptom of infection in the form of painful, round, blue-red, slightly raised, indurated rashes. Nearly 1% of patients have **pyoderma gangrenosum**. This is an ulcerating skin lesion that is often painful, at least initially, and primarily affects the calves but may also be found at other sites on the body. Ophthalmic disorders associated with IBD include **uveitis, iritis**, and **episcleritis**. Potential **hepatobiliary involvement** may range from **elevated liver enzyme levels** to **autoimmune disorders of the liver and bile ducts (autoimmune hepatitis, primary sclerosing cholangitis)**. **Pancreatitis** is also a potential complication of IBD. Potential side effects of IBD medications (such as azathioprine) on the pancreas must also be taken into consideration. Approximately 15% of patients present with the symptoms/findings of extraintestinal manifestations of IBD described here at the time of their diagnosis, a rate which increases to 30% during the first year of the disease [Dotson et al. 2010, Jose et al. 2009, Timmer et al. 2011].

Differential diagnoses

As previously described, abdominal pain is one of the most common symptoms experienced by children and adolescents, and is also initially non-specific from a diagnostic perspective. The KiGGS study conducted in Germany revealed that nearly 70% of 3–10 year olds and nearly 60% of 11–17-year-old adolescents experienced abdominal pain at least once in the prior 3 months [Schwille et al. 2009]. International studies have reported rates of 20–40% of all children and adolescents suffering regularly from abdominal pain [Chitkara et al. 2005, Hyams et al. 2016, van der Veek et al. 2010]. The most

frequent, and thus most important, differential diagnosis for IBD is **functional abdominal pain disorders** as classified by the Rome IV criteria [Hyams et al. 2016]. This group of disorders can be differentiated from IBD both by patient history and by clinical examination, and by using additional simple, less invasive, and cost-effective laboratory diagnostic methods (see Chapter 7: Diagnosis). Symptoms such as diarrhea, anemia, reduced performance, etc. may be characteristics of **celiac disease** as well as of IBD. For this reason, laboratory diagnostic testing should always include detection of immunoglobulin (Ig)A antibodies to transglutaminase (and serum IgA levels). **Fructose malabsorption** may be the cause of abdominal pain in the presence or absence of diarrhea, particularly in infants but also in toddlers. This condition is harmless and can be managed easily by education and dietary modifications. The same holds true for **lactose malabsorption**, although this condition is typically only relevant for children ages 6–10 and above depending on their personal dietary patterns. The diagnostic options for both of these conditions include collecting the patient's medical history and the possibility of diagnostic fasting from the affected sugar followed by 2–3 weeks of observation, with the hydrogen breath test representing an additional option when the proper equipment is accessible. As mentioned briefly above, it is advisable to rule out potential **gastrointestinal infections** during the initial phase of diagnosis. To this end, stool samples should be tested for **Salmonella, Shigella, Yersinia, and Campylobacter spp.** and for **Clostridium difficile toxin**. Infants and toddlers in particular should also be tested for gastrointestinal viruses, even though they rarely cause symptoms lasting longer than 14 days. Despite the fact that **Giardia infection** is typically considered to only be a threat in foreign countries, infections also occur in Germany with some frequency: As published by Sagebiel et al., 62% of the 3,651 infections reported to the Robert Koch Institute (RKI) in 2006 were acquired in Germany [Sagebiel et al. 2006]. For this reason, patients should be tested for this pathogen as a potential differential diagnosis to IBD. It is also important to note that detection of an infection does not necessarily rule out the possibility of IBD, as IBD is sometimes triggered during an infection. The key distinction is that a gastrointestinal infection will heal (with or without treatment depending on the pathogen), after which it no longer causes any symptoms.

Parents frequently ask their child's physician whether the child's symptoms might be due to a **food allergy**. This is typically not the case if

the patient's history does not provide a clear link between the symptoms and the ingestion of a specific food or food group (a temporal correlation between ingestion and reproducible onset of symptoms). However, in rare cases infants and toddlers may suffer from a unique non-IgE-mediated form of food allergy known as FPIES (food protein-induced enterocolitis syndrome), which may trigger a clinical presentation that mimics VEO-IBD with diarrhea that is often bloody, weight loss, and an overall impression of a sick child. In most cases, cow milk proteins are the trigger for this allergic reaction, although soy, egg, rice, and other protein sources have also been implicated.

This list of potential differential diagnoses is not exhaustive, but does cover the most clinically relevant conditions. Other differential diagnoses are discussed in more detail in Chapter 7 on the diagnosis of IBD.

Literature

Bequet E, Sarter H, Fumery M, Vasseur F, Armengol-Debeir L, Pariente B, et al. Incidence and Phenotype at Diagnosis of Very-early-onset Compared with Later-onset Paediatric Inflammatory Bowel Disease: A Population-based Study (1988–2011). J Crohns Colitis. 2017;11(5):519–26.

Buderus S, Scholz D, Behrens R, Classen M, De Laffolie J, Keller KM, et al. Inflammatory bowel disease in pediatric patients: Characteristics of newly diagnosed patients from the CEDATA-GPGE Registry. Dtsch Arztebl Int. 2015;112(8):121–7.

Chitkara DK, Rawat DJ, Talley NJ. The epidemiology of childhood recurrent abdominal pain in Western countries: a systematic review. Am J Gastroenterol. 2005;100(8):1868–75.

de Laffolie J, Laass MW, Scholz D, Zimmer KP, Buderus S; CEDATA-GPGE Study Group. Prevalence of Anemia in Pediatric IBD Patients and Impact on Disease Severity: Results of the Pediatric IBD-Registry CEDATA-GPGE®. Gastroenterol Res Pract. 2017;2017:8424628.

Dotson JL, Hyams JS, Markowitz J, LeLeiko NS, Mack DR, Evans JS, et al. Extraintestinal manifestations of pediatric inflammatory bowel disease and their relation to disease type and severity. J Pediatr Gastroenterol Nutr. 2010;51(2):140–5.

Greuter T, Navarini A, Vavricka SR. Skin Manifestations of Inflammatory Bowel Disease. Clin Rev Allergy Immunol. 2017;53(3):413–27.

Hyams JS, Di Lorenzo C, Saps M, Shulman RJ, Staiano A, van Tilburg M. Functional Disorders: Children and Adolescents. Gastroenterology. 2016;150(6):1456–68.e2.

Jose FA, Garnett EA, Vittinghoff E, Ferry GD, Winter HS, Baldassano RN, et al. Development of extraintestinal manifestations in pediatric patients with inflammatory bowel disease. Inflamm Bowel Dis. 2009;15(1):63–8.

Kugathasan S, Judd RH, Hoffmann RG, Heikenen J, Telega G, Khan F, et al. Epidemiologic and clinical characteristics of children with newly diagnosed inflammatory bowel disease in Wisconsin: a statewide population-based study. J Pediatr. 2003;143(4):525–31.

Langholz E, Munkholm P, Krasilnikoff PA, Binder V. Inflammatory bowel diseases with onset in childhood. Clinical features, morbidity, and mortality in a regional cohort. Scand J Gastroenterol. 1997;32(2):139–47.

Levine A, Koletzko S, Turner D, Escher JC, Cucchiara S, de Ridder L, et al. ESPGHAN revised porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. J Pediatr Gastroenterol Nutr. 2014;58(6):795–806.

Sagebiel D, Weitzel T, Stark K, Leitmeyer K. Giardiasis in kindergartens: prevalence study in Berlin, Germany, 2006. Parasitol Res. 2009;105(3):681–7.

Sawczenko A, Sandhu BK. Presenting features of inflammatory bowel disease in Great Britain and Ireland. Arch Dis Child. 2003;88(11):995–1000.

Schwille IJ, Giel KE, Ellert U, Zipfel S, Enck P. A community-based survey of abdominal pain prevalence, characteristics, and health care use among children. Clin Gastroenterol Hepatol. 2009;7(10):1062–8.

Sjöberg D, Holmström T, Larsson M, Nielsen AL, Holmquist L, Rönnblom A. Anemia in a population-based IBD cohort (ICURE): still high prevalence after 1 year, especially among pediatric patients. Inflamm Bowel Dis. 2014;20(12):2266–70.

Timmer A, Behrens R, Buderus S, Findeisen A, Hauer A, Keller KM, et al. Childhood onset inflammatory bowel disease: predictors of delayed diagnosis from the CEDATA German-language pediatric inflammatory bowel disease registry. J Pediatr. 2011;158(3):467–73.e2.

van der Veek SM, Derkx HH, de Haan E, Benninga MA, Boer F. Abdominal pain in Dutch schoolchildren: relations with physical and psychological comorbid complaints in children and their parents. J Pediatr Gastroenterol Nutr. 2010;51(4):481–7.

Wiskin AE, Fleming BJ, Wootton SA, Beattie RM. Anaemia and iron deficiency in children with inflammatory bowel disease. J Crohns Colitis. 2012;6(6):687–91.

6. Extraintestinal manifestations

Michael Melter

The topic of extraintestinal manifestations (EIMs) of inflammatory bowel disease (IBD) is frequently and unjustifiably underestimated, as up to 50% of adult IBD patients and up to 80% of pediatric IBD patients (in older studies) have been reported to develop at least one EIM [Stawarski et al. 2006].

According to one large multicenter registry, 6% of children and adolescents with IBD had at least one EIM prior to diagnosis [Jose et al. 2009]. The only risk factor identified for EIMs in this study was age (> 5 years old) [Jose et al. 2009]. Furthermore, nearly 20% of patients developed at least one EIM at a later time point (thus yielding a total incidence of around 25%), while 3% developed a second EIM and 1% a third [Jose et al. 2009]. The incidence of EIMs in the registry did not vary by the type of IBD (including indeterminate colitis), age at diagnosis, or ethnicity [Jose et al. 2009]. A few studies have reported that EIMs in adult (a)IBD are more prevalent in women, while similar findings have not (yet) been demonstrated for pediatric (p)IBD [Bernstein et al. 2001, Lakatos et al. 2003].

Different EIMs either correlate directly with the inflammatory activity of pIBD, are dependent on it, and/or are directly treatment-emergent.

When evaluating the incidence rates of EIMs, it must be kept in mind that EIMs which are not obviously apparent or clinically symptomatic (e.g. pneumologic or hepatobiliary EIMs) may require active "evaluation" to verify their presence. Consequently, many of the reported incidence rates of EIMs must be interpreted as a "minimum incidence" [Gregorio et al. 2001, Jose et al. 2009]. The most important pIBD EIMs are listed in Table 6/1 (adapted from Daebritz et al. 2017) and are described below.

Musculoskeletal manifestations

Impaired growth is a common manifestation of pIBD. It may be apparent even before the onset of intestinal symptoms and is often the only symptom of the disease up to that point [Rabizadeh et al. 2013]. In studies and registries which do not include growth as an EIM, musculoskeletal manifestations comprise approximately one-third of all EIMs (approximately 25% joint symptoms, approximately 15% osteopenia/osteoporosis) [Jose et al. 2009, Stawarski et al. 2006]. Arthritis is the most common EIM experienced prior to the diagnosis of pIBD.

The pathogenesis of osteoporosis/osteopenia has not yet been completely elucidated, but it does lead to a reduction in maximum bone mass in up to half of all pIBD patients [Thearle et al. 2000].

On the other hand, it is certain that these patients (may) develop disorders of growth and bone mineralization even in the absence of exposure to corticosteroids. The primary causal factors for these pathologies are disease activity, dietary deficiencies (e.g. calcium, vitamin D), low body mass index, insufficient physical activity, or – in most cases – a combination of these factors, since all of them essentially reflect disease activity and the management of disease activity [Compston et al. 1987, Dubner et al. 2009, Pappa et al. 2011, Thearle et al. 2000, Vestergaard 2004]. In other words, insufficient control of disease activity is the most crucial predictor of an elevated risk of bone fracture. No validated and reliable diagnostic methods of detecting bone density in pIBD patients have been identified to date [DeFilippis et al. 2016], and the data on treatment of this complication is also very meager. "Optimization" of dietary intake of calcium and vitamin D as well as the implementation of a low-weight-bearing exercise regimen have been proposed as the "primary therapy" [Ma & Gordon 2012]. The utility of bisphosphonates in treating pIBD has not been sufficiently studied, and consequently its use should be considered only a case-by-case basis [Ma & Gordon 2012].

Any myopathy observed in pIBD patients is typically associated with corticosteroid use.

Hepatobiliary manifestations

Up to 40% of pIBD patients have elevated levels of transaminases and/or other hepatic laboratory parameters, at least transiently [Pusateri et al. 2015]. Chronic hepatic pathologies associated with IBD (see below) have been reported in approximately 10% of all pIBD patients, and are initially associated with a major increase in levels of transaminases (> 4-fold of the upper limit of normal) and/or of gamma-glutamyl transferase (γGT, > 252 U/l) significantly more often [Jose et al. 2009, Valentino et al. 2015]. The most central of these pathologies are autoimmune liver diseases, which are much more frequently observed in children and adolescents with IBD than in adult IBD patients. Among these diseases, autoimmune sclerosing cholangitis (ASC) and autoimmune hepatitis (AIH, primarily type 1) are much more relevant than primary sclerosing cholangitis (PSC), especially in younger patients (Figures 6/1 and 6/2). In contrast to PSC, ASC is characterized histologically by extensive autoimmune

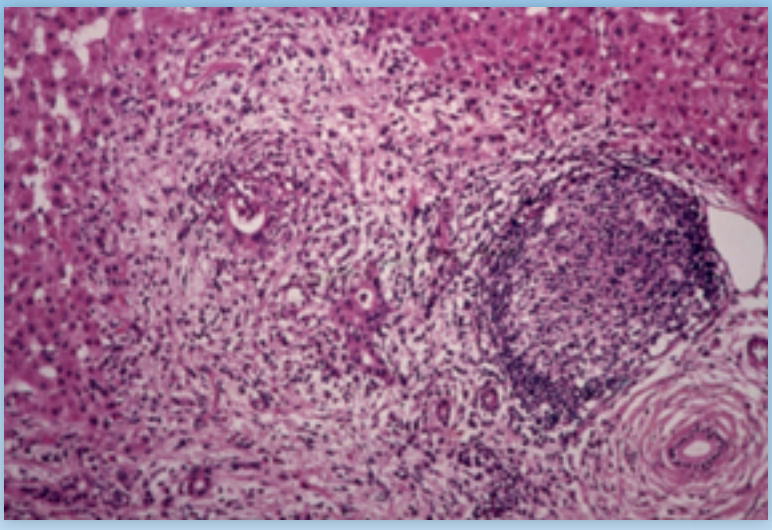


Figure 6/1: Histology image of PSC with inflammatory infiltration in a portal triad, proliferation to a bile duct, and "onion skin" fibrosis around a bile duct (lower right side of panel)

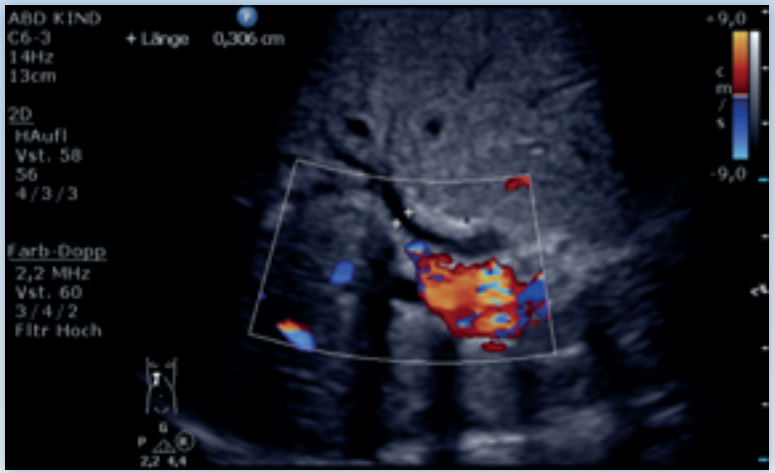


Figure 6/2: Ultrasound image of an enlarged common hepatic duct with thickened walls anterior to the portal vein in a patient with UC and PSC

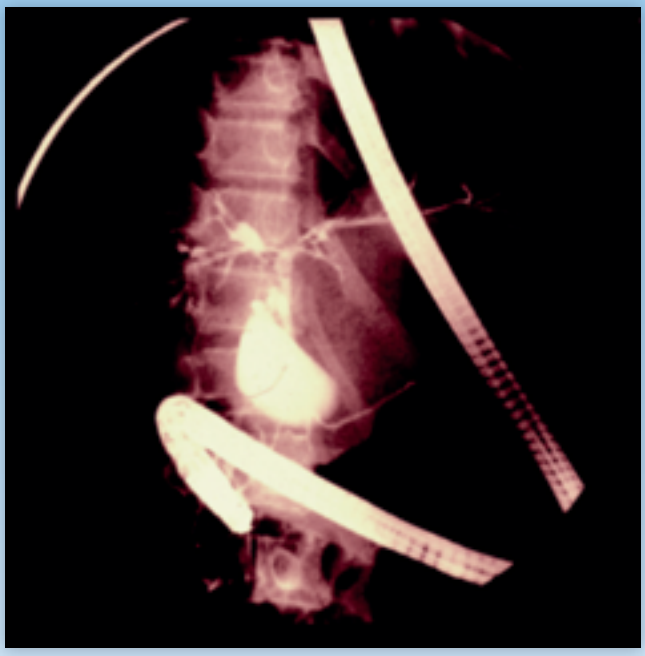


Figure 6/3: ERC with typical pathologies of PSC

inflammation with detectable autoantibodies (primarily anti-nuclear antibodies [ANA] and smooth muscle antibodies [SMA]), hypergammaglobulinemia, and interface hepatitis. ASC cannot be differentiated from type 1 AIH using these parameters alone [Gregorio et al. 2001, Mieli-Vergani & Vergani 2011]. On the other hand, perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) can be detected in about 75% of pASC patients. Because a non-trivial percentage of pASC patients have mostly normal parameters of cholestasis (γGT, alkaline phosphatase) and no histological signs of sclerosing cholangitis, yet are almost always seropositive for autoantibodies (see above) [Gregorio et al. 2001], all pIBD patients with indications of autoimmune liver disease should undergo both a liver biopsy and cholangiography (magnetic resonance cholangiopancreatography [MRCP] or endoscopic retrograde cholangiopancreatography [ERCP]) (Figure 6/3) [Gregorio et al. 2001, Mieli-Vergani & Vergani 2011]. Overall, the cumulative incidence of all forms of pediatric sclerosing cholangitis (ASC, PSC) has been reported to be higher among patients with ulcerative colitis (UC) than with Crohn's disease [Jose et al. 2009]. In addition to autoimmune liver diseases, treatment-emergent

hepatopathies are also a possibility that must be kept in mind for IBD patients [Valentino et al. 2015]. Although the prevalence of cholelithiasis has been reported to be higher for pIBD, in our clinical experience this complication is only of minor importance.

Cutaneous/mucosal manifestations

Nearly 10% of all pIBD patients have at least one cutaneous/mucosal manifestation [Jose et al. 2009]. Typical examples include erythema nodosum, pyoderma gangrenosum, and psoriasis. Erythema nodosum (Figure 6/4) presents as reddish-violet to yellowish-green granuloma formation on the shins, the knees, and the ankles, and only rarely on the upper extremities or the buttocks, and is very painful. Pyoderma gangrenosum (Figure 6/5) presents as deep and painful ulcers, primarily in areas of prior trauma. More recent studies have suggested that a much higher rate of cutaneous/mucosal manifestations of up to 20% can be expected if the dermatological side effects of anti-tumor necrosis factor drugs are defined as disease manifestations [Mälkönen et al. 2014, Perman et al. 2012]. In addition, pediatric patients with a certain genetic predisposition may develop psoriasis as a reaction to infliximab therapy, although this drug should only be discontinued if the skin reactions become severe [Sherlock et al. 2013]. While it is known that aIBD patients are at higher risk of non-melanoma skin cancer when taking thiopurines, and of melanoma when taking biologics, there is no evidence that these findings also apply to pIBD patients [Andriole et al. 2009, Ariyaratnam & Subramanian 2014, Borum et al. 2011, Ramiscal & Brewer 2013, Singh et al. 2011]. Due to the elevated lifetime risk of dermatosis and dermal malignancies, all patients should use adequate sun protection and undergo dermatological screening at least once per year [Beaugerie & Itzkowitz 2015, Mantzaris 2014, Ott & Schölmerich 2013].

Following arthritis, aphthous stomatitis is the second-most common EIM experienced prior to diagnosis of pIBD, and has been observed in about 14% of pIBD patients [Jose et al. 2009].

The presence of non-caseating granulomatous inflammation of the skin is defined as "metastatic" CD (MCD), and is not directly "continuous" with gastrointestinal tract inflammation [Mirheydar et al. 2014]. This manifestation has only been reported in a small number of pIBD cases, in all of which it was described as urogenital metastasis of CD [Siroy & Wasman 2012]. It presents as swelling, erythema, plaques, fissures, and/or ulcers in the vulvovaginal or penoscrotal region, and

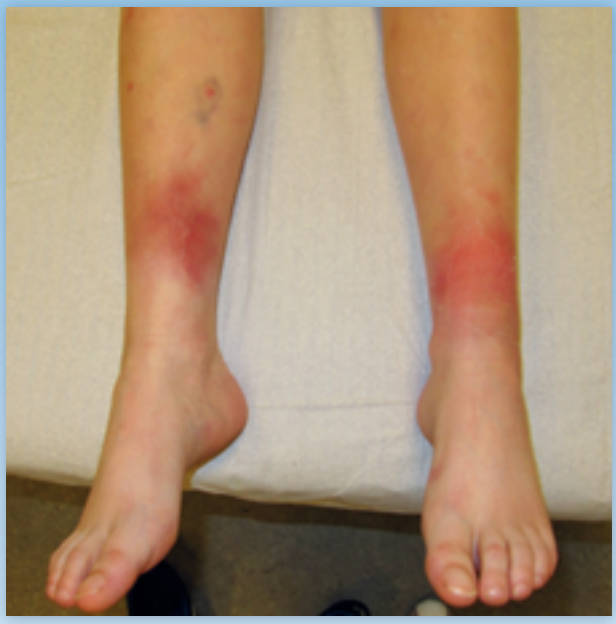


Figure 6/4: Erythema nodosum on both lower legs

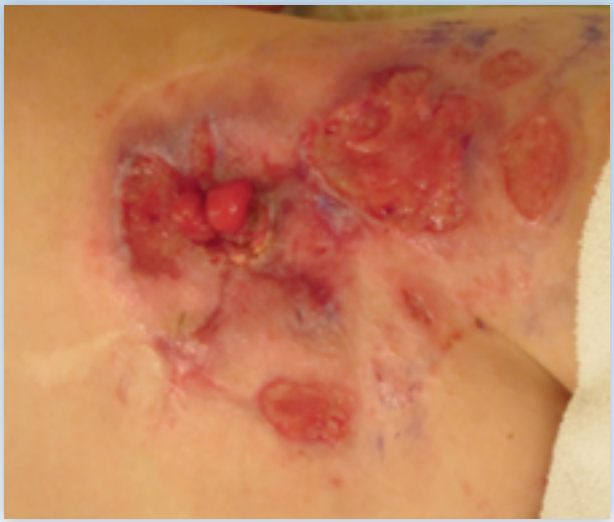


Figure 6/5: Pyoderma gangrenosum in a 16-year-old male patient with severe manifestations of CD; status post ileostomy. Multiple pyoderma gangrenosum foci on the skin of the abdomen.

typically presents prior to the initial diagnosis of CD. MCD does not correlate with the activity of the bowel disease [Rani et al. 2016].

Hematologic/thromboembolic manifestations

Anemia is a primary EIM in a large number of pIBD patients, with nearly three-quarters of patients exhibiting this manifestation at the time of their diagnosis [Gerasimidis et al. 2013]. The prevalence and severity of anemia is greater for CD than UC, although the severity typically correlates with the extent of colon inflammation in all forms of IBD [Jose et al. 2009, Sjöberg et al. 2014]. Anemia is usually triggered in pIBD by iron deficiency, which may also arise cumulatively over the course of the disease as the body's iron reserves are poorly utilized due to the (chronic active) inflammation [Jose et al. 2009]. These two forms of anemia can be differentiated by measuring levels of soluble transferrin receptor and serum ferritin [Skikne et al. 2011]. The optimal dose and route of administration of iron supplementation in pIBD are controversial, with comparative studies showing no significant differences between the intravenous and oral routes [Jose et al. 2009, Rizvi & Schoen 2011]. Intravenous administration of iron is recommended for patients with elevated levels of C-reactive protein [Stein & Dignass 2013].

More recent data have shown that folic acid and/or vitamin B_{12} deficiencies are uncommon at the time of pIBD diagnosis [Jose et al. 2009]. Nonetheless, the levels of these nutrients should be monitored very closely whenever patients receive treatments which may affect folic acid metabolism (such as methotrexate) or if the terminal ileum is heavily involved or has been resected [Jose et al. 2009]. Serum folic acid is the preferred method of measuring folic acid levels, while serum methylmalonic acid and serum homocysteine are the best method of determining vitamin B_{12} levels [Jose et al. 2009].

Numerous pathologies of the coagulation system are observed in pIBD patients, with the prevalence of venous thromboembolism being particularly high. Hypercoagulopathy is observed primarily, but not exclusively, during periods of active inflammation [Baysoy et al. 2011].

Other extraintestinal manifestations

Ocular inflammatory disorders ([epi]scleritis, anterior uveitis), papilledema, corneal infiltrates, and glaucoma have been observed in approximately 7% of all pIBD patients [Jose et al. 2009]. At the

same time, ophthalmic screening of asymptomatic pediatric patients also reveals mild uveitis in about one-quarter of this group [Ottaviano et al. 2018]. Boys with Crohn's colitis are most frequently affected [Ottaviano et al. 2018].

The **urinary tract manifestations** of IBD include nephrolithiasis (primarily calcium oxalate stones) and obstructive uropathy.

The known **pancreatic manifestations** of pIBD are heterogeneous, and the pathological mechanisms of these disorders remain mostly unclear. In addition to pancreatic pathologies which are treatment-emergent or triggered by granulomatous inflammation, acute, chronic, and autoimmune pancreatitis have all been observed [Martín-de-Carpi et al. 2017].

Bronchopulmonary manifestations have been described in < 1% of aIBD patients, with very few reports in pIBD patients [Inoue et al. 2017]. Because IBD and asthma are both triggered by similar underlying pathological mechanisms, an association between these conditions seems likely. However, a study in pIBD patients without respiratory symptoms found no evidence of a significant link to pulmonary disorders despite exhaustive investigation [Yammine et al. 2016]. In contrast, one population-based case-control study demonstrated a correlation between asthma and CD and early-onset pUC [Kuenzig et al. 2017].

Pediatric IBD patients are at risk of **psychiatric disorders**, especially during periods of flare. Of note, up to 25% of adolescents with IBD exhibit signs of depression [Rufo et al. 2012, Szigethy et al. 2010].

Poorly-controlled pIBD (especially CD) can lead to **delayed puberty**, including delayed menarche and even amenorrhea [Ballinger et al. 2003]. In cases of primary amenorrhea, it may be necessary to exclude other causes such as Turner syndrome [Durusu et al. 2005].

