Crohn’s Disease

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Abstract
Crohn’s disease (CD) in children has become increasingly common in recent years, especially in the developed world. Despite advances considering knowledge of the
pathogenesis of these diseases, the precise etiology is not understood, and there remains no permanent cure. Pain, diarrhea, and weight loss are typical symptoms of pediatric CD. Atypical symptoms and extra-intestinal manifestations may occur. The patient’s growth and nutritional status are often compromised at diagnosis of CD. The location and severity of pediatric CD differ substantially from adult-onset disease. The initial presentation is more widespread and severe that in adults. Prompt diagnosis, thereby avoiding the consequences of diagnostic delay, is essential in the work-up of suspected CD. The aim of the management of CD is to achieve rapid remission and there are several options to reach this goal. The initial treatment is medical; surgery is considered in a complicated disease course or in the case of refractory disease. Acute indications for surgery include emergent conditions such as toxic megacolon, intra-abdominal abscesses, and sepsis or severe bleeding. Elective indications for surgery are severe strictures and perianal disease, significant prepubertal growth delay, and complications of or unresponsiveness to medical therapy. CD in children requires multidisciplinary care in the context of a growing child. The management of pediatric CD focuses on controlling gut inflammation and optimizing growth, development, and quality of life.

**Keywords**

Crohn’s disease · Children · Pediatric treatment

**Introduction**

Like Ulcerative Colitis (UC), Crohn’s disease (CD) is a chronic inflammation of the bowel which is caused by an interaction of genetic and environmental factors. The exact etiology is not known, therefore there is no causal therapy available. CD is mainly found in developed countries and there is a clear South-North gradient, especially in Europe (Shivananda et al. 1996). The incidence of CD in children and adolescents ranges between 1 and 8/100,000 and has risen across Europe in the past decades (Hildebrand et al. 2003; Sawczenko et al. 2001; Turunen et al. 2006; Amil-Dias et al. 2017). In 20–25% of all patients, the disease presents before the age of 18 years and may occur even in very young children (age < 2 years) (Auvin et al. 2005; Yu and Rodriguez 2017). In children today, CD is usually reported to be more common than UC. Males and females are equally affected. CD occurs more commonly in a Caucasian population than in other ethnic groups. There are some hereditary risk factors for CD: 5–20% patients with CD have a first degree relative who has inflammatory bowel disease (IBD) and offspring of a CD patient have a 10% chance of developing CD.

There are clear differences in onset between adult and pediatric CD, in terms of natural history, the impact of the disease on the patient, and the choice of treatment strategies (Van Limbergen et al. 2008). The phenotype of CD in the young differs from adult-onset disease, with more extensive distribution at presentation and extension of disease during the first 2 years of diagnosis in approximately one third of patients (Vernier-Massouille et al. 2008). Other typical features of pediatric CD include growth failure, which is present at diagnosis in 10–40% of affected children. CD presenting in childhood and adolescence is commonly associated with marked psychological and social morbidity, which may have an impact on education, relationships, sexual development, and adherence to therapy (Mackner and Crandall 2005).

**Etiology**

The etiology of CD is unknown and is most likely multifactorial. In addition to genetic factors, immunological and microbiological factors as well as environmental factors are likely to play significant roles.

Family history is a well-known risk factor for developing inflammatory bowel diseases such as CD. A positive family history remains the strongest recognizable risk factor in 8–12% of IBD patients, with CD showing a more frequent familial pattern than UC (Santos et al. 2018). As such, the risk of developing CD has long been recognized to have a
genetic contribution. This concept has advanced considerably over the past decade as genetic studies have identified numerous loci involved in IBD susceptibility. These studies have identified key cellular pathways in IBD and enhanced our understanding of how these pathways might contribute to disease. More than a decade ago, nucleotide oligomerization domain 2 (NOD2) was identified as the first susceptibility gene for CD (Ogura et al. 2001). In the last 5 years, population-based genome-wide association studies have greatly expanded the number of CD-associated loci (Jostins et al. 2012). Genetic studies have confirmed the role of mucosal barrier function, T-cell subsets, and cytokine signaling in the pathogenesis of CD. These studies have uncovered new genes and pathways, including autophagy, interleukin 23 signaling, NOD2/CARD in innate immunity, and innate lymphoid cells.

CD-associated genes in host cells indicate that altered responses to gut microbiota may be a primary determinant of disease risk and a likely mechanism for the disease (Knights et al. 2013). The diversity and composition of the gut microbiota are major environmental factors influencing gut homeostasis. A severe imbalance in the composition of the gut microbiome has been associated with IBD (Morgan et al. 2012). Particular dietary nutrients and metabolites likely interact with host genetics to influence host–microbiome interactions and thereby contribute to inflammation. Among specific nutrients involved in the pathogenesis of CD are tryptophan, taurocholic acid, and dietary fiber.

**Pathology**

CD may involve any part of the alimentary tract. The terminal ileum is predominantly involved and, in many cases, the disease may stop at the ileocecal valve. In the colon, it affects mainly the right side and may spare the rectum. Patchy or segmental disease can affect the transverse, descending, and sigmoid colon. In some cases, the rectum also may be diseased. The appendix is frequently involved, and perianal disease is present in up to 60% of patients (see below). When CD involves the upper gastrointestinal tract, it generally occurs in conjunction with ileitis (Kleer and Appelman 2001). The prevalence of gastroduodenal involvement is unknown, but it has been suggested that microscopic foci may be present in as many as 83% of cases (Sandborn and Phillips 1995). CD may also affect the oral cavity, pharynx, and esophagus. CD of the mouth, characterized by aphthous ulcerations on the lips, buccal mucosa, or tongue, may indicate clinically unrecognized intestinal involvement (Kleer and Appelman 2001). However, CD may present in isolated parts of bowel without evidence of active disease elsewhere.

CD involves the terminal ileum and colon in 60% of cases, small bowel in only 30%, and colon in only 10% of cases. The involved bowel and also mesentery are thickened and fat often migrates towards the antimesenteric border of the bowel wall (creeping fat, fat wrapping). A variable degree of stricturing is commonly seen in the segment of bowel that is mostly affected. Skip lesions are not uncommon and represent smaller areas or patches of active disease outside the main area of involvement. Skip lesions are typically found in the small bowel proximally to the most commonly affected terminal ileum.

Histologically, mucosa is often extensively ulcerated and the inflammation is usually transmural. The inflammation is often interspersed with almost normally appearing mucosal areas. The transmural inflammatory changes may develop into fistulas that erode adjacent structures such as the bowel, bladder, vagina, perineum, and abdominal wall. Histological evidence of granulomas, that are the mainstay of histological diagnosis of CD, occurs in 40% of endoscopic biopsies taken from lesions in small bowel, in more than 60% of biopsies from gastric lesions and only 25% of biopsies from colonic lesions.

A classification of the location and behavior of pediatric CD has recently been developed based on the Montreal classification of CD (Levine et al. 2011) (Table 1). This consensus Paris classification gives a reasonably solid basis for comparisons between different patient series. Moreover, the effect of various management modalities is easier to assess in various forms of disease
When a commonly accepted classification exists.

**Diagnosis**

The diagnosis of CD is based on clinical history, endoscopic findings, imaging and on laboratory tests to a limited extent. The European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) has recently published a revised consensus on the diagnosis of IBD (including CD) in children, the so-called “Porto criteria” (Levine et al. 2013). One of the main messages of these criteria is that the exact diagnosis, severity, localization, and extent of disease should be established before any treatment is initiated. All patients with suspected CD need to have proper medical history that includes bowel symptoms, stooling pattern, general symptoms, exact data on growth during the years prior, and family history of IBD. A full physical examination is mandatory and should include oral and perianal inspection, measurement of weight and height, and assessment of the pubertal stage.