Patients with pIBD have also been observed to have higher incidences of **amyloidosis** or other forms of **malignancy**, although the overall incidence rates of these disorders are very low in the pediatric population.

Musculoskeletal manifestations – Growth retardation/delayed growth – Arthropathy, arthritis (axial and peripheral) – Osteoporosis/osteopenia, compression fractures – Corticosteroid-induced myopathy
Delayed development/puberty – Delayed menarche – Amenorrhea
Hepatobiliary manifestations – Elevated transaminases/γGT – Primary sclerosing cholangitis (PSC) – Autoimmune sclerosing cholangitis (ASC) – Autoimmune hepatitis (AIH) – Hepatic pathologies due to drug toxicity – Gallstones
Cutaneous/mucosal manifestations – Erythema nodosum – Pyoderma gangrenosum – Psoriasis – Aphthous stomatitis – „Metastatic" Crohn's disease (MCD) – Cutaneous malignancies
Ocular manifestations – Inflammation ([epi]scleritis, anterior uveitis, inflammatory corneal infiltration) – Papilledema – Glaucoma
Urinary tract manifestations – Nephrolithiasis (primarily calcium oxalate stones) – Obstructive uropathy
Pancreatic manifestations – Pancreatitis (acute, chronic, autoimmune) – Granulomatous inflammatory pancreatic pathologies
Bronchopulmonary manifestations – Asthma
Hematologic/thromboembolic manifestations – Anemia – Venous thromboembolism
Psychological manifestations
Unclassified EIMs – Amyloidosis – Malignancies

Table 6/1: Extraintestinal manifestations (EIMs) of pediatric IBD (adapted from Daebritz et al. 2017)

Literature

Andriole GL, Crawford ED, Grubb RL 3rd, Buys SS, Chia D, Church TR, et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med. 2009;360(13):1310–9.

Ariyaratnam J, Subramanian V. Association between thiopurine use and nonmelanoma skin cancers in patients with inflammatory bowel disease: a meta-analysis. Am J Gastroenterol. 2014;109(2):163–9.

Ballinger AB, Savage MO, Sanderson IR. Delayed puberty associated with inflammatory bowel disease. Pediatr Res. 2003;53(2):205–10.

Baysoy G, Daar G, Demir H, Elmas SA, Haliloğlu M, Besbas N. Internal iliac vein thrombosis in pediatric Crohn's disease. J Crohns Colitis. 2011;5(1):57–9.

Beaugerie L, Itzkowitz SH. Cancers complicating inflammatory bowel disease. N Engl J Med. 2015;372(15):1441–52.

Bernstein CN, Blanchard JF, Rawsthorne P, Yu N. The prevalence of extraintestinal diseases in inflammatory bowel disease: a population-based study. Am J Gastroenterol. 2001;96(4):1116–22.

Borum ML, Preethi Sidhu H, Bornstein L. Physicians may inadequately counsel inflammatory bowel disease patients about immunosuppressive therapy and risk of nonmelanoma skin cancer. Inflamm Bowel Dis. 2011;17(5):1246.

Compston JE, Judd D, Crawley EO, Evans WD, Evans C, Church HA, et al. Osteoporosis in patients with inflammatory bowel disease. Gut. 1987;28(4):410–5.

Däbritz J, Gerner P, Enninger A, Claßen M, Radke M. Inflammatory Bowel Disease in Childhood and Adolescence. Dtsch Arztebl Int. 2017;114(19):331–8.

DeFilippis EM, Sockolow R, Barfield E. Health Care Maintenance for the Pediatric Patient With Inflammatory Bowel Disease. Pediatrics. 2016;138(3). pii: e20151971. doi: 10.1542/peds.2015-1971.

Dubner SE, Shults J, Baldassano RN, Zemel BS, Thayu M, Burnham JM, et al. Longitudinal assessment of bone density and structure in an incident cohort of children with Crohn's disease. Gastroenterology. 2009;136(1):123–30.

Durusu M, Gürlek A, Simşek H, Balaban Y, Tatar G. Coincidence or causality: celiac and Crohn diseases in a case of Turner syndrome. Am J Med Sci. 2005;329(4):214–6.

Gerasimidis K, Barclay A, Papangelou A, Missiou D, Buchanan E, Tracey C, et al. The epidemiology of anemia in pediatric inflammatory bowel disease: prevalence and associated factors at diagnosis and follow-up and the impact of exclusive enteral nutrition. Inflamm Bowel Dis. 2013;19(11):2411–22.

Gregorio GV, Portmann B, Karani J, Harrison P, Donaldson PT, Vergani D, et al. Autoimmune hepatitis/sclerosing cholangitis overlap syndrome in childhood: a 16-year prospective study. Hepatology. 2001;33(3):544–53.

Inoue K, Kusunoki T, Fujii T. Organizing pneumonia as an extraintestinal manifestation of Crohn's disease in a child. Pediatr Pulmonol. 2017;52(10):E64–E66.

Jose FA, Garnett EA, Vittinghoff E, Ferry GD, Winter HS, Baldassano RN, et al. Development of extraintestinal manifestations in pediatric patients with inflammatory bowel disease. Inflamm Bowel Dis. 2009;15(1):63–8.

Kuenzig ME, Barnabe C, Seow CH, Eksteen B, Negron ME, Rezaie A, et al. Asthma Is Associated With Subsequent Development of Inflammatory Bowel Disease: A Population-based Case-Control Study. Clin Gastroenterol Hepatol. 2017;15(9):1405–12.e3.

Lakatos L, Pandur T, Dávid G, Balogh Z, Küronya P, Tollas A, et al. Extra-intestinal manifestation of IBD in Veszprém county (of Hungary): results of a 25-years follow-up study (Article in Hungarian). Orv Hetil. 2003;144(40):1965–75.

Ma NS, Gordon CM. Pediatric osteoporosis: where are we now? J Pediatr. 2012;161(6):983–90.

Mälkönen T, Wikström A, Heiskanen K, Merras-Salmio L, Mustonen H, Sipponen T, et al. Skin reactions during anti-TNFα therapy for pediatric inflammatory bowel disease: a 2-year prospective study. Inflamm Bowel Dis. 2014;20(8):1309–15.

Mantzaris GJ. Previous cancer and/or lymphoma in patients with refractory IBD – con: anti-TNF or conventional immunosuppressive treatment. Dig Dis. 2014;32 Suppl 1:122–7.

Martín-de-Carpi J, Moriczi M, Pujol-Muncunill G, Navas-López VM. Pancreatic Involvement in Pediatric Inflammatory Bowel Disease. Front Pediatr. 2017;5:218.

Mieli-Vergani G, Vergani D. Autoimmune hepatitis. Nat Rev Gastroenterol Hepatol. 2011;8(6):320–9.

Mirheydar HS, Friedlander SF, Kaplan GW. Prepubertal male genitourinary metastatic Crohn's disease: report of a case and review of literature. Urology. 2014;83(5):1165–9.

Ott C, Schölmerich J. Extraintestinal manifestations and complications in IBD. Nat Rev Gastroenterol Hepatol. 2013;10(10):585–95.

Ottaviano G, Salvatore S, Salvatoni A, Martelossi S, Ventura A, Naviglio S. Ocular Manifestations of Paediatric Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. J Crohns Colitis. 2018;12(7):870–9.

Pappa H, Thayu M, Sylvester F, Leonard M, Zemel B, Gordon C. Skeletal health of children and adolescents with inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2011;53(1):11–25.

Perman MJ, Lovell DJ, Denson LA, Farrell MK, Lucky AW. Five cases of anti-tumor necrosis factor alpha-induced psoriasis presenting with severe scalp involvement in children. Pediatr Dermatol. 2012;29(4):454–9.

Pusateri AJ, Kim SC, Dotson JL, Balint JP, Potter CJ, Boyle BM, et al. Incidence, pattern, and etiology of elevated liver enzymes in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2015;60(5):592–7.

Rabizadeh S, Dubinsky M. Update in pediatric inflammatory bowel disease. Rheum Dis Clin North Am. 2013;39(4):789–99.

Ramiscal JA, Brewer JD. Thiopurines and risk of nonmelanoma skin cancer in inflammatory bowel disease. JAMA Dermatol. 2013;149(1):92–4.

Rani U, Russell A, Tanaka S, Correa H, Nicholson MR. Urogenital Manifestations of Metastatic Crohn's Disease in Children: Case Series and Review of the Literature. Urology. 2016;92:117–21.

Rizvi S, Schoen RE. Supplementation with oral vs. intravenous iron for anemia with IBD or gastrointestinal bleeding: is oral iron getting a bad rap? Am J Gastroenterol. 2011;106(11):1872–9.

Rufo PA, Denson LA, Sylvester FA, Szigethy E, Sathya P, Lu Y, et al. Health supervision in the management of children and adolescents with IBD: NASPGHAN recommendations. J Pediatr Gastroenterol Nutr. 2012;55(1):93–108.

Sherlock ME, Walters T, Tabbers MM, Frost K, Zachos M, Muise A, et al. Infliximab-induced psoriasis and psoriasiform skin lesions in pediatric Crohn disease and a potential association with IL-23 receptor polymorphisms. J Pediatr Gastroenterol Nutr. 2013;56(5):512–8.

Singh H, Nugent Z, Demers AA, Bernstein CN. Increased risk of nonmelanoma skin cancers among individuals with inflammatory bowel disease. Gastroenterology. 2011;141(5):1612–20.

Siroy A, Wasman J. Metastatic Crohn disease: a rare cutaneous entity. Arch Pathol Lab Med. 2012;136(3):329–32.

Sjöberg D, Holmström T, Larsson M, Nielsen AL, Holmquist L, Rönnblom A. Anemia in a population-based IBD cohort (ICURE): still high prevalence after 1 year, especially among pediatric patients. Inflamm Bowel Dis. 2014;20(12):2266–70.

Skikne BS, Punnonen K, Caldron PH, Bennett MT, Rehu M, Gasior GH, et al. Improved differential diagnosis of anemia of chronic disease and iron deficiency anemia: a prospective multicenter evaluation of soluble transferrin receptor and the sTfR/log ferritin index. Am J Hematol. 2011;86(11):923–7.

Stawarski A, Iwańczak B, Krzesiek E, Iwańczak F. Intestinal complications and extraintestinal manifestations in children with inflammatory bowel disease [Article in Polish]. Pol Merkur Lekarski. 2006;20(115):22–5.

Stein J, Dignass AU. Management of iron deficiency anemia in inflammatory bowel disease – a practical approach. Ann Gastroenterol. 2013;26(2):104–13.

Szigethy E, McLafferty L, Goyal A. Inflammatory bowel disease. Child Adolesc Psychiatr Clin N Am. 2010;19(2):301–18, ix.

Thearle M, Horlick M, Bilezikian JP, Levy J, Gertner JM, Levine LS, et al. Osteoporosis: an unusual presentation of childhood Crohn's disease. J Clin Endocrinol Metab. 2000;85(6):2122–6.

Valentino PL, Feldman BM, Walters TD, Griffiths AM, Ling SC, Pullenayegum EM, et al. Abnormal Liver Biochemistry Is Common in Pediatric Inflammatory Bowel Disease: Prevalence and Associations. Inflamm Bowel Dis. 2015;21(12):2848–56.

Vestergaard P. Prevalence and pathogenesis of osteoporosis in patients with inflammatory bowel disease. Minerva Med. 2004;95(6):469–80.

Yammine S, Nyilas S, Casaulta C, Schibli S, Latzin P, Sokollik C. Function and Ventilation of Large and Small Airways in Children and Adolescents with Inflammatory Bowel Disease. Inflamm Bowel Dis. 2016;22(8):1915–22.

7. Diagnosis (including Porto criteria)

Stephan Buderus

The diagnosis of inflammatory bowel disease (IBD) – whether it be Crohn's disease (CD), ulcerative colitis (UC), or IBD unclassified (IBDU) – is made using a combination of the patient's medical history, clinical examination, laboratory testing, imaging of the gastrointestinal (GI) tract (magnetic resonance imaging, ultrasound, but rarely computed tomography or conventional X-rays), as well as endoscopy of the upper and lower GI tract, including histological examination of biopsy material from all regions of the GI tract probed by endoscopy [Levine et al. 2014]. It is crucial that differential diagnoses such as acute or chronic GI infections or immunodeficiencies be excluded (or taken into consideration). The objective of diagnosis is to accurately identify and describe the regions of the GI tract which are affected, meaning inflamed. Pediatric gastroenterologists use the Paris classification to describe the pattern of inflammation, which represents the phenotype of the disease [Levine et al. 2011].

Medical history and physical examination

The unique issues which need to be clarified in the medical history of patients with suspected IBD have been described above. It is worthwhile to re-emphasize the importance of using percentiles to evaluate body weight and height, as interruptions or deviations (drops) in these parameters from the child's previous development may represent potential signs of chronic bowel inflammation which often present months or years before fulminant disease itself. Delays in puberty should be interpreted in a similar manner. Although IBD is not an inherited disorder in the classical sense, it nonetheless exhibits a certain degree of genetic predisposition. For this reason, the history should always include questions about IBD among other family members. For example, the CEDATA-GPGE registry described previously [Buderus et al. 2015] reveals family linkage in 11% of cases (IBDU < 10 years old) to 22% (CD < 10 years old). Parents should also be queried as to whether they may potentially be consanguine when diagnosing IBD, as this may represent a risk factor for the presence of an immunodeficiency that may trigger chronic bowel inflammation.

A complete physical examination – including inspection and palpation of the abdomen, evaluation and documentation of Tanner puberty stage, examination of the oropharynx and oral mucosa (mouth

ulcers), and inspection of the anal region (fissures, fistulas, skin tags, abscesses) – is the clinical basis for all further diagnostic procedures.

Laboratory tests

Basic laboratory tests can be used to solidify or rule out suspicion of IBD and to evaluate important differential diagnoses. These tests should focus on blood, stool, and urine (urinalysis as a screening baseline).

Blood tests

Blood counts may reveal **anemia** (see Chapter 5: Symptoms and differential diagnoses; low hemoglobin, reduced mean corpuscular volume [MCV], elevated red blood cell distribution width [RDW]), while **thrombocytosis** may indicate chronic inflammation. The serological markers of inflammation **ESR** (erythrocyte sedimentation rate) and **CRP** (C-reactive protein) are also key tests that should always be performed. Elevated levels of either marker are potentially indicative of IBD. However, one large study [Mack et al. 2007] reported that these parameters (as well as serum albumin) were normal in 21% of all patients with mild CD and even in 54% of patients with low-grade UC. Interestingly, the same parameters were also unremarkable in 3.8% of patients with moderate to severe CD and 4.3% of patients with moderate to severe UC. Hence, normal levels of these parameters do not exclude IBD, while elevated levels do warrant special attention and further diagnosis. Additional serological diagnostic tests include **total protein and/or serum albumin** (see above), **ALT** (alanine transaminase), **γGT** (gamma-glutamyl transferase), **lipase**, and **creatinine**. These parameters all help provide indications of potential involvement by other organ systems. Whenever IBD is suspected, the major differential diagnosis of celiac disease must be excluded. This can be accomplished by measuring levels of serum immunoglobulin (Ig)A and **transglutaminase IgA antibody titers**. In patients with IgA deficiency, titers of deamidated gliadin IgG antibodies must also be measured.

Diagnostic testing must be broadened for all patients who exhibit any indications of immunodeficiency in their history or by clinical examination [Uhlig et al. 2014]: primarily by measuring immunoglobulin A, E, G, and M levels, cellular immune profiling, and by neutrophil oxidative burst testing (see also Chapter 2: Unique aspects in the pathophysiology of pediatric IBD).

Stool tests, fecal markers of inflammation

The development of tests for the fecal markers **calprotectin** and **lactoferrin** feasible for use in routine diagnosis represented a genuine milestone in the evaluation of potential gastrointestinal inflammation. Both of these markers are glycoproteins that are present in the granules of neutrophils and are secreted from these granules into the intestinal mucosa during inflammatory responses [Kopylov et al. 2014]. Elevated levels of these markers indicate inflammation, while normal levels reflect intact gut mucosa. The tests are thus particularly well-suited for screening of patients experiencing abdominal pain and diarrhea which may result from functional disorders (irritable bowel syndrome, functional abdominal pain, etc.) or IBD. When used as an adjunct to the serum parameters listed above, these markers can increase diagnostic sensitivity and specificity. The paper containing the ESPGHAN 2014 guidelines [Levine et al. 2014] cited a meta-analysis reporting a sensitivity of 97.8% for calprotectin and a specificity of 68.2% for diagnosing IBD. In contrast, a Dutch study [Holtman et al. 2017] investigated point-of-care tests for calprotectin and lactoferrin both in the primary care setting and in patients referred to pediatric gastroenterologists for further diagnosis. Screening performed solely in the primary care setting resulted in specificities of 95% (calprotectin) and 98% (lactoferrin), while calprotectin and lactoferrin both had sensitivities of 94% in referral patients, with specificities of 93% for calprotectin and a stellar 99% for lactoferrin. The authors concluded that their data confirmed that the use of fecal markers of inflammation can simplify the diagnosis of IBD, and more importantly can allow treatment to be planned in a more targeted manner. When using these tests, physicians must be aware that the tests reflect "only" inflammation – in other words, elevated lactoferrin or calprotectin levels do not indicate whether inflammation is being triggered by an infection or by IBD. **Juvenile polyps** are another important and frequent **differential diagnosis** for patients with elevated calprotectin and lactoferrin levels. These markers appear to be released from inflamed polyps whose surfaces are often eroded, and may reach high levels in this event. Patients with juvenile polyps typically visit their physician due to blood in stool with or without abdominal pain.

Endoscopy

If the suspicion of IBD has solidified for a given patient based on the results of the diagnostic tests described above (see Figure 7/1), the

next and most important examination is an **ileocolonoscopy**. Depending on the macroscopic findings, > 2 biopsies must be collected from each segment of the bowel from the ileum to the rectum for **histological examination** [Levine et al. 2014]. An upper endoscopy (esophagogastroduodenoscopy; **EGD**) is also a key component of the recommended diagnostic endoscopy regimen as a means of evaluating the esophagus, stomach, and duodenum, and to collect **biopsies from each organ**. The typical endoscopic characteristics of CD are aphthous ulcers, skip lesions, a cobblestone pattern of the mucosal surface, terminal ileitis, discontinuous inflammation, stenosis, and aphthous ulcers and ulcerous lesions in the upper GI tract. These macroscopic findings point to a diagnosis of CD. In contrast, UC is characterized by a continuous pattern of inflammation with variable involvement from the rectum to the oral cavity and a dark red tinge to mucosa with multiple, usually small, superficial erosions. The usual delicate vascular pattern is disrupted or enhanced, and vessels are exceedingly vulnerable upon contact or biopsy. In patients with pancolitis, backwash ileitis may occur, in which the mucosa in the terminal ileum appears similar to the inflamed colonic mucosa in UC. Continuous colitis with diminishing inflammatory activity from the rectal origin to the most distal localization together with a terminal ileum of normal macroscopic appearance and normal EGD findings are all characteristics of UC.

The identification and definition of atypical UC was an important step in the continuing development of the diagnosis and classification of pediatric IBD. This diagnosis comprises macroscopic and histological findings which do not meet the standard "textbook" criteria of UC: namely, bowel inflammation restricted to the mucosa that is continuous and localized only in the colon (see Table 7/1).

The term rectal sparing describes normal macroscopic findings in the rectum, while the inflammation typical of UC begins oral to the rectum. However, it is necessary to detect inflammation typical of UC by histology in order to diagnose this condition. A cecal patch is a typical macroscopic presentation of UC in the cecum, and is usually observed periappendiceal following the presence of a distal segment of colon with no inflammation (thus breaking the rule that "UC inflammation is always continuous") (Figure 7/2). Severe forms of UC may be described as transmural in a histological assessment. If the disease was only very briefly active, the extent of inflammation may differ from one focus to the next by histology (focality is usually otherwise a characteristic of CD). Typical and well-formed

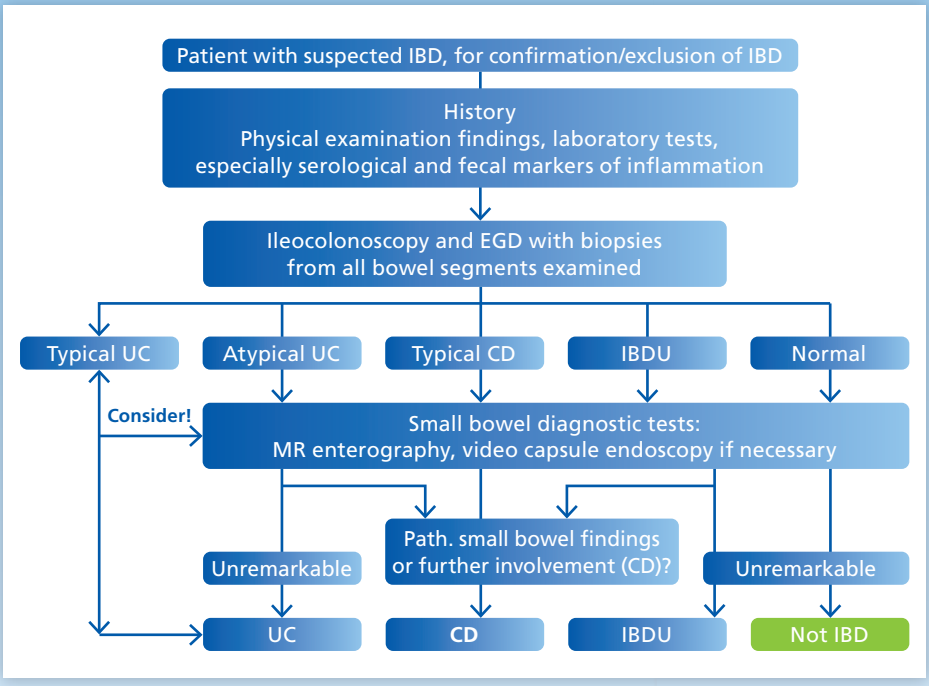


Figure 7/1: Diagnostic algorithm for pediatric patients with suspected IBD – the Porto criteria (source: mod. from Levine et al. 2014)

granulomas are a diagnostic indication of CD regardless of their localization within the GI tract. Therefore, this information should always be requested specifically on a histology order form when IBD is suspected.

The third subgroup of pediatric IBD is IBDU. This is an IBD which cannot be classified as UC or CD based on findings from endoscopy, histology, or imaging (see below). However, this diagnosis is not a hand-waving diagnosis or for use when the clinician is uncertain, but rather represents "genuine" IBD requiring medical management to the exact same extent as UC or CD. Since this disorder manifests as colitis, treatment typically follows the same principles as those used for UC (see Chapter 9: Treatment of ulcerative colitis). The text of the Porto guideline describes detailed criteria and categories ("Classes") which allow certain colitis findings to be classified or ruled out as IBDU or CD (see Table 7/2). An English-language app is now available ("IBD Classes") which queries these criteria and returns the diagnostic classification.

Type	Macroscopic appearance	Microscopic appearance
UC with rectal sparing	Rectum or rectosigmoid unremarkable	Microscopic inflammation typical of UC
UC with cecal patch	Typical colitis followed by normal segment followed by inflamed cecal patch	Typical UC histology, "patch biopsies" reveal non-specific inflammation
Acute severe colitis	Continuous inflammation from rectum onward	Inflammation may be transmural, fissuring ulcerations possible, no lymphoid aggregates, otherwise typical UC histology
Very transient colitis (usually young patients!)	Continuous inflammation from rectum onward, possibly also rectal sparing	Signs of focality by histology (instead of continuous inflammation), disrupted crypt architecture possibly not (yet) visible
UC with involvement of upper GI tract	Gastric erosions or small gastric ulcerations, no serpiginous or linear lesions	Diffuse focal gastritis

Table 7/1: Forms of atypical UC according to the 2014 revised Porto criteria (mod. from Levine et al. 2014)

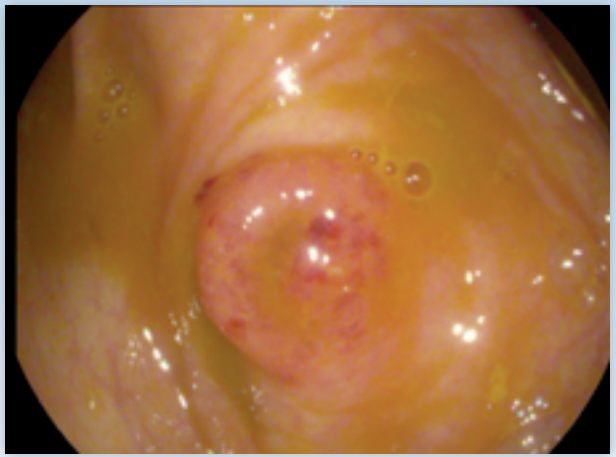


Figure 7/2: Atypical manifestations of UC with distal colitis and, here, cecal patch (view of the opening of the appendix with surrounding inflammation)

Imaging modalities

The diagnostic algorithm in the Porto guideline calls for potential small bowel IBD involvement to be assessed during primary diagnosis of all pediatric patients using an appropriate examination technique, which in most cases is **MR enterography** (Sellink technique). This technique allows the extent of gut inflammation to be evaluated, both in terms of its length and of potential inflammatory wall thickening, stenosis, and prestenotic dilatation. Moreover, magnetic resonance imaging (MRI) is the technique of choice for visualizing fistulas (in the lesser pelvis but also at enteroenteric localizations). Although **abdominal ultrasound** – which in practice is performed in nearly all children and adolescents prior to endoscopy – is valuable as a screening method and for follow-up examinations, according to the guideline its predictive power is not comparable to that of MRI for primary diagnosis. **Hydrosonography** is an approach to improving the value of a diagnosis. Similar to an MR enterography, patients drink a weight-adjusted volume of polyethylene glycol solution prior to the examination. Filling the bowel allows the intestinal walls to be visualized better, and wall thickness can be more easily measured using high-frequency linear ultrasound transducers. The administration of fluids can even help provide evidence of stenosis and prestenotic dilatations. This method is particularly well suited for evaluating the gut of young children or of patients who do not tolerate the specific conditions of MR enterography, and can be used both at the time of diagnosis as well as over the course of the disease.

Video capsule endoscopy can also be used in some patients to diagnose the small bowel. This method is particularly useful in patients with suspected CD that cannot be adequately confirmed or excluded despite endoscopy, histology, and other imaging modalities. "Typical" patients with this dilemma are those with isolated small bowel Crohn's that is localized outside of the normal "range" of upper and lower endoscopy. Analyses of the pediatric IBD registries EUROKIDS [de Bie et al. 2012] and CEDATA-GPGE [Buderus et al. 2015] have shown that this disease localization (Paris 4b, see below) is rare and is only present in about 2.9–6.7% of newly diagnosed patients.