**Clinical Features**

In children, the onset of CD is most often after the age of 10 years. However, CD may occur at almost any age; about 5% of CD patients present before the age of 10 years. There is often a significant diagnostic delay, commonly longer than...
1 year between the onset of symptoms and the definitive diagnosis. A typical early symptom of CD is nonspecific abdominal pain. Other typical symptoms include diarrhea, fever, and weight loss. Growth failure may be manifested by a delayed onset of puberty. Patients with CD are commonly more ill than those with UC.

Perianal disease, as a first presentation, occurs in up to 20% of CD patients. Typical findings are chronic anal fissures and skin tags, and chronic fistula-in-ano. In a preadolescent child, any of these should alert the clinician to suspect CD.

Many children with CD have extraintestinal manifestations (see below). Some of these may present years before the onset of bowel CD.

**Laboratory Investigations**

Laboratory findings are not diagnostic but are usually helpful. Many patients are anemic and most have elevated sedimentation rate. Serum albumin, prealbumin, and transferrin are low in many CD patients, reflecting their poor nutritional status. Fecal culture, including a *Clostridium difficile* toxin assay and microscopy for parasites, should be performed initially to rule out infectious causes of bowel symptoms.

Fecal markers of intestinal inflammation, such as fecal calprotectin and lactoferrin, are useful in the diagnosis and also follow-up of CD, especially in CD with colonic involvement. On the other hand, the role of these surrogate markers in exclusively small intestine CD is still unclear, which is unfortunate as CD commonly presents primarily and only in small intestine. Fecal calprotectin and lactoferrin tests could be used complementarily to other already used methods, before pediatric patients undergo GI endoscopy. They could be used in cases of suspected CD for supporting diagnosis and in cases of already known CD for confirming relapse. A positive result could confirm the CD diagnosis or CD relapse, due to the high sensitivity of the test, but a negative result should not exclude the disease (Kostakis et al. 2013).

It has to be kept in mind, however, that a significant percentage of patients do not have typical symptoms and the common laboratory markers may display normal values (Mack et al. 2007).

**Endoscopy**

Endoscopic work-up for CD needs to include both upper and lower fiberoptic endoscopy. Granulomas that are diagnostic for CD may be found more easily in upper gastrointestinal biopsies than in colonic biopsies. A full colonoscopy with ileal intubation is required for proper lower gastrointestinal tract work-up (Cameron 1991). Multiple biopsies should be obtained, especially from macroscopic lesions. Typical findings in CD include segmental aphthous and linear ulcers and stenotic areas that sometimes do not allow the passage of an endoscope. It is typical for CD that a severely affected segment of bowel may rapidly change to an almost normal looking bowel. In pediatric CD, it is not uncommon that the whole length of the colon may be affected by the disease, as in most cases of childhood UC. Even in cases of extensive colonic CD, the rectum may be completely or partially spared.

Capsule endoscopy is considered a diagnostic investigation in suspected small bowel CD if endoscopy and other imaging have not confirmed the diagnosis. Capsule endoscopy is a noninvasive method of endoscopic imaging that can be swallowed by the patient or, in young children, delivered into the duodenum with endoscopy. The capsules are propelled by peristalsis. Images are transmitted by radiofrequency to a sensor array and downloaded to a workstation to be viewed. The main advantage of capsule endoscopy is the ability to visualize the entire small bowel with minimal discomfort to the patient. The main limitations are the lack of bioplastic and therapeutic capabilities, a potential to miss single lesions, high rate of incidental findings, and difficulty in localizing identified lesions. Capsule retention is possible, although rare, which precludes the use of capsule endoscopy in patients with suspected obstruction or strictures (Di Nardo et al. 2012).

Balloon-assisted full enteroscopy, commonly used today in adults with suspected small bowel
lesions, has not been widely used in the diagnostic work-up of pediatric IBD. A small series, however, has shown promising results. The main limitations of enteroscopy are the invasive nature of the procedure, with the risk of bleeding and perforation, prolonged duration, and the requirement for a specially trained endoscopy team that is not usually available in pediatric services (Di Nardo et al. 2012).