Frequency in UC	Finding/symptoms	Diagnostic approach
Class 1: Non-existent	– Classical, well-formed granulomas – Fistulas (perianal or intra-abdominal) – Small bowel wall thickening or other signs of small bowel inflammation (excluding backwash ileitis) – Macroscopic and microscopic discontinuity of distribution of inflammation (exceptions: macroscopic rectal sparing and cecal patch) – Large, inflamed perianal skin tags	CD
Class 2: Rare with UC (< 5%)	– Complete rectal sparing (microscopic and macroscopic), otherwise typical UC findings – Relevant growth delay (height velocity < 2 SDS) not explained by other causes – Transmural inflammation in the absence of severe colitis – Esophageal or duodenal ulcers or aphthous ulcerations in the stomach not explained by other causes (e.g. Helicobacter pylori or NSAIDs) – Positive ASCA and negative pANCA – Reverse gradient of mucosal inflammation (i.e. colitis more severe proximal than distal)	IBDU if at least one class 2 criterion is present
Class 3: Uncommon with UC (approx. 5–10%)	– Severe scalloping/hypernodularity of the mucosa of the stomach or the duodenum not explained by other causes (e.g. H. pylori, celiac disease) – Non-bloody diarrhea – Focal chronic duodenitis on multiple biopsies	IBDU if at least two to three criteria are present
SDS = Standard deviation score; NSAIDs = Non-steroidal anti-inflammatory drugs		

Table 7/2: Diagnostic criteria for children with untreated colitis at the time of diagnosis (mod. from Levine et al. 2014)

Description of the localization of disease according to the Paris classification [Levine et al. 2011]

A precise description of the regions of the gut affected by chronic bowel inflammation is of practical importance both for diagnosis and for medical therapy at the start and over the course of treatment. The phenotype of the disease is relevant to the selection of

medication, to risk stratification for the expected phenotype, and to providing appropriate consultation to the patient and his or her family. The Paris classification was developed by a committee of pediatric experts based on the Montreal classification for adults (see Figure 7/3). For UC (E1–E4 based on extent, E4 = pancolitis), the item "severe disease" is also encoded as an additional category (S1, when present). For CD (L1–L4), the classification contains more dimensions and comprises the items of age (< 10 years old or older), possible stenosis, fistulizing disease, perianal disease, and potential delayed growth.

Paris classification of ulcerative colitis

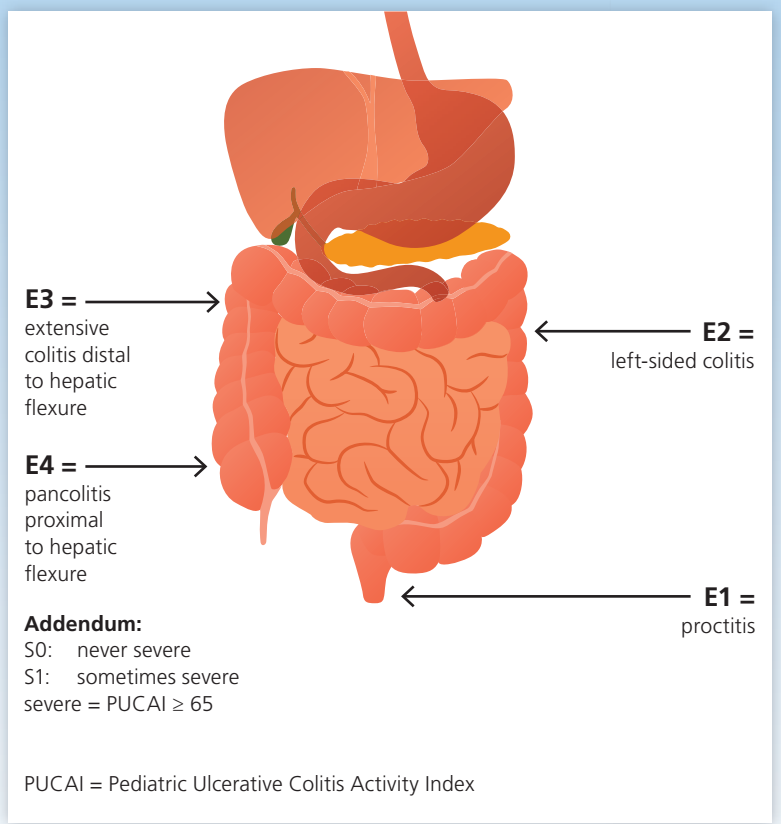


Figure 7/3: Paris classification of pediatric IBD (source: Buderus et al. 2015; mod. from Levine et al. 2011)

Paris classification of Crohn's disease

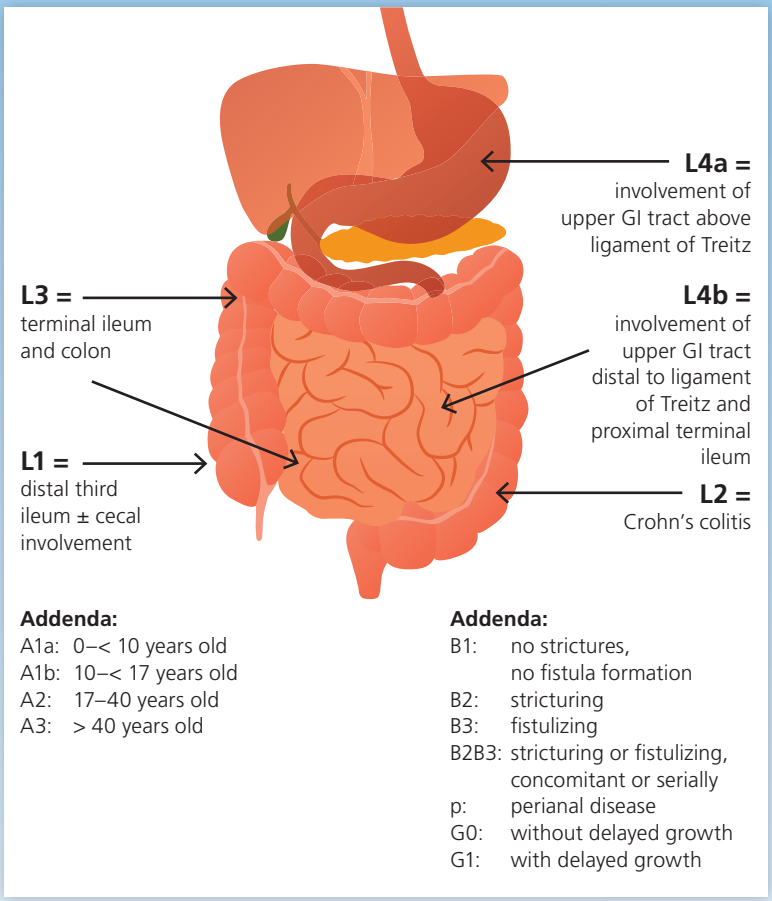


Figure 7/3 continued

Additional diagnostic issues following diagnosis of IBD

All patients diagnosed with IBD should be screened routinely for tuberculosis by intradermal skin test or interferon-gamma release assay (IGRA). It is necessary to rule out the rare yet conceivable differential diagnosis of tuberculosis due to both the potential future need for immunosuppressant therapy and in order to diagnose CD. Patients' immunization history must be surveyed in detail in order to identify and rectify any gaps in their vaccinations prior to initiating

immunosuppressant therapy. If there is any doubt, the relevant antibody titers should be measured. In terms of viral diseases, it is recommended to test serology for cytomegalovirus (CMV) and Epstein-Barr virus (EBV).

According to the Porto guideline, it may be advisable to measure titers of the serological "markers" of anti-Saccharomyces cerevisiae antibodies (ASCA; more typical of CD) and perinuclear anti-neutrophil cytoplasmic antibodies (pANCA; more typical of UC), especially if it is otherwise proving difficult to differentiate between a diagnosis of CD or UC.

Another special group of IBD patients has been increasingly identified and characterized in recent years. These patients do not suffer from the typical symptoms of IBD, but rather from chronic bowel inflammation with a symptomatic presentation resembling that of monogenic immunodeficiencies [Uhlig et al. 2014]. These patients are typically children under the age of 6, and accordingly this group of disorders has been summarized under the abbreviation VEO-IBD (very early-onset inflammatory bowel disease). Early diagnosis of this condition is key to avoid triggering complications by "normal" IBD therapy due to a failure to recognize the immunodeficiency. Thankfully, bone marrow transplantation may prove to be a curative treatment option for several of these disorders. Therefore, the authors of the Porto guideline published a table summarizing the important alarm signs and symptoms of immunodeficiency (see Table 7/3).

Positive family history of immunodeficiency
Consanguineous parents or more than 2 family members with early-onset IBD
Infantile IBD (< 2 years old)
Severe form of IBD, particularly with perianal/rectovaginal disease and/or abscesses
Recurrent infections in the absence of immunosuppressants (particularly lung and skin infections)
Neutropenia, thrombocytopenia, or abnormal immunoglobulin status (IgG) in the absence of immunosuppressants
Nail dystrophy and hair and skin abnormalities (e.g. eczema)

Table 7/3: Alarm signs and symptoms of immunodeficiency (mod. from Levine et al. 2014)

Literature

Buderus S, Scholz D, Behrens R, Classen M, De Laffolie J, Keller KM, et al. Inflammatory bowel disease in pediatric patients: Characteristics of newly diagnosed patients from the CEDATA-GPGE Registry. Dtsch Arztebl Int. 2015;112(8):121–7.

de Bie CI, Buderus S, Sandhu BK, de Ridder L, Paerregaard A, Veres G, et al. Diagnostic workup of paediatric patients with inflammatory bowel disease in Europe: results of a 5-year audit of the EUROKIDS registry. J Pediatr Gastroenterol Nutr. 2012;54(3):374–80.

Holtman GA, Lisman-van Leeuwen Y, van Rheenen PF, Kollen BJ, Escher JC, Kindermann A, et al. Evaluation of point-of-care test calprotectin and lactoferrin for inflammatory bowel disease among children with chronic gastrointestinal symptoms. Fam Pract. 2017;34(4):400–6.

Kopylov U, Rosenfeld G, Bressler B, Seidman E. Clinical utility of fecal biomarkers for the diagnosis and management of inflammatory bowel disease. Inflamm Bowel Dis. 2014;20(4):742–56.

Levine A, Griffiths A, Markowitz J, Wilson DC, Turner D, Russell RK, et al. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. Inflamm Bowel Dis. 2011;17(6):1314–21.

Levine A, Koletzko S, Turner D, Escher JC, Cucchiara S, de Ridder L, et al. ESPGHAN revised Porto Criteria for the diagnosis of inflammatory bowel disease in children and adolescents. J Pediatr Gastroenterol Nutr. 2014;58(6):795–806.

Mack DR, Langton C, Markowitz J, LeLeiko N, Griffiths A, Bousvaros A, et al. Laboratory values for children with newly diagnosed inflammatory bowel disease. Pediatrics. 2007;119(6):1113–9.

Uhlig HH, Schwerd T, Koletzko S, Shah N, Kammermeier J, Elkadri A, et al. The diagnostic approach to monogenic very early onset inflammatory bowel disease. Gastroenterology. 2014;147(5):990–1007.e3.

8. Treatment of Crohn's disease

Martin Classen

When starting to plan a treatment strategy for patients diagnosed with Crohn's disease (CD), physicians must attempt to predict the patient's disease activity and the corresponding phenotype and risk of complications (especially for patients with penetrating or stricturing phenotypes). These parameters must then be weighed against the risks of treatment [Vernier-Massouille et al. 2008]. The high risk of complications requiring surgical management, the risks of growth retardation and impaired development, and especially the risk of impaired quality of life must be conveyed realistically to parents who may be very worried. In contrast, while the potential risks of drugs, especially immunomodulators and biologics, may occasionally appear imposing, their complications are actually fairly rare.

The following predictors of poor outcome (POPO criteria) may be used to carefully formulate a prognosis. These criteria are not evidence-based, but rather stem from the experience of the authors of the ESPGHAN guideline [Ruemmele et al. 2014]:

– Deep colonic ulcerations on endoscopy (Figures 8/1 and 8/2)

– Persistent severe disease despite adequate induction therapy

– Stricturing or penetrating disease (B2 and/or B3) at diagnosis

– Severe perianal manifestations

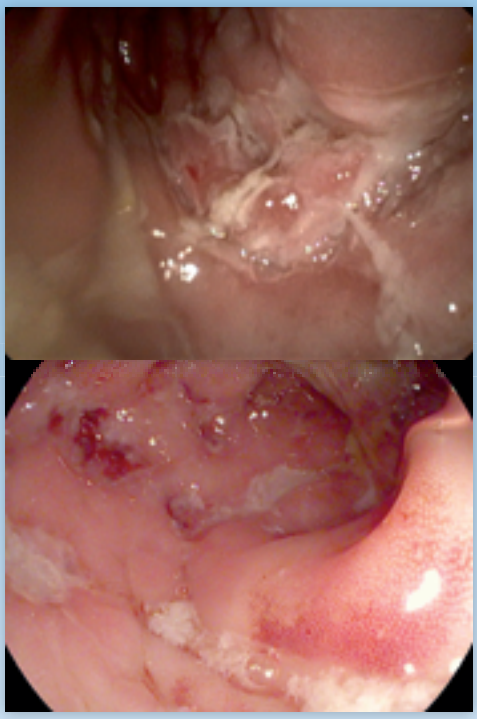
– Extensive (pan-enteric) disease

– Marked growth retardation (height < 2.5 SDS)

– Severe osteoporosis

Additional prognostic indicators may include serological parameters (e.g. ASCA), genetic markers, but also the pattern of inflammation. Multivariate analyses have identified small bowel involvement, perianal involvement, and esophageal involvement as risk factors [Mossop et al. 2008, Siegel et al. 2016].

The mandatory complete evaluation of the inflammation pattern at diagnosis should be supplemented by an examination for any possible extraintestinal manifestations, deficiencies, and growth or development retardation. These factors must be incorporated into treatment planning. A review by Daebritz et al. provides treatment strategies in the form of an algorithm [Daebritz et al. 2017].



Figures 8/1 and 8/2: Deep colonic ulcerations

Induction of remission

The first-line treatment for induction of remission is **exclusive enteral nutrition (EEN)** with a semi-elemental diet that can be drunk or fed by nasogastric tube [Narula et al. 2018, Ruemmele et al. 2014]. This treatment strategy is described in detail in Chapter 11: Nutrition and dietary therapy. It has the major advantage of being free of adverse effects and capable of balancing protein energy malnutrition; however, it imposes a burden on patients and reduces their quality of life. Comparisons versus corticosteroids have confirmed that both are of equal value [Connors et al. 2017, Grover & Lewindon 2015, Grover et al. 2016].

Systemic corticosteroid therapy with prednisolone is an alternative available for induction of remission in children who reject EEN or whose symptoms do not markedly improve within 2 weeks of EEN. Although prednisolone is still considered a standard therapy along with budesonide in adults, it should only be administered to children

and adolescents in exceptional cases as it has major negative impacts on growth and bone density, does not confer mucosal healing, and because 14–50% of patients develop steroid dependence within 1 year [Krupoves et al. 2011, Tung et al. 2006].

The ESPGHAN guideline recommends administering 1 mg/kg (max. 40 mg) in a single morning dose and tapering the drug over 10 weeks according to the following regimen:

	Week										
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Prednisolone [mg]	40	40	30	30	25	25	20	15	10	5	0
	35	35	30	30	25	20	15	15	10	5	0
	30	30	30	25	20	15	15	10	10	5	0
	25	25	25	20	20	15	15	10	5	5	0
	20	20	20	15	15	12.5	10	7.5	5	2.5	0
	15	15	15	12.5	10	10	7.5	7.5	5	2.5	0

Table 8/1: Prednisolone tapering regimen for CD (adapted from Ruemmele et al. 2014)

Corticosteroid therapy should be avoided in patients with fistulas, as these drugs elevate the risk of this complication [Brueckner et al. 2018]. Special considerations should be made for such patients, and if needed anti-tumor necrosis factor (TNF)-α antibodies should be administered to induce remission (see also Chapter 10: Surgical treatment).

Oral extended-release budesonide may be tested in patients with mild disease activity and isolated ileocecal involvement [Otley et al. 2012, Ruemmele et al. 2014]. Systemic adverse effects may also afflict children with long-term use. Our own experience suggests that the effectiveness of this drug is not sufficient in patients with marked intestinal wall thickening.

Corticosteroids are not suitable for maintaining remission. Patients on steroid therapy must be monitored for potential side effects [Aljebab et al. 2017]. This particularly includes blood pressure checks, eye examinations for early identification of cataracts and glaucoma, and monitoring patient growth. Corticosteroids also increase the risk that infections will be severe [Veereman-Wauters et al. 2012].

For patients whose primary manifestation is perianal fistulas and severe disease course who have predictors of poor outcome and are

resistant to corticosteroid therapy, **anti-TNF-α therapy** may also be discussed as a means of inducing remission (top-down strategy). One study in adults has suggested that initiating anti-TNF therapy within 2 years of diagnosis leads to a significant reduction in the frequency of surgery versus initiating it at a later time point [Ma et al. 2017]. A study in children showed a significantly higher rate of remission when anti-TNF-α therapy was initiated early. It typically takes 2–4 weeks until response can be evaluated.

Antibiotic therapy can also be used to reduce inflammatory activity, especially in patients with fistulizing disease but also in patients with luminal CD [Su et al. 2015]. The data available on this strategy in the pediatric population is relatively meager. Antibiotics are more likely to be effective in patients with colonic involvement than those with isolated small bowel disease. Experience has been reported using metronidazole (15–20 mg/kg in 2–3 single doses; oral or i.v.), ciprofloxacin (15 mg/kg oral in 2 single doses), and third-generation cephalosporins (e.g. cefotaxime 100 mg/kg, max. 2,000 mg in 3 single doses i.v.). For severe cases, an antibiotic targeting anaerobic bacteria can be combined with an antibiotic targeting gram-negative bacteria (the standard combination is metronidazole plus ciprofloxacin). The antibiotic rifaximin, which is poorly absorbed orally, has also been proven effective in studies in adults [Prantera et al. 2012]. None of the antibiotics listed above have been formally approved for the treatment of pediatric CD.

Thiopurines have demonstrated the ability to induce remission in studies in adults [Prefontaine et al. 2010]. However, due to the lack of studies in children, the slow onset of the effects of thiopurines, and their relatively low potency, they are not prescribed to children for this indication [Ruemmele et al. 2014].

Ileocecal resection may be discussed as an alternative to medical therapy to induce remission in patients with isolated ileocecal involvement.

In summary, the benefits and risks of the treatment options as well as the preferences and acceptance level of the families must be weighed at diagnosis or during acute flares of inflammation. Clear treatment objectives should be defined.

The identification of **micronutrient and vitamin deficiencies** and compensation of these deficiencies is an important adjunct measure at the time of diagnosis. However, clear recommendations for measurement and supplementation are not available for all micro-

nutrients [Miele et al. 2018]. Nonetheless, deficiencies are very common for vitamin D and iron in particular, with zinc deficiency also often occurring in patients with protracted diarrhea [Hwang et al. 2012, Weisshof & Chermesh 2015, Yoon 2016]. All identified deficiencies should be corrected due to the potential impact on the course of the disease (data is available on the impact of vitamin D) [Ananthakrishnan et al. 2013, Levin et al. 2011, Torki et al. 2015], on growth, on bone density, and on quality of life [Bischoff et al. 2014, Miele et al. 2018]. Intravenous iron supplementation in particular has proven its worth [Bonovas et al. 2016, Dignass et al. 2010, Stein et al. 2018].

Maintenance of remission

The guidelines and professional associations all agree that long-term therapies which maintain remission should be the objective for all pediatric patients, especially since the severity of the disease is usually worse in pediatric patients than in adults.

Only a very small percentage of patients is eligible for **mesalazine** therapy to maintain remission, and then only in patients with isolated colitis, no upper gastrointestinal (GI) tract manifestations, and mild disease activity [Ruemmele et al. 2014]. Due to its low frequency of side effects, mesalazine is typically initiated at high doses (50–75 mg/kg, max. 4 g/day).

If disease control is not achieved within several weeks, or if a second course of corticosteroids is required, treatment with immunosuppressants must be started. Rectal plus oral administration of mesalazine can also be tested for certain patterns of inflammation (rectal manifestation) to determine whether this approach is beneficial, as is the case for ulcerative colitis.

Following successful induction of remission, **partial enteral nutrition** may be used to maintain remission [Schulman et al. 2017, Tsertsvadze et al. 2015]. There is currently no evidence on whether specific elimination diets have a similar effect.

Immunosuppressants. Before starting any immunomodulatory therapy, the patient's vaccination record must be reviewed and replenished as needed (see also Chapter 13: Immunization of children and adolescents with IBD), and chronic hepatitis B and tuberculosis must be ruled out. The risk posed to children who contract Epstein-Barr virus (EBV) during thiopurine therapy, and who are thus at ele-

vated risk of lymphoma, is currently the topic of intense discussion [Gordon et al. 2016, Nissen et al. 2015]. This topic is not mentioned in any of the available guidelines. MTX therapy does not pose a greater risk of lymphoma, and thus should be considered as an alternative for patients who are EBV-naive.

The key **immunosuppressants and immunomodulators (IS)** are the thiopurines (azathioprine [AZA] and 6-mercaptopurine [6-MP]) and methotrexate (MTX). In light of the delayed onset of immunosuppressants, it is advisable to initiate their use early, preferably together with nutritional therapy, at the time of diagnosis [Ruemmele et al. 2014]. There are only very few children and adolescents who do not require an effective long-term therapy to maintain remission. Physicians should always choose IS for patients with upper GI tract (esophagus, proximal small bowel) involvement, a tendency toward stenosis, growth retardation, and evidence of high inflammatory activity (high levels of inflammation parameters, erythema nodosum). Infliximab is a better choice for patients with fistulizing disease. IS should be used as a steroid-free therapy for maintenance of remission [Domènech et al. 2008, Prefontaine et al. 2010, Ruemmele et al. 2014]. Thiopurines should not be administered alone as induction therapy.

The following practical aspects should be taken into consideration when prescribing **thiopurines**. First, a therapeutic effect cannot be expected until 8–14 weeks after starting therapy. AZA is administered at doses of 2–2.5 mg/kg, and 6-MP at 1–1.5 mg/kg. Both drugs are initiated at the full dose provided that thiopurine methyltransferase (TPMT) testing reveals normal activity. Blood counts and transaminase and lipase levels should be checked after 2 and 4 weeks and every 2 months thereafter. Therapy may be switched to 6-MP if liver enzyme levels rise or if gastrointestinal or flu-like symptoms appear. Pancreatitis occurring within 6 weeks of initiation is dose-independent and requires cessation of therapy. Elevated lipase levels may also be caused by the inflammatory bowel disease itself, while typical thiopurine-induced pancreatitis triggers conventional acute pancreatitis that improves rapidly following discontinuation of the medication. In the event of elevated transaminase levels, uncertain effectiveness, or uncertain adherence, measurement of the levels of AZA metabolites (6-thioguanine nucleotide [6-TGN] and 6-methylmercaptopurine [6-MMP]) is recommended. Figure 8/3 shows the metabolism of azathioprine to its active metabolites.

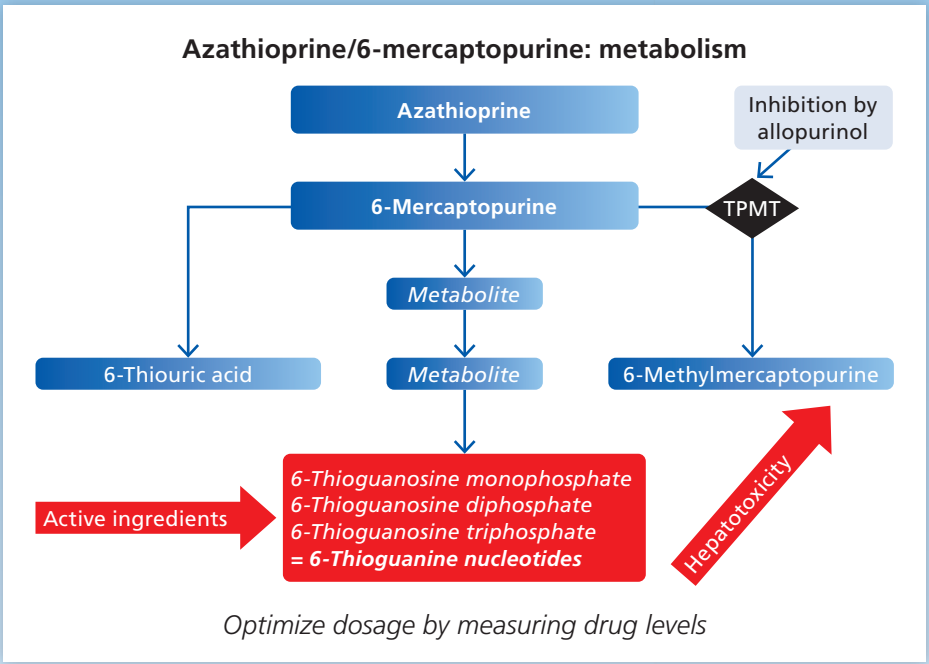


Figure 8/3: Metabolism of thiopurines

Awareness of serum levels of the drug and its metabolites can help optimize therapy and identify potential non-adherence. Table 8/2 provides an overview of which measures can be taken based on serum levels and treatment response.

If thiopurines are not tolerated or not effective, low-dose pulse **methotrexate (MTX)** can be administered as an alternative that is typically equivalent in value [Ruemmele et al. 2014]. The number of studies on MTX is much lower than that for thiopurines [Scherkenbach & Stumpf 2016], and consequently experience from the field of rheumatology should be used as a practical guide. MTX may be selected as primary maintenance therapy or in the event of thiopurine failure. Some patients who do not achieve remission on thiopurines respond well to MTX (and vice versa!). However, patients of both sexes must be informed about the need to practice effective methods of contraception. MTX is administered at a dosage of 15 mg/m² subcutaneously once per week (max. 25 mg), and autoinjectors are now available. The bioavailability of the drug fluctuates when administered orally, and consequently this route is not recom-

6-TGN (pmol/8 × 10^8 RBC)	6-MMP (pmol/8 × 10^8 RBC)	Dose-dependent adverse event	Interpretation	Recommendation
Low (< 230)	Low–normal (< 5,700)	Ineffective	Underdosing or low adherence	Increase adherence or thiopurine dose
Low (< 230)	High (≥ 5,700)	Hepatotoxicity and others, but weak therapeutic effects	TPMT hypermetabolizers	Consider allopurinol co-treatment and dose reduction to 25–33% of standard dose, or change medication
Therapeutic (230–450)	Normal or high	Weak effects, but hepatotoxicity and others	Therapy failure	If clinically resistant, change drug category
High (> 450)	Normal	Myelosuppression	Low TPMT activity (heterozygote or homozygote)	Switch type of immunomodulation if homozygote (or absent TMPT activity) or reduce dose to half if heterozygote (or moderately low TPMT activity)
High	High	Myelosuppression and hepatotoxicity	Overdose	Reduce dose and if clinically resistant, change drug category

Table 8/2: Dose optimization based on thiopurine metabolites (source: mod. from Ruemmele et al. 2014).

mended. It may be advisable to administer ondansetron 1 hour prior to the MTX dose in patients with severe nausea. Patients should then take 5 mg oral folic acid on the following day. If stable remission is achieved, the MTX dose may be reduced to 10 mg/m² per week after several months.

All patients currently or previously receiving immunosuppressants should be advised to consistently use sun protection.

Biologics. Biologics play a central role in the treatment of CD, not only because of their high therapeutic potency but also due to their risks and the development of intolerance. Only the two anti-TNF-α antibodies infliximab (IFX) and adalimumab (ADA) have been approved for pediatric CD. Although adults can be prescribed vedolizumab and ustekinumab, experience with these agents in children is limited and they are not approved for this indication.

In addition to combinations of antibiotics, thiopurines/MTX, and surgery, early therapy with a biologic agent should also be considered for **patients with fistulizing disease** (see below). Early biologic therapy should also be considered as an adjunct to nutritional therapy for patients with extensive disease involvement, severe osteoporosis, inflamed stenosis, deep ulcerations, growth retardation/failure to thrive, delayed puberty, and perianal pathologies. Biologics can be used in these patients both to induce and to maintain remission [deBruyn et al. 2018, Ruemmele et al. 2014, Walters et al. 2014].

To date, no controlled studies have compared the efficacy of the two anti-TNF-α antibodies; however, studies in adults suggest that their efficacies are comparable [Doecke et al. 2017]. Hence, the choice from among these two drugs should be made from the perspectives of practicability and of the family's requests. It may then be advisable to switch patients with primary non-response, loss of response, or severe adverse effects to the other anti-TNF-α antibody. Combining IFX in particular with an immunomodulator may be advisable to prevent the development of neutralizing antibodies [Cozijnsen et al. 2015, Day et al. 2018, Doecke et al. 2017, Dulai et al. 2014]. Patients' EBV status should also be taken into account (see above).

Trough levels and antibody levels should be monitored during the course of therapy, especially in patients with loss of response [Barnes & Allegretti 2016]. In the event of secondary loss of response, the therapeutic options (dose escalation and/or shorter intervals) for the drug currently in use should first be exhausted before switching to another agent. Should the loss of response be due to the production of anti-IFX antibodies, administration of thiopurines or MTX may suppress the production of these anti-IFX antibodies.

Duration of remission maintenance therapy

Therapy with immunomodulators or biologics should be continued as long-term therapy (at least several years) if demonstrated effective. Cessation of therapy may be considered in the following situations:

– In patients with several years of steroid-free complete remission,

– After a risk/benefit discussion with the patient,

– If growth and puberty are complete [Ruemmele et al. 2014].

The risk of relapse is lower in patients without mucosal inflammation, which can be confirmed by endoscopy, calprotectin levels, and magnetic resonance imaging (MRI)/capsule endoscopy. However, normal blood counts are not sufficient for this task!

Failure of standard therapy

The following explanations must always be considered when treatment fails:

– Non-adherence (common among adolescents)

– Infections (esp. with *Clostridium difficile* and cytomegalovirus in patients with immunosuppression)

– Change in pattern of inflammation

– Development of antibodies against the medications used

– Development of stenosis, fistulas, and abscesses

A re-evaluation may be advisable in many cases of resistance to therapy.

Consulting an experienced pediatric gastroenterologist has proven to be helpful for difficult cases (www.gpge.de). It may also be helpful to switch to a new drug or to a surgical intervention (resection, protective ileostomy). Medications which have not yet been approved for this indication, such as tacrolimus or even the "new" biologics such as vedolizumab or ustekinumab, may be other options.

Special considerations for perianal fistulizing disease [Gecse et al. 2014, de Zoeten et al. 2013]

In the CEDATA-GPGE registry, 2.1% of pediatric patients have penetrating, fistulizing disease (B3), while 11.5% have perianal pathologies with deep fissures, fistulas, or abscesses [Buderus et al. 2015]. The prevalence of anal pathologies depends on the pattern of inflammation [Adler et al. 2017]. To date, no prospective studies have investigated antibiotic treatment of fistulas in children, although adult studies have shown ciprofloxacin plus metronidazole to be effective. The combination of ciprofloxacin plus IFX may increase the rate of remission [Freire et al. 2011].

In one study, the rates of fistula healing were 54% with AZA/6-MP versus 21% in the placebo group [Korelitz & Present 1985]. Historical study data is also available on tacrolimus (one placebo-controlled

study with 46 patients: 43% response vs. 8% with placebo; Sandborn et al. 2003). Post-hoc analysis of the prospective evaluation of IFX in children [Crandall et al. 2009] and prospective data on the use of ADA [Ruemmele et al. 2018] showed beneficial effects on the closure of perianal fistula. There are several retrospective studies demonstrating these effects. Therefore, top-down strategy in cases with manifestation of perianal fistula at diagnosis is recommended [Ruemmele et al. 2014]. In conclusion, the combination of biologics (or alternatively IS) with antibiotics and surgery is the primary strategy for treating children with perianal fistulizing CD.

Literature

Adler J, Dong S, Eder SJ, Dombkowski KJ; ImproveCareNow Pediatric IBD Learning Health System. Perianal Crohn Disease in a Large Multicenter Pediatric Collaborative. J Pediatr Gastroenterol Nutr. 2017;64(5):e117–24.

Aljebab F, Choonara I, Conroy S. Systematic Review of the Toxicity of Long-Course Oral Corticosteroids in Children. PLoS One. 2017;12(1):e0170259.

Ananthakrishnan AN, Cagan A, Gainer VS, Cai T, Cheng SC, Savova G, et al. Normalization of plasma 25-hydroxy vitamin D is associated with reduced risk of surgery in Crohn's disease. Inflamm Bowel Dis. 2013;19(9):1921–7.

Barnes EL, Allegretti JR. Are Anti-Tumor Necrosis Factor Trough Levels Predictive of Mucosal Healing in Patients With Inflammatory Bowel Disease?: A Systematic Review and Meta-Analysis. J Clin Gastroenterol. 2016;50(9):733–41.

Bischoff SC, Koletzko B, Lochs H, Meier R; DGEM Steering Committee. S3-Leitlinie der Deutschen Gesellschaft für Ernährungsmedizin (DGEM) in Zusammenarbeit mit der Gesellschaft für klinische Ernährung der Schweiz (GESKES), der Österreichischen Arbeitsgemeinschaft für klinische Ernährung (AKE) und der Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS). Aktuel Ernahrungsmed. 2014;39(3):e72–98.

Bonovas S, Fiorino G, Allocca M, Lytras T, Tsantes A, Peyrin-Biroulet L, et al. Intravenous Versus Oral Iron for the Treatment of Anemia in Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Medicine (Baltimore). 2016;95(2):e2308.

Brückner A, Werkstetter KJ, de Laffolie J, Wendt C, Prell C, Weidenhausen T, et al. Incidence and Risk Factors for Perianal Disease in Pediatric Crohn Disease Patients Followed in CEDATA-GPGE Registry. J Pediatr Gastroenterol Nutr. 2018;66(1):73–8.

Buderus S, Scholz D, Behrens R, Classen M, De Laffolie J, Keller KM, et al. Inflammatory bowel disease in pediatric patients: Characteristics of newly diagnosed patients from the CEDATA-GPGE Registry. Dtsch Arztebl Int. 2015;112(8):121–7.

Connors J, Basseri S, Grant A, Giffin N, Mahdi G, Noble A, et al. Exclusive Enteral Nutrition Therapy in Paediatric Crohn's Disease Results in Long-term Avoidance of Corticosteroids: Results of a Propensity-score Matched Cohort Analysis. J Crohns Colitis. 2017;11(9):1063–70.

Cozijnsen MA, Escher JC, Griffiths A, Turner D, de Ridder L. Benefits and risks of combining anti-tumor necrosis factor with immunomodulator therapy in pediatric inflammatory bowel disease. Inflamm Bowel Dis. 2015;21(4):951–61.

Crandall W, Hyams J, Kugathasan S, Griffiths A, Zrubek J, Olson A, et al. Infliximab therapy in children with concurrent perianal Crohn disease: observations from REACH. J Pediatr Gastroenterol Nutr. 2009;49(2):183–90.

Däbritz J, Gerner P, Enninger A, Claßen M, Radke M. Inflammatory Bowel Disease in Childhood and Adolescence. Dtsch Arztebl Int. 2017;114(19):331–8.

Day AS, Gulati AS, Patel N, Boyle B, Park KT, Saeed SA. The Role of Combination Therapy in Pediatric Inflammatory Bowel Disease: A Clinical Report from the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2018;66(2):361–8.

deBruyn JC, Jacobson K, El-Matary W, Carroll M, Wine E, Wrobel I, et al. Long-term Outcomes of Infliximab Use for Pediatric Crohn Disease: A Canadian Multicenter Clinical Practice Experience. J Pediatr Gastroenterol Nutr. 2018;66(2):268–73.

Dignass A, Van Assche G, Lindsay JO, Lémann M, Söderholm J, Colombel JF, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. J Crohns Colitis. 2010;4(1):28–62.

Doecke JD, Hartnell F, Bampton P, Bell S, Mahy G, Grover Z, et al. Infliximab vs. adalimumab in Crohn's disease: results from 327 patients in an Australian and New Zealand observational cohort study. Aliment Pharmacol Ther. 2017;45(4):542–52.

Domènech E, Mañosa M, Bernal I, Garcia-Planella E, Cabré E, Piñol M, et al. Impact of azathioprine on the prevention of postoperative Crohn's disease recurrence: results of a prospective, observational, long-term follow-up study. Inflamm Bowel Dis. 2008;14(4):508–13.

Dulai PS, Siegel CA, Colombel JF, Sandborn WJ, Peyrin-Biroulet L. Systematic review: Monotherapy with antitumour necrosis factor α agents versus combination therapy with an immunosuppressive for IBD. Gut. 2014;63(12):1843–53.

Freire P, Portela F, Donato MM, Ferreira M, Andrade P, Sofia C. CARD15 mutations and perianal fistulating Crohn's disease: correlation and predictive value of antibiotic response. Dig Dis Sci. 2011;56(3):853–9.

Gecse KB, Bemelman W, Kamm MA, Stoker J, Khanna R, Ng SC, et al. A global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulising Crohn's disease. Gut. 2014;63(9):1381–92.

Gordon J, Ramaswami A, Beuttler M, Jossen J, Pittman N, Lai J, et al. EBV Status and Thiopurine Use in Pediatric IBD. J Pediatr Gastroenterol Nutr. 2016;62(5):711–4.

Grover Z, Lewindon P. Two-Year Outcomes After Exclusive Enteral Nutrition Induction Are Superior to Corticosteroids in Pediatric Crohn's Disease Treated Early with Thiopurines. Dig Dis Sci. 2015;60(10):3069–74.

Grover Z, Burgess C, Muir R, Reilly C, Lewindon PJ. Early Mucosal Healing with Exclusive Enteral Nutrition is Associated with Improved Outcomes in Newly Diagnosed Children with Luminal Crohn's disease. J Crohns Colitis. 2016;10(10):1159–64.

Hwang C, Ross V, Mahadevan U. Micronutrient deficiencies in inflammatory bowel disease: from A to zinc. Inflamm Bowel Dis. 2012;18(10):1961–81.

Korelitz BI, Present DH. Favorable effect of 6-mercaptopurine on fistulae of Crohn's disease. Dig Dis Sci. 1985;30(1):58–64.

Krupoves A, Mack DR, Seidman EG, Deslandres C, Bucionis V, Amre DK. Immediate and long-term outcomes of corticosteroid therapy in pediatric Crohn's disease patients. Inflamm Bowel Dis. 2011;17(4):954–62.

Levin AD, Wadhera V, Leach ST, Woodhead HJ, Lemberg DA, Mendoza-Cruz AC, et al. Vitamin D deficiency in children with inflammatory bowel disease. Dig Dis Sci. 2011;56(3):830–6.

Ma C, Moran GW, Benchimol EI, Targownik LE, Heitman SJ, Hubbard JN, et al. Surgical Rates for Crohn's Disease are Decreasing: A Population-Based Time Trend Analysis and Validation Study. Am J Gastroenterol. 2017;112(12):1840–8.

Miele E, Shamir R, Aloi M, Assa A, Braegger C, Bronsky J, et al. Nutrition in Pediatric Inflammatory Bowel Disease: A Position Paper on Behalf of the Porto Inflammatory Bowel Disease Group of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2018;66(4):687–708.

Mossop H, Davies P, Murphy MS. Predicting the need for azathioprine at first presentation in children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2008;47(2):123–9.

Narula N, Dhillon A, Zhang D, Sherlock ME, Tondeur M, Zachos M. Enteral nutritional therapy for induction of remission in Crohn's disease. Cochrane Database Syst Rev.2018;(4):CD000542.

Nissen LH, Nagtegaal ID, de Jong DJ, Kievit W, Derikx LA, Groenen PJ, et al. Epstein-Barr virus in inflammatory bowel disease: the spectrum of intestinal lymphoproliferative disorders. J Crohns Colitis. 2015;9(5):398–403.

Otley A, LeLeiko N, Langton C, Lerer T, Mack D, Evans J, et al. Budesonide use in pediatric Crohn disease. J Pediatr Gastroenterol Nutr. 2012;55(2):200–4.

Prantera C, Lochs H, Grimaldi M, Danese S, Scribano ML, Gionchetti P, et al. Rifaximin-extended intestinal release induces remission in patients with moderately active Crohn's disease. Gastroenterology. 2012;142(3):473–81.e4.

Prefontaine E, Macdonald JK, Sutherland LR. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2010;(6):CD000545.

Ruemmele FM, Veres G, Kolho KL, Griffiths A, Levine A, Escher JC, et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. J Crohns Colitis. 2014;8(10):1179–207.

Ruemmele FM, Rosh J, Faubion WA, Dubinsky MC, Turner D, Lazar A, et al. Efficacy of Adalimumab for Treatment of Perianal Fistula in Children with Moderately to Severely Active Crohn's Disease: Results from IMAgINE 1 and IMAgINE 2. J Crohns Colitis. 2018;12(10):1249–54.

Sandborn WJ, Present DH, Isaacs KL, Wolf DC, Greenberg E, Hanauer SB, et al. Tacrolimus for the treatment of fistulas in patients with Crohn's disease: a randomized, placebo-controlled trial. Gastroenterology. 2003;125(2):380–8.

Scherkenbach LA, Stumpf JL. Methotrexate for the Management of Crohn's Disease in Children. Ann Pharmacother. 2016;50(1):60–9.

Schulman JM, Pritzker L, Shaoul R. Maintenance of Remission with Partial Enteral Nutrition Therapy in Pediatric Crohn's Disease: A Retrospective Study. Can J Gastroenterol Hepatol. 2017;2017:5873158.

Siegel CA, Horton H, Siegel LS, Thompson KD, Mackenzie T, Stewart SK, et al. A validated web-based tool to display individualised Crohn's disease predicted outcomes based on clinical, serologic and genetic variables. Aliment Pharmacol Ther. 2016;43(2):262–71.

Stein RE, Plantz K, Maxwell EC, Mamula P, Baldassano RN. Intravenous Iron Sucrose for Treatment of Iron Deficiency Anemia in Pediatric Inflammatory Bowel Disease. J Pediatr Gastroenterol Nutr. 2018;66(2):e51–5.

Su JW, Ma JJ, Zhang HJ. Use of antibiotics in patients with Crohn's disease: a systematic review and meta-analysis. J Dig Dis. 2015;16(2):58–66.

Torki M, Gholamrezaei A, Mirbagher L, Danesh M, Kheiri S, Emami MH. Vitamin D Deficiency Associated with Disease Activity in Patients with Inflammatory Bowel Diseases. Dig Dis Sci. 2015;60(10):3085–91.

Tsertsvadze A, Gurung T, Court R, Clarke A, Sutcliffe P. Clinical effectiveness and cost-effectiveness of elemental nutrition for the maintenance of remission in Crohn's disease: a systematic review and meta-analysis. Health Technol Assess. 2015;19(26):1–138.

Tung J, Loftus EV Jr, Freese DK, El-Youssef M, Zinsmeister AR, Melton LJ 3rd, et al. A population-based study of the frequency of corticosteroid resistance and dependence in pediatric patients with Crohn's disease and ulcerative colitis. Inflamm Bowel Dis. 2006;12(12):1093–100.

Veereman-Wauters G, de Ridder L, Veres G, Kolacek S, Fell J, Malmborg P, et al. Risk of infection and prevention in pediatric patients with IBD: ESPGHAN IBD Porto Group commentary. J Pediatr Gastroenterol Nutr. 2012;54(6):830–7.

Vernier-Massouille G, Balde M, Salleron J, Turck D, Dupas JL, Mouterde O, et al. Natural history of pediatric Crohn's disease: a population-based cohort study. Gastroenterology. 2008;135(4):1106–13.

Walters TD, Kim MO, Denson LA, Griffiths AM, Dubinsky M, Markowitz J, et al. Increased effectiveness of early therapy with anti-tumor necrosis factor-α vs an immunomodulator in children with Crohn's disease. Gastroenterology. 2014;146(2):383–91.

Weisshof R, Chermesh I. Micronutrient deficiencies in inflammatory bowel disease. Curr Opin Clin Nutr Metab Care. 2015;18(6):576–81.

Yoon SM. Micronutrient deficiencies in inflammatory bowel disease: trivial or crucial? Intest Res. 2016;14(2):109–10.

de Zoeten EF, Pasternak BA, Mattei P, Kramer RE, Kader HA. Diagnosis and treatment of perianal Crohn disease: NASPGHAN clinical report and consensus statement. J Pediatr Gastroenterol Nutr. 2013;57(3):401–12.

9. Treatment of ulcerative colitis

Stephan Buderus

Objectives of treatment

From the perspective of sick patients and their families, the primary objective of treatment is clear: completely eradicating the symptoms of ulcerative colitis (UC), primarily bloody and painful diarrhea, as rapidly as possible by medical (or possibly even surgical) treatment. These children and adolescents want to return to their normal lives as quickly as possible – they want to get back to school, sports practice, and their other recreational activities as soon as they can. Following induction, remission should be maintained for as long as possible, which ideally means that "disease flares" occur only rarely or not at all. However, when viewed more closely, the demands placed on an optimal therapy have many different layers. Most experts plan therapies to induce and maintain remission in a manner that provides the greatest likelihood of achieving **mucosal healing**. According to the most common pathophysiological concepts of the disease, effective blockage of the inflammation process can lead to the healing of intestinal inflammation, which in turn leads to an overall intact mucosal surface and barrier. The adverse effects of treatment should be avoided to the greatest extent possible, and regular long-term monitoring of UC inflammation can also help prevent cancer development. Any relevant nutritional deficiencies – such as iron, other trace elements (e.g. zinc), vitamins (e.g. vitamin D), or low body weight in patients whose disease is severe and protracted prior to diagnosis – should be remedied, preferably at the start of treatment.

Examples of factors which are relevant to the treatment decision include the issue of whether the UC is newly diagnosed or relapsing, the extent of the disease (see Paris classification), the severity of the inflammation, and any prior medical treatments. The severity of disease should be evaluated by incorporating both endoscopic findings (macroscopic impression and extent of inflammatory mucosal pathologies and histological examination of the same), serological findings (ESR, CRP, Hb, thrombocytosis), and fecal markers of inflammation (calprotectin or lactoferrin). Clinical aspects such as global health status, fever, potential weight loss or low body weight, and imaging findings such as possible inflammatory wall thickening or dilation (diameter) of the colon are also relevant. The **PUCAI** (Pediatric Ulcerative Colitis Activity Index; Turner et al. 2007) allows the disease to be

classified into inactive, mild, moderate, and severe disease activity using six items which are easy to survey and assess (see Table 9/1), and its regular usage has proven to be an effective tool. The index's scores – which range from a minimum of 0 to a maximum of 85 points – have been shown to be well-correlated with endoscopic findings. It is recommended that the PUCAI be administered routinely in the care and treatment of UC patients, and should even be calculated daily for patients with acute severe colitis (PUCAI ≥ 65). In accordance with the guidelines [Turner et al. 2018a, Turner et al. 2018b], changes in PUCAI score should be the basis on which treatment decisions are made or recommended.

The current evidence-based guidelines addressing the treatment of UC in detail are the DGVS (German Society for Digestive and Metabolic Diseases) guideline [Kucharzik et al. 2018], which were compiled in collaboration with the GPGE, and the two-part specific pediatric guideline (ambulatory care and acute severe colitis) by the ESPGHAN/ECCO [Turner et al. 2018a, Turner et al. 2018b].

The most important aspects in the treatment of UC will be discussed briefly below, while more detailed information can be found in other sources, including the current guidelines cited here.

5-Aminosalicylates (5-ASA), oral and rectal. Oral 5-aminosalicylates (5-ASA) are the first-line treatment **for induction and maintenance of remission in patients with mild to moderate UC.** A combination of oral and rectal administration has proven more effective than oral therapy alone. If patients do not clearly respond after 2–3 weeks of treatment, it is recommended that treatment be intensified (e.g. by adjunct administration of prednisolone).

Because isolated proctitis (E1) and limited left-sided colitis (E2) are rare manifestations in pediatric UC, there are very few children and adolescents eligible for local rectal therapy alone. Mesalazine should be preferred to local corticosteroids for rectal therapy of UC due to its superior effectiveness.

Mesalazine is administered orally at a dose of 60–80 mg/kg BW/day (one pediatric study even investigated high-dose therapy of up to 118 mg/kg BW/day, which did not yield any superior treatment outcomes) up to a maximum dose of 4.8 g per day. Mesalazine is administered rectally at a daily dose starting at 25 mg/kg, typically either up to 1 g or maximum 2 g per day. Suppositories are also available at different strengths up to 1 g for very distal inflammation. The 2012 ESPGHAN/ECCO guidelines also mention that, when

	Symptom	Points
1	**Abdominal pain**	
	No	0
	Yes, but can be ignored	5
	Yes, cannot be ignored	10
2	**Rectal bleeding**	
	No	0
	Yes, but small amount only, in < 50% of stools	10
	Yes, small amount with most stools	20
	Large amount (> 50% of the stool content)	30
3	**Stool consistency of most stools**	
	Formed	0
	Partially formed	5
	Completely unformed	10
4	**Number of stools per 24 hours**	
	0–2	0
	3–5	5
	6–8	10
	> 8	15
5	**Nocturnal stools (any episode causing wakening)**	
	No	0
	Yes	10
6	**Activity level**	
	No limitation of activity	0
	Occasional limitation of activity	5
	Severely restricted activity	10
Maximum PUCAI score: 85 points		

Activity categories:	**Treatment response:**
Remission/inactive: < 10	Low: > 10
Mild: 10–34	Moderate > 20
Moderate: 35–64	High: > 35
Severe: ≥ 65	

Table 9/1: PUCAI = Pediatric Ulcerative Colitis Activity Index (adapted from Turner et al. 2007)

prescribed as combination therapy, the total mesalazine dose should typically not exceed 150% of the maximum oral dose, and that the maximum total dose for adults is 6.4 g per day [Turner et al. 2012]. When prescribing mesalazine as oral therapy, various extended-release formulations (granules, extended-release tablets) may promote adherence to therapy by permitting a single dose per day. Pediatric studies have shown that remission rates of 35–55% (as measured by the PUCAI) can be expected with mesalazine monotherapy. The "well-known" drug sulfasalazine is also available as an alternative. The dose of this agent is 40–70 mg/kg BW/day, with a maximum dose of 4 g per day. Increasing the dose in a stepwise manner up to the final dose over a period of 1–2 weeks may improve the tolerability of sulfasalazine. Although sulfasalazine is at least as effective as mesalazine at treating colitis, mesalazine is better tolerated overall (fewer headaches and gastrointestinal symptoms). Sulfasalazine is clearly indicated in patients with IBD-related joint pain or arthritis, as it specifically targets these symptoms while mesalazine does not. This class of drugs is very safe overall. Side effects, especially severe side effects, are rare. These side effects may include headaches, skin rash, gastrointestinal symptoms, pancreatitis, pericarditis, nephritis, myocarditis, myalgia, arthralgia, myelotoxicity, and elevated liver enzyme levels. It is recommended that the appropriate laboratory parameters be measured at least once or twice per year in patients on long-term therapy.

Steroids (prednisone, prednisolone). Corticosteroids are indicated for the **induction of remission**. They should be prescribed in oral form to patients with mild or moderate UC who have failed 5-ASA treatment. Steroids may also be administered as first-line agents for patients with more pronounced forms with moderate disease activity. For patients with severe UC (PUCAI $\geq$ 65), it is recommended that prednisolone be administered intravenously at least until response is detectable. Patients may then switch to oral therapy if desired. Selected patients (good overall clinical condition, no high levels of inflammation markers) may also be switched to oral therapy at a PUCAI of 65 on a case-by-case basis. As with Crohn's disease (CD), the dose of prednisolone is 1 mg/kg BW/day, typically as a single dose in the morning, with a maximum dose of 40 mg per day (with exceptions permitted). A dose reduction should be scheduled after 2–3 weeks (see regimen in Chapter 8: Treatment of Crohn's disease), resulting in a total of about 12 weeks of treatment. The rates of induction of remission within 3 months are 50–64% with oral corticosteroid therapy. Steroids are not used to maintain remission.

There is a relatively high likelihood that side effects will emerge over the course of corticosteroid therapy, including increased appetite, weight gain, steroid acne, mood swings, leukocytosis, etc. Most of these side effects are reversible by dose reduction or discontinuation. It must be kept in mind that corticosteroids may also have immunosuppressive effects at the doses described here. This requires extra vigilance by patients and physicians in order to prevent infections and to diagnose and treat any infections which do occur as rapidly as possible. Ophthalmic complications may also result from corticosteroid therapy (elevated intraocular pressure, glaucoma, cataract), and hence IBD patients receiving corticosteroid therapy should speak with a proper specialist on this topic. For selected patients (with mild UC who did not adequately respond to 5-ASA), a treatment attempt may be initiated with the topical corticosteroid **budesonide** (at a dose of 9 mg once daily) in an appropriate formulation (e.g. extended-release in colon) prior to starting prednisolone/prednisone, provided that patients are informed that there is currently insufficient experience on the use of this drug in the pediatric population according to its Summary of Product Characteristics. The advantage of this 8-week therapy is the fact that it triggers far fewer steroid-associated side effects. The ESPGHAN guideline also points out that even the evidence in adults is only adequate for the treatment of patients with left-sided colitis.

Patients are said to have steroid resistance or steroid dependence if they are not able to reduce their dose of corticosteroids or to discontinue their corticosteroids without a relapse of colitis within 3 months. Patients who need to resume corticosteroid therapy within 3 months of discontinuing them (i.e. early relapse of UC) are also classified as being steroid-resistant. This scenario is observed in up to 45% of pediatric UC patients (compared with approximately 8% of adults).

A scenario of this sort is also an indication for the use of **thiopurines** (usually **azathioprine [AZA]** in German-speaking countries and in the rest of Europe, but more often **6-mercaptopurine [6-MP]** in North America). This immunosuppressant is indicated for long-term **maintenance of remission** if 5-ASA is inadequate despite an optimized dose and combined oral and rectal administration, or in patients with rare 5-ASA intolerance. Inadequate response is characterized as two or more UC flares per year. AZA can also be used as first-line therapy following acute severe UC (PUCAI $\geq$ 65).