**Imaging**

Radiological imaging, especially small bowel follow-through and barium meal, has been intensively used in CD to visualize the areas of bowel that cannot be reached by endoscopy. Today, more modern imaging modalities offer more sensitive and safe tools for bowel imaging. There has been an increased use of MRI enterography (MRE) in children for small bowel imaging in IBD. This has been driven by several factors, but the most significant is a concern about ionizing radiation with conventional contrast x-ray. An adult meta-analysis has confirmed at least equivalent diagnostic capabilities of MRE for identifying small bowel CD when compared with contrast follow-through and ultrasound.

A recent systematic review and meta-analysis has demonstrated that MRE has at least as good sensitivity and specificity as contrast follow-through for detection of small bowel pathology in pediatric CD, without exposure to ionizing radiation. Therefore, MRE appears to be the best imaging modality for small bowel CD (Giles et al. 2013).

**Differential Diagnosis**

The major differential diagnostic problem in CD is its similarities to UC. Usually, it is easier to rule out UC in a patient with CD than it is to rule out CD in a child with UC. Indeterminate colitis also occurs in children, but in less than 10% of cases. Indeterminate colitis is a distinct pediatric subgroup of IBD, with a prevalence that is higher than that observed in adults. Children with indeterminate colitis have an early age of onset and a disease that rapidly progresses to pancolitis. A significant percentage of patients with indeterminate colitis later have their disease reclassified as CD or UC.

From a surgical point of view, UC should be definitively ruled out since today the golden standard for surgical management of UC is restorative proctocolectomy, which is not a suitable surgical option for CD. CD typically presents with general symptoms such as fever and unspecific abdominal pain more often than in cases of UC. Growth failure and delayed sexual maturation are also more common in CD. Acquired causes of bowel symptoms, such as infectious and parasitic gastroenteritis, particularly *Clostridium difficile* infection, have to be ruled out as a cause of symptoms. There are also very uncommon conditions, such as Behcet’s syndrome and chronic granulomatous disease that may mimic CD.

Typical clinical symptoms in CD and UC are summarized in Table 2.

**Extraintestinal Manifestations**

Extraintestinal manifestations of CD are common and affect a variety of different organs (Table 3). At least one extraintestinal manifestation affects up to 30% of pediatric CD patients (Dotson et al. 2010; Kucharska et al. 2019). Some of them associate temporally with intestinal inflammation activity, while others have an independent clinical course. In adults, the presence of one extraintestinal manifestation predisposes to the development of others. Peripheral arthritis, erythema nodosum, and episcleritis are related to disease activity, whereas axial arthropathy, pyoderma gangrenosum, uveitis, and primary sclerosing cholangitis have an independent course (Van

| Table 2 Incidence of different symptoms in UC and CD |
|-----------------------------------------------------|
| **UC (%)** | **CD (%)** |
| Bloody stools | 97 | 22 |
| Diarrhea | 90 | 88 |
| Abdominal pain | 33 | 82 |
| Weight loss | 15 | 60 |
| Fever | 15 | 77 |
| Growth failure | 3 | 30 |
Assche et al. 2010). Impaired intestinal absorptive function and bowel resections essentially contribute to development of some noninflammatory extraintestinal disorders associated with CD, such as nephrolithiasis and metabolic bone disease. In children, the majority of extraintestinal manifestations occur within the first year after onset of CD, while the presence of any extraintestinal manifestation, arthralgia, and erythema nodosum are increasing among patients with high disease activity at diagnosis. There appears to be no correlation between disease distribution or perianal disease and extraintestinal manifestations (Dotson et al. 2010).

Arthritis is less common than arthralgias, but their combination constitutes the most common (20%) extraintestinal manifestation in young CD patients. Arthritis is also the most common presenting extraintestinal clinical manifestation preceding development of intestinal disease. Almost 10% of patients have aphthous stomatitis. Erythema nodosum is the most common cutaneous lesion characterized by raised, tender, and red subcutaneous nodules particularly on the extensor surfaces occurring in a few percent of patients. Pyoderma gangrenosum presents as erythematous papules or pustules with subsequent dermal necrosis and ulcerations. Ocular manifestations are less common than in adults. Primary sclerosing cholangitis occurs less commonly than in UC and is often detected by raised liver enzyme values on screening. Magnetic resonance cholangiography should be performed with low threshold, especially if serological tests for other liver diseases and ultrasound examination are normal.