A dose of 2–2.5(–3) mg AZA/kg/day (or 1–1.5 mg 6-MP/kg/day) is administered. It may be useful to characterize the genotype or phe-

notype of thiopurine methyltransferase (TPMT), which is the enzyme responsible for metabolizing AZA. This may provide early identification of patients with low or no enzyme activity, who are thus at an elevated or high risk of myelosuppression. Measurement of 6-thioguanine (6-TGN; active substance) levels can help monitor whether effective levels have been achieved, while measuring 6-methylmercaptopurine (6-MMP; metabolite) levels can indicate whether hepatotoxicity is expected. Low levels may also be an indication that patients are not taking their medication regularly (poor adherence to therapy) despite being at a "good dose". When planning therapy, it must be kept in mind that it may take 10–12 weeks before AZA exerts its full effects. However, if inflammation control is still not successful or detectable after this time and after effective levels of the drug have been attained, other therapeutic alternatives need to be considered. Patients must be informed of the need to consistently use sun protection during treatment. A very rare but potentially life-threatening complication of AZA therapy is the development of hepatosplenic T-cell lymphoma (HSTCL), which afflicts adolescent males in particular. A negative Epstein-Barr virus (EBV) status prior to the start of treatment also appears to be a risk factor. These risks must be discussed in detail with the patient before starting treatment. Please refer to Chapter 8 on treatment of CD for more information on side effects and required laboratory tests. AZA is indicated for long-term treatment (meaning over the course of years) if it proves to be effective at maintaining remission. Before considering discontinuation of AZA, the UC patient's disease activity should be re-evaluated, including recommended renewed endoscopy with biopsy removal and histology. The current guideline recommends "complete mucosal healing" as a prerequisite for discontinuation.

In contrast to the treatment of CD, **methotrexate (MTX)** is only of minor importance for the treatment of UC and is not considered to be part of the standard therapeutic repertoire. However, it may be an option in rare cases of failure on or intolerance to AZA therapy.

Probiotics (*Escherichia coli* Nissle or the VSL#3 preparation of multiple strains, if available) may be considered for the treatment of UC patients with mild disease activity as an adjunct to 5-ASA or as an alternative for patients intolerant to 5-ASA.

Biologics (antibody-based therapies) are indicated for patients for whom induction of remission fails despite optimized 5-ASA and immunosuppressant therapy, patients who have frequent flares, or patients with primary steroid resistance. The only drug currently

approved for the treatment of UC in children (ages 6 and older) and adolescents in addition to adults remains the anti-tumor necrosis factor (TNF)-α antibody **infliximab (IFX)**. The dose of IFX is 5 mg/kg BW i.v. at time points 0 and after 2 and 4 weeks, and every 8 weeks thereafter. However, recent experience suggests that UC patients in particular may require more intensive care on a case-by-case basis, which may indicate a higher dosage and/or shorter intervals in order to induce or maintain remission. It may be helpful to measure effective trough levels (and antibody levels) in order to optimize therapy. For patients who have experienced 6 months remission on IFX plus AZA combination therapy and who have stable trough IFX levels of > 5 µg/ml, the new ESPGHAN guideline states that discontinuation of AZA may be considered, especially for male patients, in order to reduce the risk of side effects. However, this decision would also increase the risk of developing antibodies to IFX, which in turn would reduce the effectiveness of that medication. **Adalimumab** and **golimumab** represent two alternative anti-TNF antibodies which are both administered subcutaneously and are approved for the treatment of adult UC. In contrast, **vedolizumab** utilizes a different mechanism of action. This antibody targets $\alpha_4\beta_7$ integrins, thereby preventing or inhibiting the migration of inflammatory T lymphocytes into the gut mucosa. This feature makes this antibody especially indicated in patients who respond inadequately to anti-TNF-α therapy. Vedolizumab is administered by infusion and is approved for use in adults. The onset of its effects takes about 6–14 weeks, which may require intermittent resumption of steroid administration in some cases. Pediatric case series have also demonstrated the efficacy of vedolizumab in children (Ledder et al. 2017: 37% after 14 weeks in this subgroup of children with very severe UC).

Acute severe colitis (ASC; **PUCAI ≥ 65!**) is a particularly challenging scenario in the treatment of pediatric UC, which is reflected by the dedication of an entire separate section of the ESPGHAN guideline to the topic. It is thought that up to 28% of pediatric UC patients suffer from at least one episode of ASC in the first 2–3 years of disease. It is again necessary to rule out the possibility of an infectious etiology either before or during intensive or interdisciplinary care (pediatric surgery/surgery/radiology) and treatment (see Chapter 7: Diagnosis). Pain management should preferably be conducted with acetaminophen. Non-steroidal anti-inflammatory drugs (NSAIDs) should not be prescribed, and opiates should only be used in exceptional cases with close monitoring. Thromboprophylaxis should be considered, especially for adolescents. All patients

should be monitored closely for weight changes and fluid and electrolyte imbalances, and oral 5-ASA therapy should be temporarily discontinued. Although routine antibiotic treatment is not recommended, it may be advisable for patients with suspected or potential infections. Several case series have also demonstrated the effectiveness of "antibiotic cocktails" (metronidazole, amoxicillin, doxycycline, and vancomycin) at treating ASC. Corticosteroids (prednisolone, methylprednisolone, in this scenario up to 60 mg) must be administered intravenously. The possibility of toxic megacolon must be excluded by clinical examination and imaging (colon diameter > 55 mm or > 40 mm in children < 10 years old, affects approximately 1–2% of the pediatric population with ASC). Patients must be stabilized, and the (pediatric) surgeons must be notified of any indication for surgery. If patients still have a PUCAI ≥ 45 on the third day of intravenous corticosteroid therapy, planning for the next steps must begin. These include the possibility of transferring the patient to a facility with more experience at treating pediatric gastroenterological IBD, potential sigmoidoscopy (infection, particularly cytomegalovirus, granulomas), measuring markers of inflammation (changes in CRP), and a review of any upcoming tests for infectious agents. Patients with a PUCAI > 65 on day 5 have an indication for starting second-line therapy, for which either IFX or the **calcineurin inhibitors cyclosporine A (CsA)** or **tacrolimus** (previously unmentioned) are suitable options. This is also the time point at which the patient and his or her parents should be informed about the possible upcoming need for colectomy. Corticosteroid therapy can be reduced in a tailored stepwise fashion, as it will have been ineffective by this point. Patients should also be administered antibiotic prophylaxis against opportunistic infections which may result from the use of multiple immunosuppressants. The effectiveness of the second-line therapy should also be monitored by daily measurement of PUCAI score. If response is not clearly apparent after a maximum of 4–7 days (PUCAI 35–60), the guideline recommends colectomy as the next therapeutic step. Nonetheless, in rare cases, institutions with sufficient experience with this indication may also attempt a third-line therapy, for example CsA following the failure of IFX or vice versa. However, adjunct corticosteroids may no longer be administered at this point in time. The guideline paper explicitly points out that no pediatric data is currently available for this type of approach. The published data in adults is quite heterogeneous and reveals a mean response rate of 62%, a remission rate of 39%, and colectomy rates of 28% and 42% after 3 and 12 months, respectively.

Figure 9/1 provides an overview of the treatment options for CD and UC.

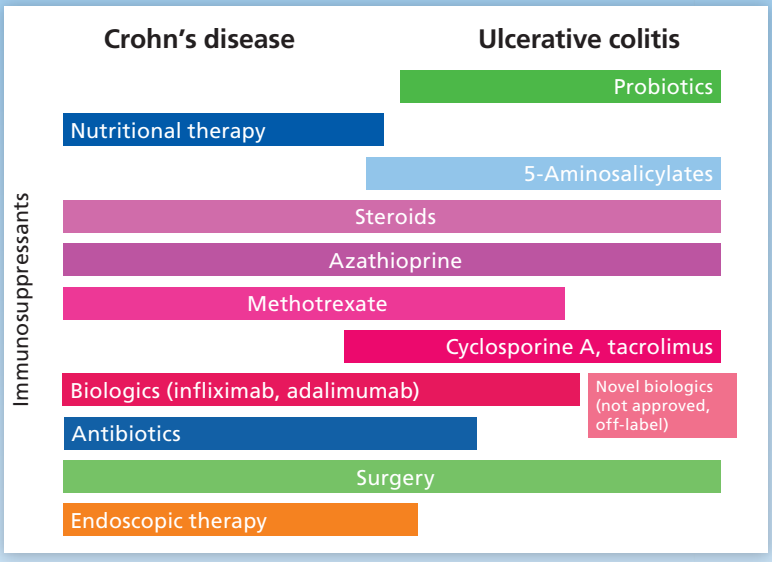


Figure 9/1: Treatment of IBD

Literature

Kucharzik T, Dignass AU, Atreya R, Bokemeyer B, Esters P, Herrlinger K, et al. [Updated S3-Guideline Colitis ulcerosa. German Society for Digestive and Metabolic Diseases (DGVS) - AWMF Registry 021/009]. Z Gastroenterol. 2018;56(9):1087–169.

Ledder O, Assa A, Levine A, Escher JC, de Ridder L, Ruemmele F, et al. Vedolizumab in Paediatric Inflammatory Bowel Disease: A Retrospective Multi-Centre Experience From the Paediatric IBD Porto Group of ESPGHAN. J Crohns Colitis. 2017;11(10):1230–37.

Turner D, Otley AR, Mack D, Hyams J, de Bruijne J, Uusoue K, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. Gastroenterology. 2007;133(2):423–32.

Turner D, Levine A, Escher JC, Griffiths AM, Russell RK, Dignass A, et al. Management of pediatric ulcerative colitis: joint ECCO and ESPGHAN evidence-based consensus guidelines. J Pediatr Gastroenterol Nutr. 2012;55(3):340–61.

Turner D, Ruemmele FM, Orlanski-Meyer E, Griffiths AM, de Carpi JM, Bronsky J, et al. Management of Paediatric Ulcerative Colitis, Part 1: Ambulatory Care-An Evidence-based Guideline From European Crohn's and Colitis Organization and European Society of Paediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2018a;67(2):257–91.

Turner D, Ruemmele FM, Orlanski-Meyer E, Griffiths AM, de Carpi JM, Bronsky J, et al. Management of Paediatric Ulcerative Colitis, Part 2: Acute Severe Colitis-An Evidence-based Consensus Guideline From the European Crohn's and Colitis Organization and the European Society of Paediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2018b;67(2):292–310.

10. Surgical treatment

Martin Classen

Surgical interventions play an important role in the treatment of inflammatory bowel disease (IBD), both as an option to induce remission for patients with severe forms of the disease, and as a means to treat complications. Nonetheless, all efforts should be made to reduce the need for surgery, especially in pediatric patients, by providing an effective therapy from the very beginning (treat-to-target). However, this strategy is not always successful, as demonstrated by a registry study (EPIMAD) using (historical) data from 1988–2004 (692 patients, 532 CD, 160 UC), which reported that 153 of these patients (128 CD, 25 UC) required bowel resection at a median of 18 months after diagnosis [Vernier-Massouille et al. 2008]. The introduction of novel therapeutic agents has resulted in a reduction in the frequency of surgical interventions at the population level [Kerur et al. 2018, Mao et al. 2017].

Crohn's disease (CD)

Surgery may be a necessary component of treatment for CD patients with both penetrating and stricturing phenotypes [Amil-Dias et al. 2017, Blackburn et al. 2014, de Zoeten et al. 2013]. Long-term studies in children have shown that the need for surgery increases with the duration of the disease, as is also the case for adults. One longitudinal study in adults (> 30 years) reported that nearly 60% of patients had undergone at least one abdominal surgical intervention after 30 years [Peyrin-Biroulet et al. 2012]. At another center, 69 of 286 CD patients (24%) required surgery within a 10-year period at a mean of 9 months after the onset of disease (range 0 days to 7 years). The indications for surgery were strictures in 35 patients, resistance to therapy in 13 patients, and perianal disease in 10 patients. Ileocecal resection was performed in 40 patients and stoma formation in 8 patients [Blackburn et al. 2014].

Indications for surgery in CD may include:

– Stenosis/strictures
– Fistulas and abscesses
– Severe bleeding
– Resistance to therapy and failure of medical therapies

Elective surgery to control disease activity is a particularly suitable option for pediatric patients when medical therapy is inadequately effective or associated with intolerable side effects. This is especially the case for adolescents who are prepubertal or in early puberty with growth retardation and isolated ileocecal disease. Elective surgery may also be considered as a primary treatment option to induce remission. Diverting ileostomy can also lead to a major reduction in disease activity in patients with severe Crohn's colitis with or without fistulizing or stricturing disease [Maxwell et al. 2017].

Stenosis and strictures

Stenosis and strictures caused by inflammation may form as a result of swelling and/or fibrosis of the bowel wall. The following methods should be weighed as treatment options in interdisciplinary discussions between pediatric gastroenterologists and surgeons:

– Intensification of anti-inflammatory therapy (medical or enteral nutrition)
– Endoscopic balloon dilation
– Surgical strictureplasty
– Stricture resection and anastomosis

The decision of whether to operate and which method to use should be made based on the following questions, information, and considerations:

– Localization and length of the stricture (is it endoscopically accessible? longitudinal? curved?)
– Is there evidence of intramural abscesses?
– Extent of inflammation versus fibrosis. The following parameters may be useful to help answer this question:
  · Levels of inflammation markers in blood and stool (high CRP levels suggest a likelihood that anti-inflammatory therapy will be superior. However, patients with stenosis/strictures frequently have elevated fecal levels of calprotectin)
  · Time elapsed between diagnosis and development of symptoms of stenosis
  · Inflammation revealed by magnetic resonance imaging (MRI)
– Ultrasound plus Doppler
– Have medical therapy options been exhausted?
– Are there complications of medical therapy?
– Acute ileus? → urgent indication

– Would the option of enteral nutrition be feasible? This approach has anti-inflammatory effects on stenosis and facilitates improved bowel passage by reducing fibers. However, the long-term effectiveness of this approach is limited

The desires and preferences of the patient and his or her family must of course also be taken into consideration.

The following information should be collected and/or the following general conditions should be met in order to **determine the best time point for surgery**, provided there is no urgent indication:

– Diagnosis has been clearly confirmed
– Nutritional status and micronutrient intake should be optimized, since protein-energy malnutrition may increase the risk of postoperative wound complications
– Steroid therapy should be discontinued or adjusted to a low dose whenever possible
– Studies in adults have reported that infliximab (IFX) does not increase the risk of surgical complications [Colombel et al. 2004, Nasir et al. 2010]
– The current extent/localization of the disease should be known so that the proper surgical method can be selected

Fistulas

The disease can have a tendency to form fistulas in some patients. There are several different types of fistulas:

– Enteroenteric
– Enterovesical or enterovaginal
– Enterocutaneous
– Into the retroperitoneum

Fistulas may be asymptomatic but they can also trigger symptoms. Depending on the bowel segment and the organ targeted by the fistula, symptoms such as secretion, pain, urinary tract infections, incontinence, diarrhea, and/or malabsorption syndrome may occur. A typical complication of fistulas is abscesses, which may present with pain, fever, swelling, and bowel obstruction.

Fistulas most commonly manifest in the rectal and perianal regions of pediatric patients [Brueckner et al. 2018, Buderus et al. 2015]. Fistulas are classified as simple or complex. A retrospective study of 6,679 patients (41% female, mean age of 12.4 years at diag-

nosis [interquartile range: 9.9–14.8]) from the US registry Improve-CareNow reported that 1,399 patients (21%) experienced a perianal manifestation during the observation period. For 98 patients, their diagnosis was changed from UC to CD due to the manifestation of an anal fistula [Adler et al. 2017].

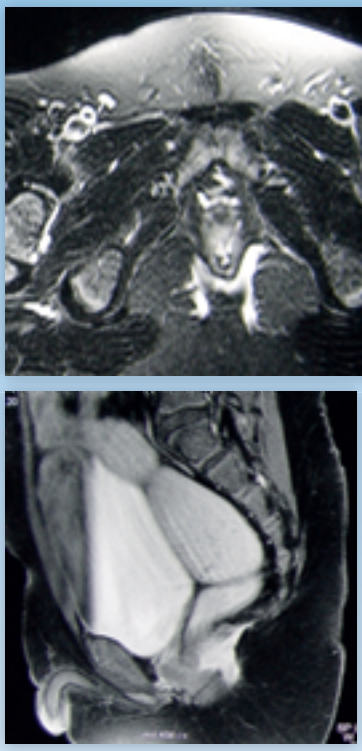
Treatment of patients with anal fistulas should be planned on a case-by-case basis, with close collaboration between specialists in conservative treatment and in surgical treatment of IBD. A clinical examination (under anesthesia if needed) and MRI of the lesser pelvis should ideally be performed before any decision is made (Figures 10/1a and b). Surgical drainage is typically required for perianal abscesses. Attempts should also be made to prevent further fistula activity or renewed abscess formation. A combination of biologics, antibiotics, and surgery is often helpful for this purpose [Amil-Dias et al. 2017, de Zoeten et al. 2013]. One objective of these measures is to close the internal opening of the fistula, which explains why conservative therapy to induce mucosal healing may offer the best chances of success. The most suitable options for this objective are biologics and possibly immunomodulators [Amil-Dias et al. 2017, Ruemmele et al. 2014]. Data from prospective studies is only available for IFX [Duff et al. 2012].

Short-term antibiotic therapy may also be useful (metronidazole, possibly in combination with ciprofloxacin) [Iwańczak et al. 2016, Ruemmele et al. 2014, Su et al. 2015]. These antibiotics have not been formally approved for this indication in children. Enteral nutrition has not been established as effective at alleviating fistulizing disease.

The surgical options for perianal fistulas are as follows:

– Seton drains, which convert a complex fistula into a simple one (especially important to prevent abscess formation)
– Excision of fistula
– Attempt to close the internal fistula opening by flap mobilization or other methods (e.g. fistula plug) [de Zoeten et al. 2013]

Any surgical interventions should avoid damaging the sphincter to the greatest extent possible [Van Assche et al. 2010]. Rectovaginal fistulas are a type of fistula that can be especially painful for affected women. Protective ileostomy is an option that should be considered for patients with treatment-resistant perianal fistulas, multiple painful fistulas, or symptomatic enterovaginal fistulas, as it promotes fistula healing [Maxwell et al. 2017].



Figures 10/1a and b: MRI image of a retrorectal H-type fistula in a prepubertal boy

Risk of postoperative relapse and prevention of relapse after resection in CD patients

In one pediatric case series, the rate of clinical relapse was 17% after 1 year, 38% after 3 years, and 60% after 5 years [Baldassano et al. 2001]. A meta-analysis reported a clinical rate of postoperative relapse of 20–25% and an endoscopic rate of 65–90% after 1 year [Renna et al. 2008]. This risk is much higher among adults with a stricturing phenotype (Montreal classification B2) than with a penetrating phenotype.

Factors which appear to increase the risk of relapse include:

– Young age at initial onset
– Smoking
– Prolonged disease
– Prior resections

– Perforating disease
– NOD2/CARD15 mutations
– Presence of granulomas in resected tissues
[Ruemmele et al. 2014]

Accordingly, prophylactic therapy should be given to each patient after surgery [Splawski et al. 2017]. The ESPGHAN guideline recommends thiopurine therapy as the first-choice drug (evidence level 3), with partial enteral nutrition or an anti-tumor necrosis factor (TNF)-α antibody as an alternative [Ruemmele et al. 2014].

– Azathioprine/6-mercaptopurine are recommended for patients with extensive disease and a high rate of relapse regardless of whether they were treated with either of these drugs prior to surgery. However, their absolute effects are limited.
– Studies in adults suggest that a combination of 1 year of azathioprine plus 3 months of metronidazole may have prophylactic effects, while the effects of adjunct antibiotics are limited [D'Haens et al. 2008, Mañosa et al. 2013].
– The study results are contradictory for 5-aminosalicylates (5-ASA) but show only weak effects in the best case; moreover, pediatric data are lacking. Prophylactic administration of 5-ASA is not recommended in the ESPGHAN consensus.
– Administration of IFX to adults following ileal resection reduces the number of endoscopic relapses but not clinical relapses [Regueiro et al. 2016].

Postoperative monitoring is recommended. Fecal markers of inflammation should be normalized after 2 months, and a persistent increase or renewed increase in these parameters indicates the need for endoscopic follow-up. An endoscopic re-evaluation should typically be carried out 6 months after surgery. In the event that local relapse is detected at the anastomosis, treatment should be intensified, for example by administering anti-TNF-α antibodies [Splawski et al. 2017]. Cessation of long-term therapy may be attempted in patients with complete remission as long as fecal markers of inflammation continue to be monitored.

Ulcerative colitis (UC)

There are five scenarios for UC in which surgery is required or should be taken into consideration [Romano et al. 2016, Ruemmele et al. 2014, Turner et al. 2018a, Turner et al. 2018b]:

1. Acute severe colitis that does not respond to medical therapy (including second- and third-line medications such as IFX or calcineurin inhibitors) (see Chapter 9: Treatment of ulcerative colitis)
2. Colon perforation in the context of toxic megacolon
3. Severe, uncontrollable bleeding
4. Sustained high disease activity with steroid dependence, non-response to medical treatment attempts; PUCAI > 65 on days 11–14 of rescue immunosuppression
5. Detection of high-grade dysplasia by colonoscopy surveillance

Twenty percent of children require surgery within 10 years [Fumery et al. 2016]. The first choice for surgery is proctocolectomy. The type of entry (open vs. laparoscopic; Diamond et al. 2010) and the number of stages (one/two/three) must be selected based on the patient's indication and condition and the urgency of the situation. In patients with toxic megacolon or perforation who are taking high-dose corticosteroids or immunosuppressants, the three-stage approach (1. colectomy with insertion of an ileostomy leaving a rectal stump, 2. rectal resection and creation of an ileoanal pouch with temporary upstream ileostomy, 3. removal of ileostomy) is associated with a lower rate of complications. For elective colectomy, one-stage or two-stage procedures with protective ileostomy may be chosen [Dayan & Turner 2012].

The indication for surgery should be made in collaboration with a pediatric center experienced at treating IBD. Before elective surgery can be indicated, it must be confirmed that patients do not have CD [Shannon et al. 2016]. In most cases, an ileoanal pouch is created. The success of surgery depends on the experience of the surgeon, and hence hospitals which perform large numbers of operations should be contacted. There are good arguments for a laparoscopic approach to elective procedures [Fraser et al. 2010].

Although arguments for colectomy frequently cite the possibility of "healing" UC, patients need to be informed about potentially impaired continence resulting from suboptimal pouch function [de Zeeuw et al. 2012], and especially about the high risk (56%) of pouchitis [Dharmaraj et al. 2016]. Should pouchitis occur, the possibility of infection with *Clostridium difficile* or cytomegalovirus must be kept in mind. Despite these concerns, most patients experience an improvement in their quality of life thanks to this surgery [Dalal et al. 2012]. Female patients may be impacted by reduced fertility (from about 10% to 25–30%) following pouch creation [Dayan & Turner 2012]. For this reason, a rectal stump may be left in place in these

patients despite the risks this harbors [Turner et al. 2012]. The incidence of postoperative complications following pouch creation (wound infections, fistulas, abscesses) was particularly high among patients with prednisolone doses > 20 mg, hyperalbuminemia, and malnutrition [Markel et al. 2008].

Literature

Adler J, Dong S, Eder SJ, Dombkowski KJ; ImproveCareNow Pediatric IBD Learning Health System. Perianal Crohn Disease in a Large Multicenter Pediatric Collaborative. J Pediatr Gastroenterol Nutr. 2017;64(5):e117–24.

Amil-Dias J, Kolacek S, Turner D, Pærregaard A, Rintala R, Afzal NA, et al. Surgical Management of Crohn Disease in Children: Guidelines From the Paediatric IBD Porto Group of ESPGHAN. J Pediatr Gastroenterol Nutr. 2017;64(5):818–35.

Baldassano RN, Han PD, Jeshion WC, Berlin JA, Piccoli DA, Lautenbach E, et al. Pediatric Crohn's disease: risk factors for postoperative recurrence. Am J Gastroenterol. 2001;96(7):2169–76.

Blackburn SC, Wiskin AE, Barnes C, Dick K, Afzal NA, Griffiths DM, et al. Surgery for children with Crohn's disease: indications, complications and outcome. Arch Dis Child. 2014;99(5):420–6.

Brückner A, Werkstetter KJ, de Laffolie J, Wendt C, Prell C, Weidenhausen T, et al. Incidence and Risk Factors for Perianal Disease in Pediatric Crohn Disease Patients Followed in CEDATA-GPGE Registry. J Pediatr Gastroenterol Nutr. 2018;66(1):73–8.

Buderus S, Scholz D, Behrens R, Classen M, De Laffolie J, Keller KM, et al. Inflammatory bowel disease in pediatric patients: Characteristics of newly diagnosed patients from the CEDATA-GPGE Registry. Dtsch Arztebl Int. 2015;112(8):121–7.

Colombel JF, Loftus EV Jr, Tremaine WJ, Pemberton JH, Wolff BG, Young-Fadok T, et al. Early postoperative complications are not increased in patients with Crohn's disease treated perioperatively with infliximab or immunosuppressive therapy. Am J Gastroenterol. 2004;99(5):878–83.

Dalal DH, Patton D, Wojcicki JM, Clark AL, Garnett EA, Heyman MB. Quality of life in patients postcolectomy for pediatric-onset ulcerative colitis. J Pediatr Gastroenterol Nutr. 2012;55(4):425–8.

Dayan B, Turner D. Role of surgery in severe ulcerative colitis in the era of medical rescue therapy. World J Gastroenterol. 2012;18(29):3833–8.

D'Haens GR, Vermeire S, Van Assche G, Noman M, Aerden I, Van Olmen G, et al. Therapy of metronidazole with azathioprine to prevent postoperative recurrence of Crohn's disease: a controlled randomized trial. Gastroenterology. 2008;135(4):1123–9.

Dharmaraj R, Dasgupta M, Simpson P, Noe J. Predictors of Pouchitis After Ileal Pouch-Anal Anastomosis in Children. J Pediatr Gastroenterol Nutr. 2016;63(4):e58–62.

Diamond IR, Gerstle JT, Kim PC, Langer JC. Outcomes after laparoscopic surgery in children with inflammatory bowel disease. Surg Endosc. 2010;24(11):2796–802.

Duff S, Sagar PM, Rao M, Dolling S, Sprakes M, Hamlin PJ. Infliximab and surgical treatment of complex anal Crohn's disease. Colorectal Dis. 2012;14(8):972–6.

Fraser JD, Garey CL, Laituri CA, Sharp RJ, Ostlie DJ, St Peter SD. Outcomes of laparoscopic and open total colectomy in the pediatric population. J Laparoendosc Adv Surg Tech A. 2010;20(7):659–60.

Fumery M, Duricova D, Gower-Rousseau C, Annese V, Peyrin-Biroulet L, Lakatos PL. Review article: the natural history of paediatric-onset ulcerative colitis in population-based studies. Aliment Pharmacol Ther. 2016;43(3):346–55.

Iwańczak BM, Ryżko J, Jankowski P, Sładek M, Wasilewska A, Szczepanik M, et al. Induction and Maintenance Infliximab Therapy for the Treatment of Crohn's Disease with Perianal Fistulas in Children: Retrospective, Multicenter Study. Adv Clin Exp Med. 2016;25(3):523–30.

Kerur B, Machan JT, Shapiro JM, Cerezo CS, Markowitz J, Mack DR, et al. Biologics Delay Progression of Crohn's Disease, but Not Early Surgery, in Children. Clin Gastroenterol Hepatol. 2018;16(9):1467–73.

Mañosa M, Cabré E, Bernal I, Esteve M, Garcia-Planella E, Ricart E, et al. Addition of metronidazole to azathioprine for the prevention of postoperative recurrence of Crohn's disease: a randomized, double-blind, placebo-controlled trial. Inflamm Bowel Dis. 2013;19(9):1889–95.

Mao EJ, Hazlewood GS, Kaplan GG, Peyrin-Biroulet L, Ananthakrishnan AN. Systematic review with meta-analysis: comparative efficacy of immunosuppressants and biologics for reducing hospitalisation and surgery in Crohn's disease and ulcerative colitis. Aliment Pharmacol Ther. 2017;45(1):3–13.

Markel TA, Lou DC, Pfefferkorn M, Scherer LR 3rd, West K, Rouse T, et al. Steroids and poor nutrition are associated with infectious wound complications in children undergoing first stage procedures for ulcerative colitis. Surgery. 2008;144(4):540–5; discussion 545–7.

Maxwell EC, Dawany N, Baldassano RN, Mamula P, Mattei P, Albenberg L, et al. Diverting Ileostomy for the Treatment of Severe, Refractory, Pediatric Inflammatory Bowel Disease. J Pediatr Gastroenterol Nutr. 2017;65(3):299–305.

Nasir BS, Dozois EJ, Cima RR, Pemberton JH, Wolff BG, Sandborn WJ, et al. Perioperative anti-tumor necrosis factor therapy does not increase the rate of early postoperative complications in Crohn's disease. J Gastrointest Surg. 2010;14(12):1859–65; discussion 1865–6.

Peyrin-Biroulet L, Harmsen WS, Tremaine WJ, Zinsmeister AR, Sandborn WJ, Loftus EV Jr. Surgery in a population-based cohort of Crohn's disease from Olmsted County, Minnesota (1970–2004). Am J Gastroenterol. 2012;107(11):1693–701.

Regueiro M, Feagan BG, Zou B, Johanns J, Blank MA, Chevrier M, et al. Infliximab Reduces Endoscopic, but Not Clinical, Recurrence of Crohn's Disease After Ileocolonic Resection. Gastroenterology. 2016;150(7):1568–78.

Renna S, Cammà C, Modesto I, Cabibbo G, Scimeca D, Civitavecchia G, et al. Meta-analysis of the placebo rates of clinical relapse and severe endoscopic recurrence in postoperative Crohn's disease. Gastroenterology. 2008;135(5):1500–9.

Romano C, Syed S, Valenti S, Kugathasan S. Management of Acute Severe Colitis in Children With Ulcerative Colitis in the Biologics Era. Pediatrics. 2016;137(5). pii: e20151184. doi: 10.1542/peds.2015-1184.

Ruemmele FM, Veres G, Kolho KL, Griffiths A, Levine A, Escher JC, et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. J Crohns Colitis. 2014;8(10):1179–207.

Shannon A, Eng K, Kay M, Blanchard S, Wyllie R, Mahajan L, et al. Long-term follow up of ileal pouch anal anastomosis in a large cohort of pediatric and young adult patients with ulcerative colitis. J Pediatr Surg. 2016;51(7):1181–6.

Splawski JB, Pffefferkorn MD, Schaefer ME, Day AS, Soldes OS, et al. NASPGHAN Clinical Report on Postoperative Recurrence in Pediatric Crohn Disease. J Pediatr Gastroenterol Nutr. 2017;65(4):475–86.

Su JW, Ma JJ, Zhang HJ. Use of antibiotics in patients with Crohn's disease: a systematic review and meta-analysis. J Dig Dis. 2015;16(2):58–66.

Turner D, Levine A, Escher JC, Griffiths AM, Russell RK, Dignass A, et al. Management of pediatric ulcerative colitis: joint ECCO and ESPGHAN evidence-based consensus guidelines. J Pediatr Gastroenterol Nutr. 2012;55(3):340–61.

Turner D, Ruemmele FM, Orlanski-Meyer E, Griffiths AM, de Carpi JM, Bronsky J, et al. Management of Paediatric Ulcerative Colitis, Part 1: Ambulatory Care – An Evidence-based Guideline From European Crohn's and Colitis Organization and European Society of Paediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2018a;67(2):257–91.

Turner D, Ruemmele FM, Orlanski-Meyer E, Griffiths AM, de Carpi JM, Bronsky J, et al. Management of Paediatric Ulcerative Colitis, Part 2: Acute Severe Colitis – An Evidence-based Consensus Guideline From the European Crohn's and Colitis Organization and the European Society of Paediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2018b;67(2):292–310.

Van Assche G, Dignass A, Reinisch W, van der Woude CJ, Sturm A, De Vos M, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Special situations. J Crohns Colitis. 2010;4(1):63–101.

Vernier-Massouille G, Balde M, Salleron J, Turck D, Dupas JL, Mouterde O, et al. Natural history of pediatric Crohn's disease: a population-based cohort study. Gastroenterology. 2008;135(4):1106–13.

de Zeeuw S, Ahmed Ali U, Donders RA, Hueting WE, Keus F, van Laarhoven CJ. Update of complications and functional outcome of the ileo-pouch anal anastomosis: overview of evidence and meta-analysis of 96 observational studies. Int J Colorectal Dis. 2012;27(7):843–53.

de Zoeten EF, Pasternak BA, Mattei P, Kramer RE, Kader HA. Diagnosis and treatment of perianal Crohn disease: NASPGHAN clinical report and consensus statement. J Pediatr Gastroenterol Nutr. 2013;57(3):401–12.

11. Nutrition and dietary therapy

Axel Enninger

Nutrition and the gut are closely intertwined. As a consequence, both parents and physicians are quick to raise questions about whether dietary changes or special diets are advisable whenever confronted by a child with a gut disorder.

It is generally recommended that patients with Crohn's disease (CD) and ulcerative colitis (UC) consume the same normal, healthy balanced diet as is recommended for all other children and adolescents. A balanced diet means eating regular fruits and vegetables while limiting the intake of sugary foods and beverages. While a vegetarian diet is theoretically feasible, patients with inflammatory bowel disease (IBD) need to be constantly monitored for signs of iron deficiency, which must be treated if discovered [Shah et al. 2015].

However, a non-trivial segment of patients do not tolerate specific foods and experience negative effects after eating them. This can be thought of as "IBS in IBD", meaning IBD patients with elements of irritable bowel syndrome. These trigger foods are frequently items which cause severe flatulence, but may also include very spicy foods and even large amounts of whole grain products for some patients. Patients with small bowel CD also frequently exhibit secondary lactose malabsorption.

All patients should also generally eat normal levels of fiber in their diet, although patients with stenoses must take care not to ingest too much fiber. For these patients, it is recommended that patients talk with their physician and a nutritional specialist about the possibility of excluding specific foods in order to avoid triggering negative symptoms. When communicating dietary restrictions to patients, it must always be kept in mind that the primary objective of these modifications is the alleviation of symptoms, not treatment of the underlying disease.

A special option for CD patients is **enteral nutrition**, which is particularly highly effective in newly diagnosed patients regardless of disease localization. Enteral nutrition is the standard treatment for newly diagnosed CD, and has now been incorporated into the current ECCO (European Crohn's and Colitis Organisation) guideline [Ruemmele et al. 2014]. In practice, enteral nutrition involves the patient consuming a special liquid-only diet for a fixed period, typically 6-8-10 weeks. This is frequently practical for patients who

are well-motivated and through the use of aroma supplements but without the need for a nasogastric tube or percutaneous endoscopic gastrostomy. In other words, the patient does not eat "normal" foods or drink any beverages other than water during this period. Enteral nutrition has the dual benefits of effectively treating inflammatory activity while simultaneously compensating for micronutrient deficiencies. This is particularly important in adolescent CD patients since nutritional status impacts linear growth at this age [Lee et al. 2010]. Nutritional therapy thus also represents an effective treatment of potential growth retardation. Although the literature frequently mentions difficulties with patient resistance to enteral nutrition, these issues can typically be easily overcome and patients can be convinced to adhere to this therapy if the entire treatment team is also well-motivated. However, this treatment is not effective for UC [Turner et al. 2012].

Once the initially set time period is complete, a normal diet is gradually resumed. This diet must also adhere to the principles listed above: a healthy, balanced diet that accommodates individual food intolerances.

Partial enteral nutrition may also be useful as an adjunct measure for maintaining remission, for example by providing one-quarter of caloric requirements by enteral nutrition [Wilschanski et al. 1996].

But if health is supposed to start in the gut, why not alter diets after all?

There is no question that a healthy diet is key for managing or preventing many diseases. It is thus no surprise that many patients perceive a need to alter their diet at the onset of a bowel disorder from their previous diet in order to "do something good" for their gastrointestinal tract. While this sentiment is quite understandable, to date there is still no validated and sensible "diet" that can be recommended to all patients. Research is presently ongoing, especially in Israel (in the group of A. Levine) on the subject of changes to our normal diet involving the exclusion of a number of products [Sigall-Boneh et al. 2014]. However, reliable and conclusive results have yet to be delivered [Shah et al. 2015]. For this reason, the current opinion of the ESPGHAN (European Society for Paediatric Gastroenterology, Hepatology and Nutrition) discourages attempts at untargeted diets, as expressed in a summary published in 2018 [Miele et al. 2018]. This opinion is based on the facts that a) this effect has not been proven, and b) the burden on patients' daily lives is already great enough

thanks to the need to adapt to the new disease and the likely need to regularly take new medications that it would be counterproductive to further burden these patients with unnecessary "diets". After all, eating is an aspect of daily pleasure and quality of life. It is wise to have a certain degree of sensitivity to this topic when dealing with patients with chronic diseases, and to only recommend measures which have actually proven effective and which do not negatively impact patients' daily lives and quality of life.

Are vitamin products or other dietary supplements necessary or advisable?

Our primary goal should be to ensure that all patients can meet their requirements for energy, vitamins, and trace elements from their normal diet. However, it may sometimes be necessary to provide targeted supplements, such as vitamin D or iron, which should first be identified by appropriate laboratory testing and then discussed with the patient. There is no need for wide-ranging vitamin supplementation. Patients with significant iron deficiency often require parenteral iron supplementation, which is now highly effective and can be administered with few side effects.

Partial enteral nutrition using, for example, 500 ml per day to maintain remission following induction of remission is another measure which is often helpful for patients with micronutrient deficiencies combined with residual disease activity (or as a measure to prevent relapse).

Literature

Lee JJ, Escher JC, Shuman MJ, Forbes PW, Delemarre LC, Harr BW, et al. Final adult height of children with inflammatory bowel disease is predicted by parental height and patient minimum height Z-score. Inflamm Bowel Dis. 2010;16(10):1669–77.

Miele E, Shamir R, Aloi M, Assa A, Braegger C, Bronsky J, et al. Nutrition in Pediatric Inflammatory Bowel Disease: A Position Paper on Behalf of the Porto Inflammatory Bowel Disease Group of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2018;66(4):687–708.

Ruemmele FM, Veres G, Kolho KL, Griffiths A, Levine A, Escher JC, et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. J Crohns Colitis. 2014;8(10):1179–207.

Shah ND, Parian AM, Mullin GE, Limketkai BN. Oral Diets and Nutrition Support for Inflammatory Bowel Disease: What Is the Evidence? Nutr Clin Pract. 2015;30(4):462–73.

Sigall-Boneh R, Pfeffer-Gik T, Segal I, Zangen T, Boaz M, Levine A. Partial enteral nutrition with a Crohn's disease exclusion diet is effective for induction of remission in children and young adults with Crohn's disease. Inflamm Bowel Dis. 2014;20(8):1353–60.

Turner D, Levine A, Escher JC, Griffiths AM, Russell RK, Dignass A, et al. Management of pediatric ulcerative colitis: joint ECCO and ESPGHAN evidence-based consensus guidelines. J Pediatr Gastroenterol Nutr. 2012;55(3):340–61.

Wilschanski M, Sherman P, Pencharz P, Davis L, Corey M, Griffiths A. Supplementary enteral nutrition maintains remission in paediatric Crohn's disease. Gut. 1996;38(4):543–8.

12. Complementary and alternative medicine for IBD

Martin Classen

Definition of complementary and alternative medicine (CAM)

There is no universal or harmonized definition for the term complementary medicine; rather, it is used to cover a wide range of therapeutic methods and practices. One common definition used in the United States describes complementary medicine as "a diverse group of medical and health systems, practices, and products that are currently not considered to be part of conventional medicine". The term "*Alternativmedizin*" is frequently used in Germany to describe methods used in place of conventional medicine. Some of these procedures are credited with accounting for psychological, spiritual, and social aspects and not only dealing with somatic symptoms [Zezos & Nguyen 2017].

Whether dietary interventions such as omega-3 fatty acids, curcumin, or probiotic therapies should be classified as complementary methods is a topic of debate, as these approaches are also being increasingly evaluated and even applied by scientific medicine when they prove effective [Langhorst et al. 2015]. One objective of many CAM techniques is to directly or indirectly influence the microbiota, which is by all means a sensible approach [Basson et al. 2017].

Motivation for families

The knowledge that inflammatory bowel disease (IBD) is generally incurable and that medications such as immunosuppressants or biologics may be necessary (as well as the associated risks which must be explained) provides an impetus for many families to seek other "gentler" methods of therapy. Internet research often leads to a number of different methods and providers, and families frequently find it difficult to evaluate these techniques. It has therefore proven helpful to touch upon the topic of complementary medicine as early as the discussions surrounding the initial diagnosis, and to provide families the opportunity to talk openly about different procedures and experiences. This candor makes it easier to hold constructive discussions later about whether specific procedures might be useless or utterly worthless for their child's unique situation. Pediatric gastroenterologists should be familiar with studies on this topic and be able to discuss the pros and cons of these techniques [Cheifetz et al. 2017].

Frequency of CAM use

Studies on the frequency of use of complementary medicine for pediatric IBD have reported frequencies between 6.7% and 72% depending on the country [Day 2013, Heuschkel et al. 2002, Wong et al. 2009]. Many families try out two to three methods in parallel. The most common therapies used were probiotics, fish oil, herbs (aloe vera, evening primrose oil, Boswellia serrata), vitamin formulations, and trace elements.

Homeopathic measures are in great supply in Germany in particular, as are traditional Chinese medicine (TCM), craniosacral therapy, osteopathy, and many others [Langhorst et al. 2015]. Quality of life was worse in adult IBD patients who used CAM compared with those who did not [Opheim et al. 2016].

Inclusion of CAM in an "integrated" treatment approach

Only 26% of patients/parents notify their primary care physicians that they are using CAM. Users of CAM have a tendency to discontinue their conventional therapies. However, it is perfectly feasible to combine some of the methods offered by CAM proponents (such as dietary modifications, probiotics, dietary supplements) with the treatment methods of conventional methods, or to integrate them into the overall therapeutic strategy. Probiotics, micronutrients, vitamins, and other topics are all discussed as options in other chapters of this booklet. Keeping an open mind and open communication about the techniques of CAM may indeed prove beneficial for the therapeutic relationship with the family.

However, the use of CAM may not cause effective medical treatments to be interrupted or discontinued, as has been observed in a study among CAM users [Nguyen et al. 2016].

Data on the effectiveness of CAM

Despite the widespread use of CAM, only 12% of parents report that it was effective. There are no prospective studies which have investigated individual CAM practices or products in children with IBD, including their risks and side effects.

The data is somewhat better for adults, for whom recommendations exist for Plantago ovata, curcumin, acupuncture, and multimodal, complementary mind-body therapy [Langhorst et al. 2015]. One institute in Germany focuses on the scientific study of the use of CAM

in adults. The DGVS commented as follows: "An integrative approach in which conventional and complementary treatment methods coalesce into best practices is the ideal objective."

CAM as a bridge to psychotherapy, mindfulness, and stress reduction

In light of the negative image of using psychotherapeutic interventions to process the burden and stress of illness, adopting the label of "complementary medicine" may lower the threshold for the acceptance of interventions such as yoga, relaxation therapy, and hypnotherapy. However, no prospective interventions on this topic are known.

Conclusion

There is currently no method among the large number of CAM techniques which has been demonstrated to be sufficiently safe and effective in pediatric patients. A number of interventions, such as acupuncture, homeopathy, or hypnotherapy, appear to be relatively harmless in terms of side effects and may prove useful as a bridge to improved mindfulness and increased body awareness.

In our own experience, actively addressing and openly discussing these topics with families is often helpful. In routine practice, about half of all families can be expected to try out CAM or even utilize it on a long-term basis. However, CAM therapies may never lead to the discontinuation of effective therapies or cause families to experience financial difficulties due to the additional expenses incurred.

Literature

Basson AR, Lam M, Cominelli F. Complementary and Alternative Medicine Strategies for Therapeutic Gut Microbiota Modulation in Inflammatory Bowel Disease and their Next-Generation Approaches. Gastroenterol Clin North Am. 2017;46(4):689–729.

Cheifetz AS, Gianotti R, Luber R, Gibson PR. Complementary and Alternative Medicines Used by Patients With Inflammatory Bowel Diseases. Gastroenterology. 2017;152(2):415–29.e15.

Day AS. A review of the use of complementary and alternative medicines by children with inflammatory bowel disease. Front Pediatr. 2013;1:9.

Heuschkel R, Afzal N, Wuerth A, Zurakowski D, Leichtner A, Kemper K, et al. Complementary medicine use in children and young adults with inflammatory bowel disease. Am J Gastroenterol. 2002;97(2):382–8.

Langhorst J, Wulfert H, Lauche R, Klose P, Cramer H, Dobos GJ, et al. Systematic review of complementary and alternative medicine treatments in inflammatory bowel diseases. J Crohns Colitis. 2015;9(1):86–106.

Nguyen GC, Croitoru K, Silverberg MS, Steinhart AH, Weizman AV. Use of Complementary and Alternative Medicine for Inflammatory Bowel Disease Is Associated with Worse Adherence to Conventional Therapy: The COMPLIANT Study. Inflamm Bowel Dis. 2016;22(6):1412–7.

Opheim R, Lie Høivik M, Bernklev T, Jelsness-Jørgensen LP, Moum B. The Use of Complementary and Alternative Medicine among Patients with Inflammatory Bowel Disease Is Associated with Reduced Health-Related Quality of Life. Gastroenterol Res Pract. 2016;2016:6453657.

Wong AP, Clark AL, Garnett EA, Acree M, Cohen SA, Ferry GD, et al. Use of complementary medicine in pediatric patients with inflammatory bowel disease: results from a multicenter survey. J Pediatr Gastroenterol Nutr. 2009;48(1):55–60.

Zezos P, Nguyen GC. Use of Complementary and Alternative Medicine in Inflammatory Bowel Disease Around the World. Gastroenterol Clin North Am. 2017;46(4):679–88.

13. Immunization of children and adolescents with IBD

Carsten Posovszky

Vaccinations are an important topic in the care of pediatric patients with inflammatory bowel disease (IBD). These patients are frequently administered immunosuppressants (IS) for therapeutic purposes, and are thus often immunocompromised at ages when the immunization schedule calls for routine initial or booster immunizations [Heijstek et al. 2011, Niehues et al. 2017, Rubin et al. 2014, STIKO 2005]. Although several recommendations on immunization of patients with immunodeficiencies or IS already exist, uncertainties surrounding the implementation and responsibilities remain in clinical practice [Melmed 2012]. Studies have also shown that gastroenterologists are not sufficiently knowledgeable on immunizations [Wasan et al. 2011]. Their knowledge is especially lacking on the topic of live vaccines and the question of whether IS can be modified or interrupted for longer periods of time due to the risk of increasing disease activity.

Epidemiological aspects

Vaccinations represent the most important first-line measure to prevent severe infectious diseases, since many infected individuals are not aware that they are contagious and thus cannot take any post-exposure measures [Reiter & Rasch 2004]. By instilling immunity to a specific agent, vaccines prevent infection of the vaccinated person him- or herself, but also prevent the transmission of the infection to unprotected individuals through the mechanism of herd immunity.

The effectiveness of each vaccine differs, and it is not possible to immunize each child at the optimal time point due to infections, active underlying bowel disease, lack of information, or a refusal to be immunized [Reiter & Rasch 2004]. A study in German children revealed that vaccination rates vary greatly at school accession, from 15% for pneumococcal immunization to 96% for the first dose of the measles vaccine [Reiter 2012].

Immunization recommendations

In Germany, the Standing Committee on Vaccination (STIKO) at the Robert Koch Institute issues recommendations for initial immunization of children and for booster immunizations and elective immunizations (STIKO@rki-App) [STIKO 2017].

Similar interdisciplinary immunization recommendations are available for patients receiving immunosuppressant therapy from the STIKO [STIKO 2005], the Swiss Federal Vaccination Commission (EKIF) [BAG/EKIF 2014], the Austrian Society for Infectious Diseases and Tropical Medicine (ÖGIT) [Burgmann & Wenisch 2010], the Centers for Disease Control and Prevention (CDC) [Kroger et al. 2006] and the Infectious Disease Society of America (IDSA) [Rubin et al. 2014] in the United States, or from individual professional societies such as the European League Against Rheumatism (EULAR) [Heijstek et al. 2011, van Assen et al. 2011] or the European Crohn's and Colitis Organisation (ECCO) [Rahier et al. 2014], as well as age-specific recommendations for IBD patients [Sands et al. 2004].

Implementation of the immunization recommendations for patients and their close relatives should be the common objective of the patient's primary care physician, pediatrician, and IBD specialist [Melmed 2012, Rubin et al. 2014, STIKO 2017]. These practitioners must judge in collaboration whether each individual vaccination is indicated and also about the best time point in terms of the course of the disease and the patient's therapy. In general, if there is no conclusive recommendation for a vaccination in a specific disease situation, the instructions in the Summary of Product Characteristics can be used as a rational guide [Niehues et al. 2017, Rubin et al. 2014, Speth & Minden 2015].

Prevention of infection

Immunosuppressant therapy increases the patient's risk of severe infections, either generally or for specific pathogens depending on the target, duration, and dose of the drug [Rahier et al. 2014]. For example, increased rates of invasive pneumococcal infections have been reported for IBD patients receiving azathioprine [Kantsø et al. 2015]. Kindergartens, daycares, and schools represent the largest reservoirs for infection in society. Thus, in order to increase the safety and effectiveness of immunizations, risk stratification and infection prevention should be carried out for pediatric IBD patients prior to initiating IS therapy by completing routine immunizations and adding any elective immunizations which may be required.

Effects of immunosuppressants on the immune system and the immune response to vaccines

It is important to stratify the intensity of IS when planning immunizations of patients taking IS. This step helps gauge whether patients

are at a relevant risk of becoming infected by the virus in a live vaccine, predict the immunogenicity of the vaccine during the current phase of treatment, and decide whether to check the success of the vaccination. The STIKO, the German Society for Rheumatology (DGRh), the EULAR, and the IDSA have all provided expert recommendations on this topic [Rubin et al. 2014, Heijstek et al. 2011, Warnatz & Goldacker 2014].

Effectiveness of vaccinations during IS therapy

Both the type of IS and the intensity (dose) of the IS taken may impair the immune response to a vaccination. The data available on this topic is limited, partially contradictory, and varies by vaccine, immunosuppressant, and underlying disease. A large share of the initial data on live vaccines was collected from leukemia patients during a 2-week interruption of treatment [Levin 2008]. The outcome of vaccination must be tested on a case-by-case basis. It is highly recommended that titers be measured after vaccination for both live and inactivated vaccine in patients with novel IS, IS dose escalation, vaccines known to have uncertain efficacy (e.g. hepatitis B), and novel vaccines (e.g. meningococcal B vaccine). High-risk patients may be administered boosters for elective vaccinations for rapidly invasive infections by encapsulated bacteria such as pneumococci, meningococci, and *Haemophilus influenzae* type b (Hib) every 3–5 years or earlier based on vaccination titer results. The professional societies have not yet issued recommendations on this topic due to the lack of data and the wide heterogeneity among the group of immunosuppressants used.

Practical implementation of immunization recommendations

Patients' immunization status should be determined in clinical practice at the time of the first onset of IBD before any long-term immunosuppressant therapy is initiated, and this status should be updated at regular intervals over the course of the disease (Figure 13/1) [Rahier et al. 2014, Rufo et al. 2012].

The optimal approach for these patients is to complete the initial immunization for all childhood vaccines before initiating immunosuppressant therapy (Figure 13/2) [Rahier et al. 2014, Rubin et al. 2014, Sands et al. 2004, Schwerd & Koletzko 2017]. However, this goal is frequently not attained [Carrera et al. 2013]. This phenomenon was illustrated by a survey of pediatric gastroenterologists, of whom only 17% reported that they were able to implement the immuni-

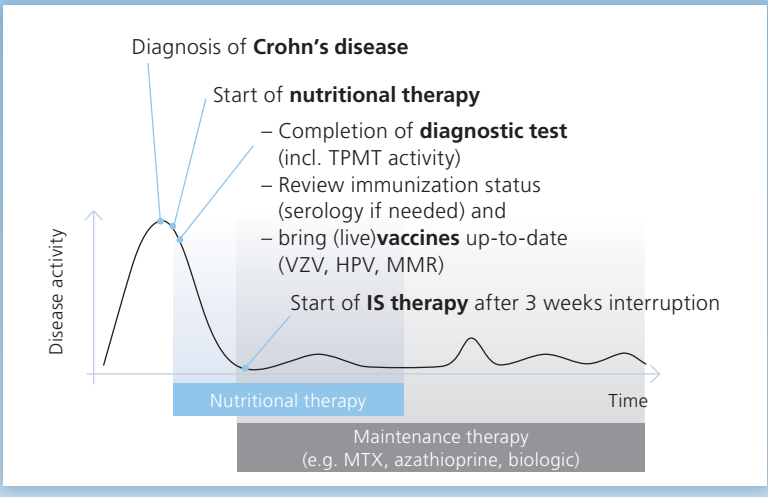


Figure 13/1: Procedure for initial diagnosis of IBD

Abbreviations: HPV = Human papilloma virus; MMR = Measles, mumps, rubella; MTX = Methotrexate; TPMT = Thiopurine methyltransferase; VZV = Varicella zoster virus (adapted from Schwerd & Koletzko 2017)

zation recommendations prior to the start of treatment for an estimated 50–75% of their patients, whereas 23% of the physicians surveyed did not perform any vaccinations prior to the start of treatment (own unpublished data). This inattention to vaccination is frequently due to the prioritization of controlling disease activity, which often requires timely immunosuppressant therapy.

This phenomenon initiates the dilemma observed in clinical practice of inadequately immunized, immunocompromised IBD patients who are at risk of infections but whose disease can often only be maintained in stable remission through long-term immunosuppressant therapy. Enteral nutrition of Crohn's disease (CD) is the only treatment option that can induce and maintain remission and provide a stable phase without IS, thereby allowing immunizations to be completed with no complications (Figure 13/2) [Rahier et al. 2014, Rufo & Bousvaros 2006].