Acute pancreatitis occurs rarely and may be related to drug therapy (azathioprine, mercaptopurine and 5-ASA), primary sclerosing cholangitis or biliary stone disease. In ileal dysfunction, due to active inflammation or resection, malabsorbed fatty acids escape to the colon and bind calcium. Increased amounts of oxalate remain unbound for colonic absorption and subsequent excretion of oxalates by the kidneys predisposes to urinary tract stones. Decreased bone mineral density is a frequent finding in newly diagnosed children (Van Assche et al. 2010). Active intestinal inflammation, impaired nutrition, and corticosteroid therapy predispose to metabolic bone disease, which demands monitoring with densitometric scanning (DEXA).

### Table 3 Extraintestinal manifestations of CD

| Manifestation                          |
|---------------------------------------|
| Arthropathy                           |
| Peripheral                            |
| Axial (sacroilitis, ankylosing spondylitis) |
| Aphthous stomatitis                   |
| Skin                                  |
| Erythema nodosum                      |
| Pyoderma gangrenosum                  |
| Eyes                                  |
| Episcleritis                          |
| Uveitis                               |
| Hepatobiliary                         |
| Primary sclerosing cholangitis        |
| Chronic active hepatitis              |
| Gall stones                           |
| Pancreatitis                          |
| Renal stone disease                   |
| Hypercoagulability                    |
| Metabolic bone disease                |

Medical Treatment

The full extent, location, and severity of CD should be established at diagnosis before starting medical treatment, because initial treatment is guided by disease severity and distribution (Van Assche et al. 2010). The classic treatment goals are induction and maintenance of remission with effective symptom control while optimizing growth (Sherlock and Griffiths 2012). More recently, medical treatment of pediatric CD has shifted towards a more aggressive approach at presentation, aiming at enhanced immunomodulation at the early stage of disease, higher rate of mucosal healing, and more effective prevention of complications associated with disease progression in children with long life expectancy.

Both systemic corticosteroids and exclusive enteral nutrition are used for induction of remission. Enteral nutrition has fewer side effects, but may be less effective in severe disease and complicated by poor compliance due to the frequent
requirement of nasogastric tube feeding (Sherlock and Griffiths 2012). Most pediatric patients respond to corticosteroids, while initial steroid resistance is encountered in 11–17%. One year after the diagnosis, 30% are steroid dependent. Oral budesonide that is released in the ileum is also effective in mild to moderate ileocecal CD with fewer side effects (Sherlock and Griffiths 2012). The role of mesalazine, antibiotics, or probiotics in achieving remission is limited (Van Assche et al. 2010), although antibiotics are often combined in treatment of fistulous disease. Corticosteroids should not be used as a maintenance treatment in children with CD, but replaced with thiopurines or anti-TNF therapy. Thiopurines, azathioprine and mercaptopurine, have commonly been used to maintain remission. If they are not tolerated or are ineffective, methotrexate may alternatively be used. Thiopurines are introduced early at the time of remission induction in children with newly diagnosed severe or extensive disease.

Zimmerman and Bousvaros recently reviewed the various therapeutic options for the treatment of children with CD (Zimmerman and Bousvaros 2019). Exclusive enteral nutrition, corticosteroids, and biologics (including anti-TNF inhibitors) may be used for induction of remission in patients with active flare of disease. Immunosuppressants and TNF inhibitors may be used for maintenance of remission. Early use of anti-TNF inhibitors in patients with moderate to severe CD improves efficacy and prevents complications of disease (Zimmerman and Bousvaros 2019).