Although numerous studies on inactivated vaccine immunization of IBD patients receiving IS generally report statistically decreased vaccination titers compared to healthy individuals [Carrera et al. 2013], the antibodies which are produced appear to provide adequate protection [Banaszkiewicz et al. 2017, Carrera et al. 2013]. If childhood immunizations are completed prior to the start of IS therapy, booster

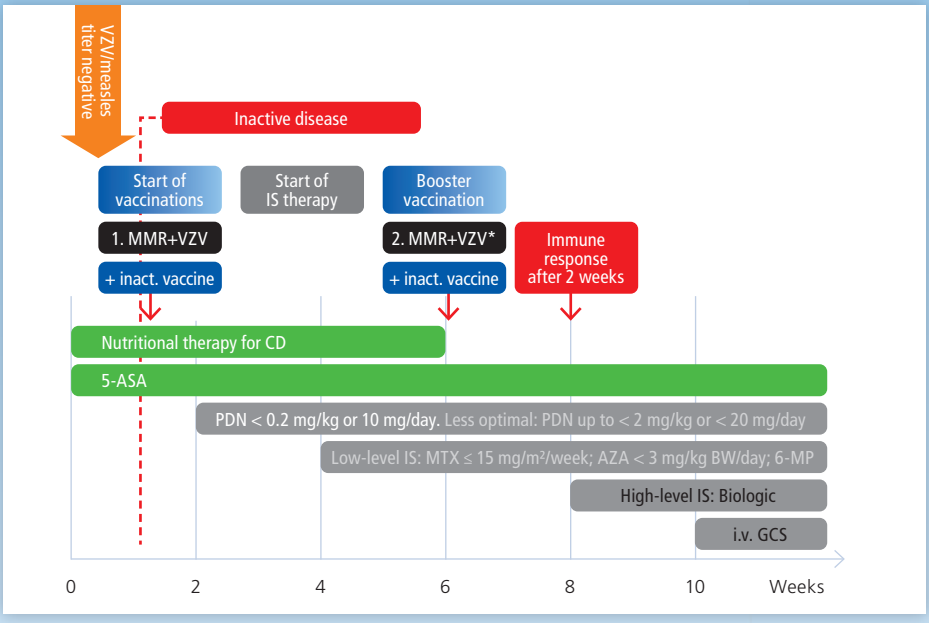


Figure 13/2: Suggested approach for vaccinating IBD patients at initial diagnosis

* Administer second dose of MMR and VZV vaccine separately for patients with IS due to product liability. Booster vaccinations of live vaccines are not approved for patients taking MTX, but are supported by study data and EULAR immunization recommendations for patients taking MTX < 15 mg/m²/week and low-dose GCS therapy [Heijstek et al. 2011]. Do not administer acetylsalicylic acid for 6 weeks after VZV vaccination. No study data is available on the tetravalent MMRV vaccine (source: adapted and modified from Schleker et al. 2016).

Abbreviations: 5-ASA = 5-Aminosalicylic acid; AZA = Azathioprine; i.v. GCS = Intravenous glucocorticosteroids; MMR = Measles, mumps, rubella; 6-MP = 6-Mercaptopurine; MTX = Methotrexate; PDN = Prednisolone; VZV = Varicella zoster virus

immunizations with inactivated vaccines can be particularly effective for patients with long-term immunosuppressant therapy. The effectiveness of booster immunizations with tetanus and diphtheria vaccines yielded comparable titers between healthy children and children post kidney transplant receiving IS therapy with cyclosporine A, tacrolimus, azathioprine, and prednisolone [Enke et al. 1997]. The question of how long these protective titers will persist remains unanswered. Children with very early-onset IBD represent an additional problem, as these patients have frequently not completed their childhood immunizations yet are exposed to a high risk of infection, and many of them almost certainly also harbor an immunodeficiency or immune dysregulation as part of their disease.

Furthermore, for patients taking biologics with long half-lives (such as infliximab), all immunizations with inactivated vaccines must be administered at the end of the cycle of the biologic prior to the planned start of the next cycle, and the start of the next cycle must be delayed by 1 week to allow enough time for an adequate immune response to the vaccine. An interval of 1 week after immunization before the first dose of rituximab therapy is also sufficient for the development of an immune response to the vaccine [Speth & Minden 2015]. Figure 13/3 shows the approach to planning immunizations with inactivated vaccines for patients with IS therapy.

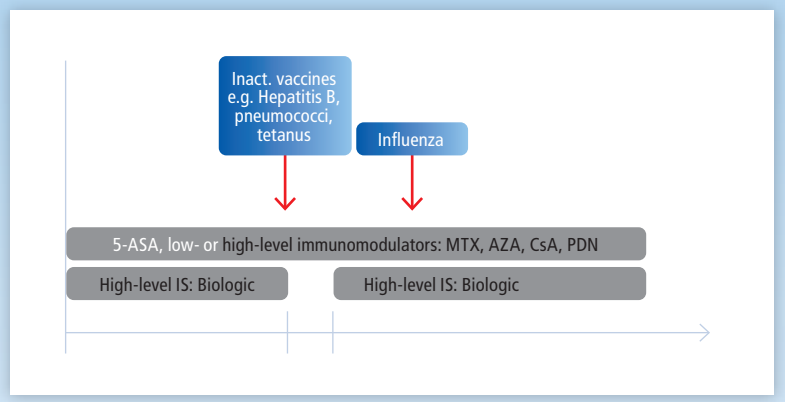


Figure 13/3: Planning administration of inactivated vaccines to IBD patients with various treatments

Catch-up and elective immunizations should be administered at least 7 days prior to B-cell depletion with rituximab (exception: inactivated influenza vaccine also possible after B-cell depletion), and an interval of about 1 week prior to the next dose should also be upheld for other biologics (source: adapted and modified from Schleker et al. 2016).

Abbreviations: 5-ASA = 5-Aminosalicylic acid; AZA = Azathioprine; CsA = Cyclosporine A; MTX = Methotrexate; PDN = Prednisolone

Live vaccines and IS therapy

Caution must be exercised when live vaccines are administered to patients taking IS therapy, as live vaccines do represent the greatest challenge for IBD patients [Niehues et al. 2017]. Although the official guidelines on this topic are worded clearly and recommend completing all live vaccines at least 2 weeks before starting IS therapy, they thus leave little room for individual variation [Rahier et al. 2014]. For example, the ECCO guideline requires interrupting immunosuppressants for 3 to 6 months prior to VZV vaccination [Rahier et al.

2014]. The primary objective of this measure is to safely prevent illness caused by the vaccine virus [Niehues et al. 2017]. Furthermore, live vaccines should also be administered during a remission phase. Unfortunately, this condition is often not achieved for years due to flares of inflammatory bowel disease, especially after discontinuing IS. This raises the question of what conditions would actually allow this group of patients to be immunized during immunosuppressant therapy given their elevated risk of infection. In rare cases, immunization with a live vaccine can be considered for selected patients with adequate immune function [Niehues et al. 2017]. The STIKO recommends that the extent of IS be taken into consideration when planning immunization with a live vaccine [Niehues et al. 2017].

The decision to immunize a patient with ongoing IS therapy with a live vaccine must be made cautiously on a case-by-case basis in line with the recommendations by EULAR, ACIP (Advisory Committee on Immunization Practices of the CDC), and STIKO, and must incorporate: 1. the individual risk and benefit of immunization by an experienced physician, 2. positive prior immunological testing, and 3. the patient's consent to waive product liability.

Postexposure prophylaxis

Should unvaccinated patients or incompletely vaccinated patients taking IS have contact to an index patient infected with MMRV (measles, mumps, rubella, or varicella), postexposure prophylaxis may be effective. This may take the form of a postexposure immunization or administration of immunoglobulins.

Literature

Banaszkiewicz A, Gawronska A, Klincewicz B, Kofla-Dłubacz A, Grzybowska-Chlebowczyk U, Toporowska-Kowalska E, et al. Immunogenicity of Pertussis Booster Vaccination in Children and Adolescents with Inflammatory Bowel Disease: A Controlled Study. Inflamm Bowel Dis. 2017;23(5):847–52.

Bundesamt für Gesundheit (BAG) und Eidgenössische Kommission für Impffragen (EKIF). Impfprinzipien und Empfehlungen für Personen mit autoimmun-entzündlichen rheumatischen Erkrankungen. Bulletin 8, 17. Februar 2014: S. 146–8.

Burgmann H, Wenisch C. Impfungen bei Immunschwäche & Immunsuppression. Österreichische Ärztezeitung (ÖAZ). 2010;Supplement.

Carrera E, Manzano R, Garrido E. Efficacy of the vaccination in inflammatory bowel disease. World J Gastroenterol. 2013;19(9):1349–53.

Enke BU, Bökenkamp A, Offner G, Bartmann P, Brodehl J. Response to diphtheria and tetanus booster vaccination in pediatric renal transplant recipients. Transplantation. 1997;64(2):237–41.

Heijstek MW, Ott de Bruin LM, Bijl M, Borrow R, van der Klis F, Koné-Paut I, et al. EULAR recommendations for vaccination in paediatric patients with rheumatic diseases. Ann Rheum Dis. 2011;70(10):1704–12.

Kantsø B, Simonsen J, Hoffmann S, Valentiner-Branth P, Petersen AM, Jess T. Inflammatory Bowel Disease Patients Are at Increased Risk of Invasive Pneumococcal Disease: A Nationwide Danish Cohort Study 1977–2013. Am J Gastroenterol. 2015;110(11):1582–7.

Kroger AT, Atkinson WL, Marcuse EK, Pickering LK; Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC). General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2006;55(RR-15):1–48.

Levin MJ. Varicella vaccination of immunocompromised children. J Infect Dis. 2008;197 Suppl 2:S200–6.

Melmed GY. Immunizations and IBD: whose responsibility is it? If I'm the prescribing doctor, shouldn't it be mine? Inflamm Bowel Dis. 2012;18(1):41–2.

Niehues T, Bogdan C, Hecht J, Mertens T, Wiese-Posselt M, Zepp F. Impfen bei Immundefizienz: Anwendungshinweise zu den von der Ständigen Impfkommission empfohlenen Impfungen (I) Grundlagenpapier. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2017;60(6):674–84.

Rahier JF, Magro F, Abreu C, Armuzzi A, Ben-Horin S, Chowers Y, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. J Crohns Colitis. 2014;8(6):443–68.

Reiter S. Impfquoten bei der Schuleingangsuntersuchung in Deutschland 2010. In: Robert Koch-Institut, Hrsg. Epidemiol Bull. 2012;16:135–42.

Reiter S, Rasch G. Schutzimpfungen. Gesundheitsberichtserstattung des Bundes: Heft 1: Robert Koch-Institut; 2004.

Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014;58(3):e44–100.

Rufo PA, Bousvaros A. Current therapy of inflammatory bowel disease in children. Paediatr Drugs. 2006;8(5):279–302.

Rufo PA, Denson LA, Sylvester FA, Szigethy E, Sathya P, Lu Y, et al. Health supervision in the management of children and adolescents with IBD: NASPGHAN recommendations. J Pediatr Gastroenterol Nutr. 2012;55(1):93–108.

Sands BE, Cuffari C, Katz J, Kugathasan S, Onken J, Vitek C, et al. Guidelines for immunizations in patients with inflammatory bowel disease. Inflamm Bowel Dis. 2004;10(5):677–92.

Schleker T, Speth F, Posovszky C. Impfen beim immunsupprimierten Kind. Pädiatrische Praxis. 2016;85(3):363–84.

Schwerd T, Koletzko S. Chronisch entzündliche Darmerkrankungen. Monatsschr Kinderheilkd. 2017;165(3):257–70.

Speth F, Minden K. Impfungen bei Kindern und Jugendlichen mit rheumatischen und muskuloskelettalen Erkrankungen. Hinweise für das Vorgehen im Alltag. Arthritis und Rheuma. 2015;35(1):44–55.

STIKO. Hinweise zu Impfungen für Patienten mit Immundefizienz (Sonderdruck). Epidemiol Bull. 2005.

STIKO. Empfehlungen der Ständigen Impfkommission (STIKO) am Robert Koch-Institut – 2017/2018. Epidemiol Bull. 2017;34:333–80.

van Assen S, Agmon-Levin N, Elkayam O, Cervera R, Doran MF, Dougados M, et al. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis. 2011;70(3):414–22.

Warnatz K, Goldacker S. Impfungen bei rheumatischen Erkrankungen. Aktuelle Empfehlungen der STIKO und der DGRh. Arthritis und Rheuma. 2014;34(3):140–9.

Wasan SK, Coukos JA, Farraye FA. Vaccinating the inflammatory bowel disease patient: deficiencies in gastroenterologists knowledge. Inflamm Bowel Dis. 2011;17(12):2536–40.

Author's note: This article is based on the manuscript by Schleker T, Speth F, Posovszky C. *Impfen beim immunsupprimierten Kind*. Pädiatrische Praxis. 2016;85(3):363–84.

14. Psychosocial aspects, support programs, and psychotherapy

Martin Classen

Psychosocial issues facing children and adolescents with IBD

Compared with healthy children, pediatric inflammatory bowel disease (IBD) patients have a greater risk of emotional and behavioral issues and difficulties interacting with their families [Mackner et al. 2004, Mackner et al. 2013].

Table 14/1 provides a list of common stress factors with IBD which may lead to psychological issues or psychiatric comorbidities.

These factors may greatly impair the psychosocial well-being of many patients (for example self-esteem, quality of life, educational and professional opportunities). Furthermore, insufficient adherence to and refusal of treatment are even larger issues when dealing with pubertal adolescents and young adults [Greenley et al. 2010b, Hommel et al. 2008].

Typical psychological stress factors in adolescents with IBD
Exhaustion
Eating a reduced variety of foods, reduced appetite, nausea
Difficulty sleeping
Conflicts over diet
Delayed onset of puberty, short stature/delayed growth
Frequent defecation and/or incontinence that hinders participation in academic or social activities
Side effects of corticosteroids (cosmetic, growth, weight gain, mood swings)
Social stigma due to special diet or stoma
Constant need to take medications; uncomfortable routes of application (e.g. enema)
Need for hospitalization and surgery
Shame/embarrassment/incontinence
Difficulties becoming personally independent
Worries about own future
Depression
Anxiety
Decreased self-esteem
Altered body image

Table 14/1

These psychological factors may also influence inflammatory activity and disease flares via effects on cytokines and mast cells mediated by the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system. Stress is a modulator of these processes. In theory, a bidirectional interaction can be postulated: On the one hand, psychological factors can play a role in modulating disease activity; while on the other hand, inflammation also affects a patient's psychological health [Mackner et al. 2011].

Quality of life

It would seem trivial to note that the quality of life of pediatric IBD patients depends first and foremost on their disease activity [Gray et al. 2011, Reed-Knight et al. 2016]. However, patients may also be burdened by stress from their parents, which also tends to increase with disease activity [Gray et al. 2013, Gray et al. 2015]. Other factors affecting quality of life are listed in Figure 14/1.

Consequently, in order to maintain the highest level of quality of life possible, practitioners should always strive to achieve optimal control of disease activity at all times and should not accept persistent inflammation. At the same time, mental health issues and psychological care must also be integrated into holistic treatment approaches.

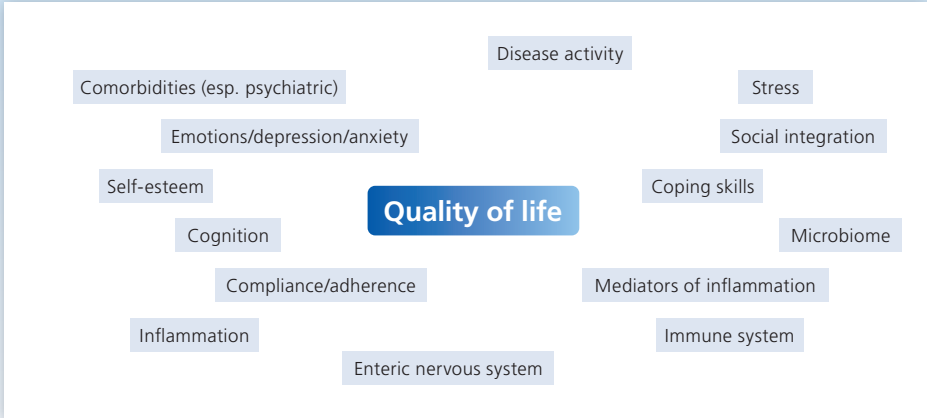


Figure 14/1: Factors affecting quality of life

Psychiatric comorbidities are common with IBD

One meta-analysis of 19 studies illustrated the entire spectrum of psychiatric comorbidities afflicting children and adolescents with IBD [Greenley et al. 2010a]. Several studies have reported that adolescent IBD patients have high rates of apparent depression (up to 25%) which vary by health status [Castaneda 2013, Clark et al. 2014, Reed-Knight et al. 2014, Szigethy et al. 2009]. Anxiety disorders also play a major role. In one study, 30% of pediatric patients with Crohn's disease (CD) reported increased anxiety, with the extent of the anxiety symptoms correlating with the intensity of the disease symptoms [Reigada et al. 2015]. Patients with higher anxiety scores had more flares than patients with lower levels of anxiety [Reigada et al. 2016].

The 2015 Heidelberg study also revealed a high prevalence of psychiatric comorbidities among IBD patients in Germany. This study in 47 adolescent IBD patients measured disease activity (PUCAI/PCDAI) and quality of life, and also included mental health evaluations of both parents and children by child and adolescent psychiatrists. Of these patients, 55.3% met the DSM-IV criteria for one or more psychiatric diagnoses(!) [Engelmann et al. 2015]. The additional burden of psychiatric comorbidities significantly reduces patients' quality of life.

Figure 14/2 lists neurobiological factors associated with depression in children with IBD.

Support programs for IBD

Support programs have been shown to improve patients' knowledge of their disease, coping, quality of life, and disease outcomes for a number of chronic diseases (including asthma, neurodermatitis, headaches, irritable bowel syndrome). In light of the issues with disease management and adherence among adolescents with IBD illustrated above, it makes sense to utilize such support programs for IBD as well. Studies have shown that there are large gaps in adolescents' understanding of their disease [Haaland et al. 2014]. There is also room for improvement of patients' knowledge during the transition process [Benchimol et al. 2011].

The typical objectives of support programs for IBD patients include:

– Establishing and promoting capable disease self-management
– Promoting self-responsibility, developing strengths and resources for handling the disease

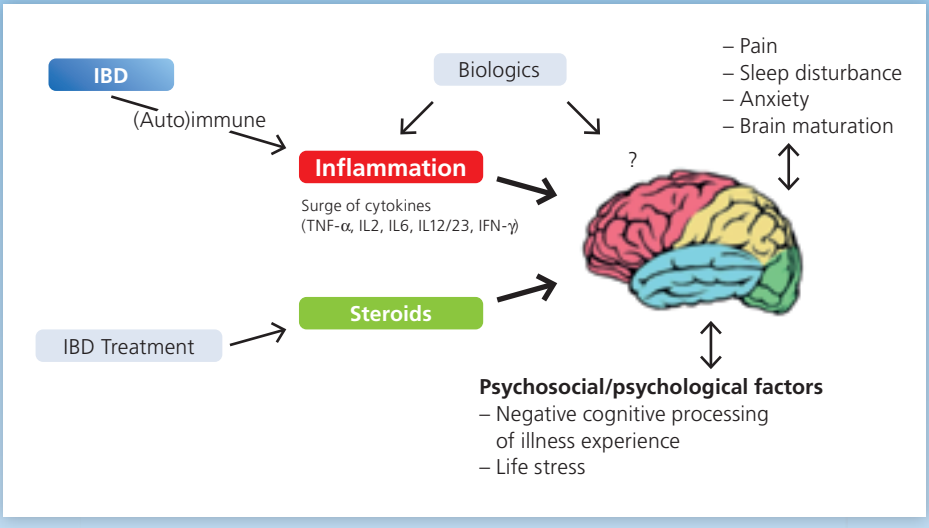


Figure 14/2: Neurobiological factors associated with depression in children with IBD (adapted from Keethy et al. 2014)

– Improving self-assessment
– Educating patients about CD and UC (pathophysiology and genetics, symptoms, outcomes and complications, medical and non-medical therapies)
– Educating patients about healthy eating and lifestyle habits
– Accepting the disease as a chronic condition with a variable course
– Reducing disease-related anxiety and providing emotional relief
– Instilling an appropriate body perception
– Empowering patients to manage disease-related stress
– Recognizing and avoiding stress factors that can jeopardize well-being
– Discussions with other patients
– Inclusion of parents/family (siblings!) in some of the topics listed above

These objectives can be subdivided into cognitive, behavioral and skills-based, emotional, and social objectives.

Interactions between participants and sharing personal experiences about the disease are a large segment of these support programs. These interactions also take place informally during group activities such as group games, sporting events, or filming self-made movies.

Topics and units in support programs (adapted from Classen et al. 2014)
Children – Getting acquainted – Role playing, imaginary journeys – Art therapy – Game nights – Physical activities/sporting events – Stress and stress management – Relaxation techniques – Medical education – Nutrition – Cooking together
Parents – Getting acquainted – Medical information – Nutrition – Sharing personal experiences – Art therapy

Table 14/2

According to evaluations of feedback forms, adolescents find these interactions to be a central aspect of the support programs. They provide participants with a lasting feeling of not being left alone with a difficult disease.

A study of participants in a summer camp in the United States for adolescents with IBD in which no medical information or specific educational content was provided revealed that the camp significantly improved participants' quality of life despite the fact that they had no changes in any specific parameters of disease activity [Plevinksy & Greenley 2014, Shepanski et al. 2005].

Studies on adult support programs have demonstrated mixed to no effects on disease activity or quality of life depending on the intervention and the type of program [Oxelmark et al. 2007]; while a small study in children showed a positive impact [Grootenhuis et al. 2009]. However, another study on the effectiveness of an adult program involving education and specific instructions for self-management demonstrated that hospitalizations were significantly decreased after 1 year and that patients' self-confidence at managing their disease was increased [Kennedy et al. 2004].

Educating children and adolescents with IBD about their disease may contribute to improvements in patients' quality of life, and may lead to long-term optimization of disease management, adherence, and

self-management. Support programs of this nature are offered at several hospitals in Germany [Classen et al. 2014].

Psychotherapy for IBD patients

Special attention must be paid to psychiatric comorbidities in children with IBD, both at the time of their diagnosis and over the course of the disease [Greenley et al. 2010a, Mackner et al. 2013, Rufo et al. 2012]. Ideally, this need would be met by routine involvement of psychological specialists both on inpatient wards and at outpatient facilities, but unfortunately there is currently no financial support for this option.

Consequently, pediatric gastroenterologists are the first line for the recognition of depression and anxiety disorders (and may be aided by the use of questionnaires) [Rufo et al. 2012]. Patients exhibiting any signs of these disorders must then be referred to the appropriate psychotherapeutic interventions (reviewed in Eccleston et al. 2014).

Several studies have investigated the use of cognitive behavioral therapy methods for the treatment of depression and anxiety [Keethy et al. 2014, Szigethy et al. 2014]. In addition to improving patients' psychiatric disorders, these interventions also frequently improve their quality of life and disease activity as well. Very little evidence is available on the use of antidepressant pharmacotherapy in IBD patients, although some exists for fluoxetine and sertraline for depression and venlafaxine for anxiety disorders [Mackner et al. 2013]. Potential interactions between IBD medications and the gastrointestinal side effects of psychiatric medications must be taken into consideration for patients on medical therapy. Child and adolescent psychiatrists should be contacted on topics of psychotherapy and psychiatric medications.

Conclusion

In conclusion, the intricate bidirectional interactions between the mind and the gut require routine psychological care, low-threshold supportive measures such as support programs, and collaboration with psychiatric specialists at all pediatric gastroenterology treatment centers. However, all of these measures are impossible without proper funding.

Literature

Benchimol EI, Walters TD, Kaufman M, Frost K, Fiedler K, Chinea Z, et al. Assessment of knowledge in adolescents with inflammatory bowel disease using a novel transition tool. Inflamm Bowel Dis. 2011;17(5):1131–7.

Castaneda AE, Tuulio-Henriksson A, Aronen ET, Marttunen M, Kolho KL. Cognitive functioning and depressive symptoms in adolescents with inflammatory bowel disease. World J Gastroenterol. 2013;19(10):1611–7.

Clark JG, Srinath AI, Youk AO, Kirshner MA, McCarthy FN, Keljo DJ, et al. Predictors of depression in youth with Crohn disease. J Pediatr Gastroenterol Nutr. 2014;58(5):569–73.

Claßen M, Kretzschmar B, Kretzschmar A, Kunert D, Faiß M, Iven E. Schulung für Kinder und Jugendliche mit chronisch entzündlichen Darmerkrankungen. Lengerich: Papst Science Publishers; 2014.

Eccleston C, Palermo TM, Williams AC, Lewandowski Holley A, Morley S, Fisher E, et al. Psychological therapies for the management of chronic and recurrent pain in children and adolescents. Cochrane Database Syst Rev. 2014;(5):CD003968.

Engelmann G, Erhard D, Petersen M, Parzer P, Schlarb AA, Resch F, et al. Health-related quality of life in adolescents with inflammatory bowel disease depends on disease activity and psychiatric comorbidity. Child Psychiatry Hum Dev. 2015;46(2):300–7.

Gray WN, Denson LA, Baldassano RN, Hommel KA. Disease activity, behavioral dysfunction, and health-related quality of life in adolescents with inflammatory bowel disease. Inflamm Bowel Dis. 2011;17(7):1581–6.

Gray WN, Graef DM, Schuman SS, Janicke DM, Hommel KA. Parenting stress in pediatric IBD: relations with child psychopathology, family functioning, and disease severity. J Dev Behav Pediatr. 2013;34(4):237–44.

Gray WN, Resmini AR, Baker KD, Holbrook E, Morgan PJ, Ryan J, et al. Concerns, Barriers, and Recommendations to Improve Transition from Pediatric to Adult IBD Care: Perspectives of Patients, Parents, and Health Professionals. Inflamm Bowel Dis. 2015;21(7):1641–51.

Greenley RN, Hommel KA, Nebel J, Raboin T, Li SH, Simpson P, et al. A meta-analytic review of the psychosocial adjustment of youth with inflammatory bowel disease. J Pediatr Psychol. 2010a;35(8):857–69.

Greenley RN, Stephens M, Doughty A, Raboin T, Kugathasan S. Barriers to adherence among adolescents with inflammatory bowel disease. Inflamm Bowel Dis. 2010b;16(1):36–41.

Grootenhuis MA, Maurice-Stam H, Derkx BH, Last BF. Evaluation of a psychoeducational intervention for adolescents with inflammatory bowel disease. Eur J Gastroenterol Hepatol. 2009;21(4):430–5.

Haaland D, Day AS, Otley A. Development and validation of a pediatric IBD knowledge inventory device: the IBD-KID. J Pediatr Gastroenterol Nutr. 2014;58(3):313–9.

Hommel KA, Denson LA, Crandall WV, Mackner LM. Behavioral Functioning and Treatment Adherence in Pediatric Inflammatory Bowel Disease: Review and Recommendations for Practice. Gastroenterol Hepatol (NY). 2008;4(11):785.

Keethy D, Mrakotsky C, Szigethy E. Pediatric inflammatory bowel disease and depression: treatment implications. Curr Opin Pediatr. 2014;26(5):561–7.