Infliximab is effective for induction of remission in pediatric CD (Van Assche et al. 2010; de Bie et al. 2012). It may be introduced as the first line treatment or when standard induction therapy is ineffective or not tolerated. Regular infliximab infusions are effective therapy for maintenance of remission in pediatric CD, in fistulizing (perianal) disease, and in certain extraintestinal manifestations. Infliximab infusions (5 mg/kg) are administered at 0, 2, and 6 weeks for induction and continued with maintenance infusions every 8 weeks. However, approximately 10% of patients do not respond to induction and a significant proportion of patients lose the initial response and require dose adjustments to maintain response (de Bie et al. 2012). Early pediatric experiences with a newer anti-TNF drug, adalimumab, parallel those of infliximab, while data on certolizumab is still limited. Approximatively one third of patients develop anti-infliximab antibodies associated with a shortened response duration, acute infusion reactions, and delayed hypersensitivity. Infliximab therapy has been combined with immunosuppressive medication in order to prevent formation of antibodies. This approach may increase the rate of toxic side effects, especially T-cell lymphoma. In addition to the risk of malignancy, adverse effects of infliximab treatment include serious or opportunistic infections, formation of autoimmune antibodies, and psoriasiform skin lesions. Elective surgical treatment should be considered in children with disease refractory to medical treatment, especially in children with unfinished puberty and localized disease (Van Assche et al. 2010).

### Perianal Disease

Children and adolescents with CD are commonly affected by perianal disease, which is defined as inflammation of the anus or anal region including skin tags, fissures, fistulae, abscesses, and stenosis. Depending on definitions, perianal CD is observed in up to 62% of patients (de Zoeten et al. 2013). Fissures are encountered most commonly (51%), followed by skin tags (35%), fistulae (15%), and abscesses (13%) (Palder et al. 1991).

Skin tags can precede manifestation of intestinal disease, but they rarely cause symptoms and should be left alone. Fissures in CD patients may be large with raised edges and occur anywhere in the anal circumference. They can be a source of pain, bleeding, discharge, and pruritus, but often heal without treatment. Nitrate-based topical treatment may be attempted initially. Synchronous activation of intestinal disease should be treated medically. Intersphincteric botulinum toxin injection or rarely surgical excision may be considered for refractory symptomatic chronic
fissures, only after acute inflammation has subsided.

The presence of a perianal fistula guides both medical and surgical therapy of CD. Perianal abscess usually occurs in conjunction with a fistula and presents as a tender, sometimes fluctuating mass or discharge. Etiology of perianal fistulas is unclear, but may involve a combination of intramural enteric inflammation, exposure to feces, pressure caused by defecation and infection of anal glands (de Zoeten et al. 2013). Most abscesses are perianal (60%) or (30%) ischiorectal, while a few percent are pelvirectal, above the levator ani muscle. Different classifications can be used to describe fistula location in relation to the anal sphincter and levator ani musculature. Most fistulas involve or traverse the sphincteric muscles, while suprasphincteric fistulas running cranial to the anal sphincters and superficial subcutaneous fistulas occur more rarely. A simple fistula involves a single low intersphincteric or transphincteric location with an internal and an external opening close to the anal verge. A complex fistula has more substantial sphincter involvement, and it may have multiple tracts or branching with an internal opening above the dentate line and an external opening further away from the anus, with or without an associated abscess. Excluding simple subcutaneous fistulas, perianal fistulas are best assessed by MRI prior to any surgical interventions. MRI provides detailed information on location, possible branching and the number of fistulas, as well as delineating the presence of associated abscesses, guiding subsequent medical therapy and surgical drainage procedures.

Examination under anesthesia is combined with endoscopic examination. The entire anal region and genital area is inspected carefully and examined digitally. Abscess cavities are incised, evacuated, and drained with a soft silicone band. All fistula openings and suspicious dimples are gently probed to establish connection between the rectum and anoderm. Superficial fistulous tracts are laid open. Loose noncutting silicon seton bands are placed in tracks of more complex fistulas to prevent premature closure of the fistula and recurrence. Infliximab therapy can be solely given, started at the time or shortly after seton placement, which are removed only several months after cessation of the drainage. Both treatment modalities are effective but the combined therapy with infliximab and setons appears to provide higher response rates (Hukkinen et al. 2014). Resolving of the fistula tract takes much longer than healing of the external orifice and the safest approach is to confirm healing of fistulas with MRI before seton removal. Abscesses should be drained before initiation of infliximab. Setons are tolerated extremely well by patients; their use does not compromise fecal continence and is associated with well-preserved anorectal function (Hukkinen et al. 2014). Patients with the most complicated extensive abscesses or fistulas benefit from additional temporary fecal diversion for 6–12 months. More complex surgery, such as advancement flaps, remains rarely indicated and should be performed in the absence of inflammation with a covering ostomy.