Kennedy AP, Nelson E, Reeves D, Richardson G, Roberts C, Robinson A, et al. A randomised controlled trial to assess the effectiveness and cost of a patient orientated self management approach to chronic inflammatory bowel disease. Gut. 2004;53(11):1639–45.

Mackner LM, Sisson DP, Crandall WV. Review: psychosocial issues in pediatric inflammatory bowel disease. J Pediatr Psychol. 2004;29(4):243–57.

Mackner LM, Clough-Paabo E, Pajer K, Lourie A, Crandall WV. Psychoneuroimmunologic factors in inflammatory bowel disease. Inflamm Bowel Dis. 2011;17(3):849–57.

Mackner LM, Greenley RN, Szigethy E, Herzer M, Deer K, Hommel KA. Psychosocial issues in pediatric inflammatory bowel disease: report of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr. 2013;56(4):449–58.

Oxelmark L, Magnusson A, Löfberg R, Hillerås P. Group-based intervention program in inflammatory bowel disease patients: effects on quality of life. Inflamm Bowel Dis. 2007;13(2):182–90.

Plevinsky JM, Greenley RN. Exploring health-related quality of life and social functioning in adolescents with inflammatory bowel diseases after attending camp oasis and participating in a Facebook group. Inflamm Bowel Dis. 2014;20(9):1611–7.

Reed-Knight B, Lobato D, Hagin S, McQuaid EL, Seifer R, Kopel SJ, et al. Depressive symptoms in youth with inflammatory bowel disease compared with a community sample. Inflamm Bowel Dis. 2014;20(4):614–21.

Reed-Knight B, Lee JL, Greenley RN, Lewis JD, Blount RL. Disease Activity Does Not Explain It All: How Internalizing Symptoms and Caregiver Depressive Symptoms Relate to Health-related Quality of Life Among Youth with Inflammatory Bowel Disease. Inflamm Bowel Dis. 2016;22(4):963–7.

Reigada LC, Hoogendoorn CJ, Walsh LC, Lai J, Szigethy E, Cohen BH, et al. Anxiety symptoms and disease severity in children and adolescents with Crohn disease. J Pediatr Gastroenterol Nutr. 2015;60(1):30–5.

Reigada LC, Satpute A, Hoogendoorn CJ, Cohen BH, Lai J, Bao R, et al. Patient-reported Anxiety: A Possible Predictor of Pediatric Inflammatory Bowel Disease Health Care Use. Inflamm Bowel Dis. 2016;22(9):2127–33.

Rufo PA, Denson LA, Sylvester FA, Szigethy E, Sathya P, Lu Y, et al. Health supervision in the management of children and adolescents with IBD: NASPGHAN recommendations. J Pediatr Gastroenterol Nutr. 2012;55(1):93–108.

Shepanski MA, Hurd LB, Culton K, Markowitz JE, Mamula P, Baldassano RN. Health-related quality of life improves in children and adolescents with inflammatory bowel disease after attending a camp sponsored by the Crohn's and Colitis Foundation of America. Inflamm Bowel Dis. 2005;11(2):164–70.

Szigethy E, Craig AE, Iobst EA, Grand RJ, Keljo D, DeMaso D, Noll R. Profile of depression in adolescents with inflammatory bowel disease: implications for treatment. Inflamm Bowel Dis. 2009;15(1):69–74.

Szigethy E, Bujoreanu SI, Youk AO, Weisz J, Benhayon D, Fairclough D, et al. Randomized efficacy trial of two psychotherapies for depression in youth with inflammatory bowel disease. J Am Acad Child Adolesc Psychiatry. 2014;53(7):726–35.

15. Growth and puberty

Burkhard Rodeck

About 25% of cases of inflammatory bowel disease (IBD) have a pediatric onset, the majority of which are diagnosed shortly before or during puberty. The onset of puberty ranges between the ages of 8 to 14 in girls and 9 to 14 in boys. IBD interferes with normal weight changes and delays normal growth and puberty, and its impacts may be particularly noticeable during pubertal growth spurts. These impacts are more relevant for patients with Crohn's disease (CD) and less so for those with ulcerative colitis (UC) [Gasparetto & Guariso 2014, Hill 2014]. Growth retardation is caused by malnutrition associated with the underlying IBD, but is also very likely due to the cytokine secretion associated with chronic inflammation [Wong et al. 2006].

Achieving normal growth and pubertal development is thus a primary objective in the management of IBD.

In addition to measuring height and weight, growth velocity is the most useful parameter for evaluating growth patterns. Patients' pubertal development should be classified by Tanner stage, and their height, weight, body mass index, and puberty stage should be documented at regular intervals. Other anthropometric measurements such as skinfold testing or circumference are additional options for assessing normal development. Potential lags in bone age can be evaluated by X-ray imaging of the left hand.

Epidemiology

Reduced growth velocity has been reported in up to 46% of CD patients, in many cases even before the onset of gastrointestinal symptoms [Kanof et al. 1988]. Approximately 11–35% of adult CD patients with pediatric onset have a shorter height compared with their parental height [Lee et al. 2010]. These effects are much less pronounced in UC, likely due to the shorter phase of diagnostic latency as well as the shorter periods of systemic inflammatory activity.

Pathophysiology

It has been shown in a rat model of colitis that inflammatory activity is responsible for 30–40% of growth retardation regardless of dietary supplementation [Ballinger 2002]. Ballinger found a negative correlation between the plasma concentrations of growth hormones and

levels of insulin-like growth factor (IGF-1), which suggests that inflammation renders hepatocytes resistant to growth hormone stimulation. In other animal models, the high levels of proinflammatory cytokines such as interleukin (IL)6 were correlated with low levels of IGF-1 secretion. In addition to the direct effects of inflammation on the hypothalamic-pituitary-growth axis, tumor necrosis factor (TNF)-α can also apparently lead to growth retardation via other pathways. TNF-α blocker therapy had a positive effect on the growth rate in rats despite having no effects on IGF-1 secretion [Ezri et al. 2012].

A further cause of growth retardation in many patients is malnutrition, which can be driven by numerous factors such as loss of appetite, abdominal pain, reduced nutrient uptake, increased nutrient loss, and high energy consumption due to chronic inflammation.

Proinflammatory cytokines such as IL1 or TNF-α inhibit the production of sexual hormones via direct effects on the gonads or by suppressing the secretion of GnRH (gonadotropin-releasing hormone). Leptin controls the onset of puberty, and hence reduced leptin levels secondary to anorexia with reduced body fat percentage may be an additional cause of delayed puberty.

Treatment of IBD

The objective of treatment is to control and, in the best-case scenario, reverse the inflammatory activity of IBD, ideally with mucosal healing. Several different treatment options are available for this task, including corticosteroid therapy. Although long-term or repeated hydrocortisone therapy increases appetite, it also leads to additional growth retardation. Therefore, corticosteroid treatment should be avoided in children and adolescents with IBD to the greatest extent possible. Nutritional therapy is a good alternative. In addition to other parameters (laboratory tests, etc.), normal physical development is a sign that the disease is being controlled well.

Specific hormonal treatment of delayed puberty (e.g. testosterone for boys or estradiol for girls) is required only in very rare cases, and growth hormone therapy is also not a standard option for IBD.

It is absolutely crucial that treatment of IBD be continuously modified to ensure that the chronic inflammation is being controlled well, which will allow growth and puberty to proceed normally.

Literature

Ballinger A. Fundamental mechanisms of growth failure in inflammatory bowel disease. Horm Res. 2002;58 Suppl 1:7–10.

Ezri J, Marques-Vidal P, Nydegger A. Impact of disease and treatments on growth and puberty of pediatric patients with inflammatory bowel disease. Digestion. 2012;85(4):308–19.

Gasparetto M, Guariso G. Crohn's disease and growth deficiency in children and adolescents. World J Gastroenterol. 2014;20(37):13219–33.

Hill RJ. Update on nutritional status, body composition and growth in paediatric inflammatory bowel disease. World J Gastroenterol. 2014;20(12):3191–7.

Kanof ME, Lake AM, Bayless TM. Decreased height velocity in children and adolescents before the diagnosis of Crohn's disease. Gastroenterology. 1988;95(6):1523–7.

Lee JJ, Escher JC, Shuman MJ, Forbes PW, Delemarre LC, Harr BW, et al. Final adult height of children with inflammatory bowel disease is predicted by parental height and patient minimum height Z-score. Inflamm Bowel Dis. 2010;16(10):1669–77.

Wong SC, Macrae VE, McGrogan P, Ahmed SF. The role of pro-inflammatory cytokines in inflammatory bowel disease growth retardation. J Pediatr Gastroenterol Nutr. 2006;43(2):144–55.

16. Social aspects of IBD

Jan de Laffolie

Inflammatory bowel disease (IBD) is of major importance for pediatric patients, especially with regard to the crucial end points of physical and psychosocial development as well as to their later transition to a professional career. The typical course of IBD is characterized by symptomatic phases with flares of inflammatory activity and often-devastating complications interspersed with periods of remission [Louis et al. 2015].

Childhood and adolescence are vulnerable phases of life with regard to physical growth and to the developmental end points mentioned above. According to pre-examination, children with IBD cite dystrophy, weight loss, and delayed puberty as major symptoms which are important to them [Mallon & Suskind 2010, Vadan et al. 2011, Walters & Griffiths 2009].

The psychosocial challenges to patients and those around them posed by this chronic illness must be identified and attacked precisely. The patient's perception of his or her own disease, his or her coping strategies (and those of the parents), and targeted support are all important criteria for patients' personal psychosocial development, especially for patients with forms of the disease that are severe or at times unstable [Mackner et al. 2013].

Pediatric gastroenterology centers should be proactive about providing the patients they treat with **options for psychological care, psychotherapy, or even consultation-liaison (psychosomatic) options**, as these measures represent an integral component of IBD treatment. Such centers should provide different levels of options which can be implemented rapidly. For example, in some circumstances inpatient treatment options must be considered, such as a specific department or clinic for consultation-liaison (psychosomatic) psychiatry.

Health insurance companies should be contacted about arrangements for reimbursement of these services. Patient advocacy groups, such as the German Crohn's and Colitis Association (DCCV e.V.), often provide contact addresses and reviews of these services. Physicians should consult with the treatment team at such facilities, and should integrate a psychotherapy or consultation-liaison therapy visit into the patient's treatment strategy. Collaborations with providers and provider systems subject to different funding mechanisms (cross-

sector or integrated care) can require extra effort and interaction on the part of the treatment team. However, integrated psychotherapeutic care should not be considered to be distinct from disease activity or from the somatic aspect of the disease, as both elements interact with each other via positive and negative mechanisms. This phenomenon is reflected by the close link between disease severity and adherence to therapy [Hommel et al. 2011, Ingerski et al. 2010, Mackner et al. 2013].

In addition to psychological, psychotherapeutic, and consultation-liaison interventions, approaches involving **patient empowerment**, support and education of persons close to the patient, and meetings with other patients of the same age to share personal experiences may all prove beneficial [Crandall et al. 2012, Mackner et al. 2013]. These measures are currently being actively supported in GPGE projects such as CEDATA GPGE.

Problems at school are very common among IBD patients. In addition to lower academic performance and frequent absences, the (un)availability of appropriate toilets and sanitary facilities at schools also represents a real problem. Although IBD patients in Germany are authorized to use handicapped restrooms if they have a physician's certificate, the use of these facilities may still prove difficult (since the student needs to go to the teachers' room to retrieve the key and needs to supply their own toilet paper, etc.). This can lead to even more (and avoidable) absences from school.

Adolescents and young adults with IBD also face a number of crucial decisions regarding **occupational disability insurance and life insurance** at the start of their career. Patients with chronic diseases can typically only obtain policies with either considerable risk premiums or with exclusion clauses. Nonetheless, occupational disability coverage in particular is crucial due to the risk of unemployability prior to the age of eligibility for a pension. All options should be weighed carefully, and it may be helpful to consult with an independent broker to compare multiple offers.

The disease should not be the driving force behind the selection of **education and career**. However, patients should undergo a psychological evaluation, an examination by a specialist, and suitability testing for their chosen field and should include these factors together with their academic performance, desires, talents, and interests in the decision-making process. IBD specialists frequently advise

their patients that regular working hours can be beneficial, but tend to discourage them from taking jobs requiring shift work, frequent travel, or great physical exertion.

The **German Disabilities Act** (*Schwerbehindertengesetz*, SchwbG) provides protections for disabled workers. Although it mandates increased protection from dismissal, special vacation rules, and tax benefits, applying for disability status can have some drawbacks as well as benefits. Patients should take these into consideration, especially when applying for their first job.

Patients should be advised to seek out an experienced support center when deciding whether to apply for recognition of disability status under the German Disabilities Act, and all of the legal and psychosocial consequences this status brings. The document "*Anhaltspunkte für die ärztliche Gutachtertätigkeit*" ["Criteria for Medical Assessment"] for German social compensation law and for the German Disabilities Act which is published by the German Federal Ministry of Labor and Social Affairs provides some general guidelines for this application but is by no means exhaustive. Patients should be aware of the risks of making imprudent or uninformed decisions.

Free **consultation on social law issues** is often provided by municipal support centers for people with disabilities, the social service centers of health authorities, and most importantly social services embedded within a hospital's multidisciplinary treatment and consultation team.

The DCCV e.V. is another contact point for questions on occupational and social law, as well as being a **patient advocacy group**.

Literature

Crandall WV, Margolis PA, Kappelman MD, King EC, Pratt JM, Boyle BM, et al. Improved outcomes in a quality improvement collaborative for pediatric inflammatory bowel disease. Pediatrics. 2012;129(4):e1030–41.

Hommel KA, Denson LA, Baldassano RN. Oral medication adherence and disease severity in pediatric inflammatory bowel disease. Eur J Gastroenterol Hepatol. 2011;23(3):250–4.

Ingerski LM, Baldassano RN, Denson LA, Hommel KA. Barriers to oral medication adherence for adolescents with inflammatory bowel disease. J Pediatr Psychol. 2010;35(6):683–91.

Louis E, Dotan I, Ghosh S, Mlynarsky L, Reenaers C, Schreiber S. Optimising the Inflammatory Bowel Disease Unit to Improve Quality of Care: Expert Recommendations. J Crohns Colitis. 2015;9(8):685–91.

Mackner LM, Greenley RN, Szigethy E, Herzer M, Deer K, Hommel KA. Psychosocial issues in pediatric inflammatory bowel disease: report of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr. 2013;56(4):449–58.

Mallon DP, Suskind DL. Nutrition in pediatric inflammatory bowel disease. Nutr Clin Pract. 2010;25(4):335–9.

Vadan R, Gheorghe LS, Constantinescu A, Gheorghe C. The prevalence of malnutrition and the evolution of nutritional status in patients with moderate to severe forms of Crohn's disease treated with Infliximab. Clin Nutr. 2011;30(1):86–91.

Walters TD, Griffiths AM. Mechanisms of growth impairment in pediatric Crohn's disease. Nat Rev Gastroenterol Hepatol. 2009;6(9):513–23.

17. Transitioning IBD care

Burkhard Rodeck

Transition is a term used to describe the transfer of medical care from pediatric care to adult care. As with other chronic illnesses, the transition of care often results in inadequate adherence or even treatment discontinuation by patients with inflammatory bowel disease (IBD). These issues are due to basic problems with transferring the responsibility for disease evaluation, treatment guidance, and disease management from the parents to the patient during an especially sensitive phase of life which is characterized by departing from the family setting and increasing autonomy.

Adult physicians practice health care using a different style than pediatricians. Pediatric care embeds patients within a triangle together with their parents and the pediatrician, and pediatricians often take a more authoritative and educational tone. This frequently has the unintended consequence of withholding age-appropriate autonomy from the patient until a (too) late age. In contrast, an adult physician expects his or her patients to be autonomous, and conducts a bilateral relationship with the patient in which the patient is primarily responsible for the management of his or her condition. Parents are not welcome at these visits.

During the phase of late adolescence and early adulthood, patients take over not only responsibility for management of their illness from their parents, but also responsibility for their entire lives. These parents have frequently held their children's hands through all challenges in life up to that point, and may thus have difficulty letting go.

Physicians and physician groups often disagree on the need for guidance or supervision to facilitate a smooth transition from one phase of life to the next. For example, half of all adult gastroenterologists do not consider themselves to be competent on matters of pubertal development and growth [Hait et al. 2009]. On the other hand, an English review reported that 80% of pediatric gastroenterologists considered a structured transition program to be of great importance, compared with 47% of adult gastroenterologists [Sebastian et al. 2012]. Pediatricians have a tendency to want a very close, even family-like bond with their patients, which often results in their retaining care of these patients past the conclusion of puberty and their 18th birthday. Up to one-third of patients with diabetes mellitus

also remain in the care of their pediatrician up to or even past age 25 [Goodhand et al. 2011].

There are also other aspects which are unique to the IBD patient cohort.

Adult gastroenterologists should generally be very familiar with the disorders Crohn's disease (CD) and ulcerative colitis (UC), and hence they can be expected to be competent at managing adult cases of these disorders. However, there are also several unique characteristics of pediatric IBD – the phenotype of the disorders, their aggressiveness in adolescents, and in pediatric treatment strategies – of which adult physicians may not always be adequately informed. One example is the fact that nutritional therapy, not steroids, is the primary treatment for inducing remission of CD in pediatric medicine. Additionally, a stricter indication is required in pediatric medicine for invasive endoscopic diagnosis. In Germany, adolescents with IBD are typically treated in the pediatrics departments of special outpatient clinics affiliated with large hospitals or university medical centers. In these facilities, it is easy to incorporate "in-house" psychosocial teams or nutritional experts into a holistic treatment approach. A strategy of this nature is beyond the capabilities of most gastroenterologists in private practice due to the structure of statutory health insurance reimbursement in Germany.

IBD during adolescence is a non-normative life event that is unwanted and unexpected, and that invades the patient's life. It influences all of the patient's thoughts, actions, and feelings and has far-reaching consequences for his or her psychosocial development. However, due to the unique features of IBD (Table 17/1), patients' impairment is not only greater than that of their healthy same-age peers, but also greater than that of other adolescents with chronic diseases [Greenley et al. 2010].

The combination of debilitating gastrointestinal symptoms, corticosteroid therapies, and the release of centrally active proinflammatory cytokines reduces the quality of life of adolescent patients and increases their prevalence of psychological disorders, particularly depression, compared with their healthy same-age peers [Szigethy et al. 2009]. These factors make the holistic treatment approach described above, including psychosocial support, all the more important.

Transitioning can be viewed as a dynamic process that should ideally be discussed and integrated into the treatment strategy in late childhood. The actual transfer to an adult physician is but one component

Stress caused by external appearance: short stature, delayed puberty, side effects of corticosteroids (stretch marks, moon face, acne) and other extraintestinal manifestations and adverse drug reactions
Impact of inflammatory cytokines on appetite and mental health
Chronic or recurrent pain (abdominal pain, tenesmus, arthralgia)
Reduced resilience and mobility caused by malnutrition and episodes of diarrhea
Impact of absences at school, vocational education
Impaired sexual development and psychosocial development
Less establishment of autonomy and independence from parents
Frequent dissimulation
Difficulties with lack of understanding of disease among peer group or society in general

Table 17/1: IBD-specific stress factors in adolescence (adapted from Koletzko & Saldo 2012)

of this transition process. There is no set age at which adolescents must switch from a pediatrician to an adult physician; rather, the transfer should take place at the point in time at which all stakeholders are ready and have fulfilled their "tasks" listed in Figure 17/1 [Hait et al. 2006, Keller 2010].

A case manager can – and, in the case of patients with severe IBD, should – be commissioned with connecting the various providers and organizing the transition process within the framework of a structured transition program. This case manager can provide long-term support for the adolescent patient and the family, and can ensure that the transition is orderly with a seamless continuation of treatment [Muether et al. 2014]. This approach can help prevent interruptions in treatment or inadequate adherence to medications. The Berlin Transition Program is one example of this type of national, interdisciplinary transition program (http://www.drk-kliniken-berlin.de/westend/krankenhaus-westend/berliner-transitionsprogramm/). This is the program preferred by the Transition task force convened in 2012 by several major medical societies: the German Society of Pediatrics and Adolescent Medicine (DGKJ), the German Society for Internal Medicine (DGIM), and the German Society of Neurology (DGN).

Support using educational programs

Adolescents are initially educated about their condition by their pediatric gastroenterologist on a one-on-one basis as part of the usual physician-patient relationship. Patients and their parents are rarely able to absorb all of the information presented to them in the emo-

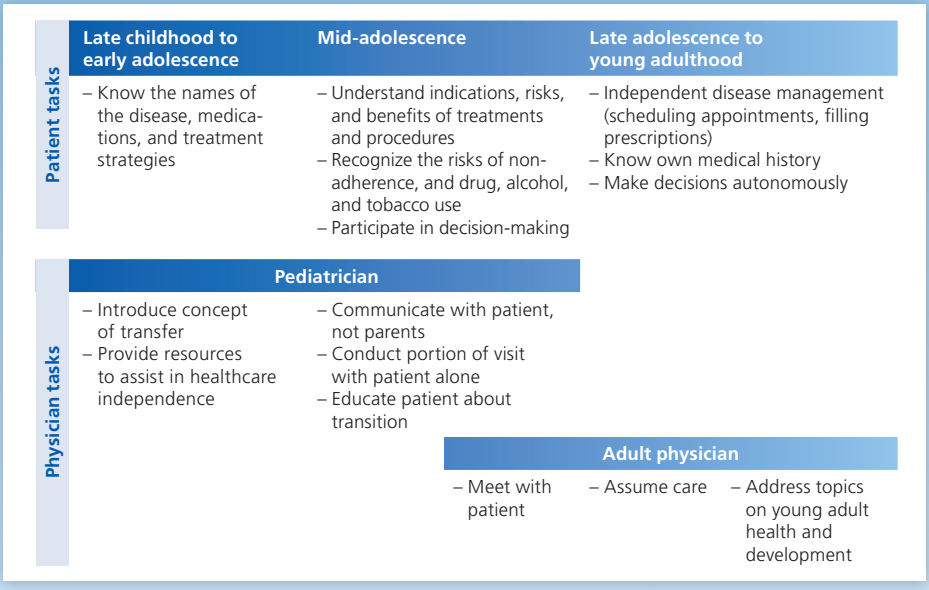


Figure 17/1: Allocation of tasks during the transition process (adapted from Philpott 2011).

tional anguish surrounding the initial disclosure of the patient's diagnosis, which makes additional discussions necessary. However, the need for ongoing care often leaves too little time for physicians to convey basic information about the disease [Classen et al. 2014].

The patient education network *Kompetenznetz Patientenschulung e.V.* (KomPaS) was founded in Osnabrück, Germany in 2008 (www.kompetenznetz-patientenschulung.de). A group of experts from a wide range of professions (medicine, psychology, education, pediatric nursing, nutrition science, movement therapy) established a modular education program (*ModuS*) which has also been used successfully for IBD. The website http://between-kompas.com is definitely worth a visit, as it contains much more information on the topic of transition than can be covered in this booklet.

Is the patient ready to transition?

Several years ago, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) published a checklist to help patients assess their own capabilities [Baldassano et al. 2002].

NASPGHAN checklist
Early adolescence (age 12–14) ***New knowledge and responsibilities*** – I can describe my GI condition. – I can name my medications, the amount and times I take them. – I can describe the common side effects of my medications. – I know my doctors' and nurses' names and roles. – I can use and read a thermometer. – I can answer at least one question during my health care visit. – I can manage my regular medical tasks at school. – I can call my doctor's office to make or change an appointment. – I can describe how my GI condition affects me on a daily basis.
Mid adolescence (age 14–17) ***Building knowledge and practicing independence*** – I know the names and purposes of the tests that are done. – I know what can trigger a flare of my disease. – I know my medical history. – I know if I need to transition to an adult gastroenterologist. – I reorder my medications and call my doctor for refills. – I answer many questions during a health care visit. – I spend most of my time alone with the doctor during visit. – I understand the risk of medical non-adherence. – I understand the impact of drugs and alcohol on my condition. – I understand the impact of my GI condition on my sexuality.
Late adolescence (age 17+) ***Taking charge*** – I can describe what medications I should not take because they might interact with the medications I am taking for my health condition. – I am alone with the doctor or choose who is with me during a health care visit. – I can tell someone what new legal rights and responsibilities I gained when I turned 18. – I manage all my medical tasks outside the home (school, work). – I know how to get more information about IBD. – I can book my own appointments, refill prescriptions and contact medical team. – I can tell someone how long I can be covered under my parents' health insurance plan and what I need to do to maintain coverage for the next two years. – I carry insurance information (card) with me in my wallet/purse/backpack.

Literature

Baldassano R, Ferry G, Griffiths A, Mack D, Markowitz J, Winter H. Transition of the patient with inflammatory bowel disease from pediatric to adult care: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2002;34(3):245–8.

Claßen M, Kretzschmar B, Kretzschmar A, Kunert D, Faiß M, Iven E. Schulung für Kinder und Jugendliche mit chronisch entzündlichen Darmerkrankungen. Lengerich: Papst Science Publishers; 2014.

Goodhand J, Hedin CR, Croft NM, Lindsay JO. Adolescents with IBD: the importance of structured transition care. J Crohns Colitis. 2011;5(6):509–19.

Greenley RN, Hommel KA, Nebel J, Raboin T, Li SH, Simpson P, et al. A meta-analytic review of the psychosocial adjustment of youth with inflammatory bowel disease. J Pediatr Psychol. 2010;35(8):857–69.

Hait E, Arnold JH, Fishman LN. Educate, communicate, anticipate-practical recommendations for transitioning adolescents with IBD to adult health care. Inflamm Bowel Dis. 2006;12(1):70–3.

Hait EJ, Barendse RM, Arnold JH, Valim C, Sands BE, Korzenik JR, et al. Transition of adolescents with inflammatory bowel disease from pediatric to adult care: a survey of adult gastroenterologists. J Pediatr Gastroenterol Nutr. 2009;48(1):61–5.

Keller KM. Transition bei Jugendlichen mit CED. Monatsschr Kinderheilkd. 2010;158(8):738–44.

Koletzko S, Saldo A. Jugendliche mit chronisch entzündlichen Darmerkrankungen (CED): Transition ohne Bauchschmerzen. In: Reincke M, Zepp F. Medizinische Versorgung in der Transition. Köln: Deutscher Ärzteverlag; 2012. p. 93–103.

Müther S, Rodeck B, Wurst C, Nolting HD. Transition von Jugendlichen mit chronischen Erkrankungen in die Erwachsenenmedizin. Monatsschr Kinderheilkd. 2014;162(8):711–8.

Philpott JR. Transitional care in inflammatory bowel disease. Gastroenterol Hepatol (NY). 2011;7(1):26–32.

Sebastian S, Jenkins H, McCartney S, Ahmad T, Arnott I, Croft N, et al. The requirements and barriers to successful transition of adolescents with inflammatory bowel disease: differing perceptions from a survey of adult and paediatric gastroenterologists. J Crohns Colitis. 2012;6(8):830–44.

Szigethy E, Craig AE, Iobst EA, Grand RJ, Keljo D, DeMaso D, et al. Profile of depression in adolescents with inflammatory bowel disease: implications for treatment. Inflamm Bowel Dis. 2009;15(1):69–74.

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