Rectal stenosis or strictures occur rarely in children with CD (de Zoeten et al. 2013). They result from circumferential bowel inflammation, usually located at the dentate line. Most patients respond to repeated anal dilatations under anesthesia. A refractory short symptomatic stricture may be amenable for random flap stricturoplasty. More extensive strictures may require fecal diversion, with or without proctectomy.

Surgical Treatment

Principles and Indications

CD is a lifelong, chronic, inflammatory disease of the gastrointestinal tract and although new modalities of medical treatment have been invented, 80% of patients will eventually undergo surgery. Of patients with pediatric-onset CD, 19–34% undergo surgery before the age of 18 years (Pacilli et al. 2011; Hojsak et al. 2014). In the USA, between 1997 and 2009, the incidence of intestinal resections for pediatric CD exceeded those for UC (1.0 vs. 0.6 /100,000 children). The resections for CD showed an annual rise of 2.1% (Debruyn et al. 2013). The high number of resections
reflects the fact that CD cannot be cured by surgery and, because of high the rate of recurrence re-
operations are common. Recently, the Paediatric IBD Porto Group of ESPGHAN produced guide-
lines for the surgical management of CD in children (Amil-Dias et al. 2017). They produced
evidence-based guidelines regarding indications for surgery in pediatric CD, considerations and
type of surgery, pre- and postoperative care, and risks associated with surgery and the surgical
management if perianal disease (Amil-Dias et al. 2017).

The indications for elective or semi-elective surgery in 60–70% of patients are continuing dis-
ase activity and growth failure unresponsive to optimal medical treatment, in 10–25% obstructive
symptoms, whereas 20–25% undergo emergency surgery for toxic megacolon, bleeding, perfora-
tion, and abscess (Pacilli et al. 2011; Piekkala et al. 2013). Although surgery is considered as the
last resort after the failure of medical treatment, surgery can be considered as the primary treat-
ment in patients presenting with obstructive disease without inflammatory activity, or for those
patients whose obstructive symptoms persist after steroid therapy. The most common surgical pro-
cedures are segmental resection of the small bowel, ileocolic resection, segmental or subtotal
resection of the colon and total proctocolectomy. In surgery for CD, preservation of as long seg-
ments of the bowel as possible should be the guiding principle.

**Timing**

Pediatric CD is associated with significant nutritional and growth impairment resulting in delayed puberty and it is important to induce remission before the onset of puberty. If the onset of puberty is delayed beyond 14 years of age, patients’ final height may be compromised. Surgery is generally advocated in prepubertal children with growth failure, despite medical treatment and despite a high rate of recurrence, improved nutritional sta-
tus after surgery is beneficial to growth during puberty. If surgical remission is achieved after puberty no catch-up growth occurs. Colonic
dysplasia and cancer are extremely rare in childhood CD, but both require operative treatment without delay.

**Preoperative Assessment**

Pediatric CD often presents as colitis without small intestinal involvement, rendering differential diagnosis between CD and UC challenging. In order to reach the correct diagnosis, careful assessment of both colonic and extracolonic fea-
tures, endoscopic histology, serologic markers, capsule endoscopy, and MRE is of utmost impor-
tance (Levine et al. 2013). A patient with CD, initially misdiagnosed as UC, may undergo an ileoanal pull-through and later experience postop-
erative fistulous pelvic complications, failure, and pouch removal. Nutritionally compromised
patients, or patients with a recent major weight loss, anemia or hypoalbuminemia should undergo
a period of preoperative nutritional support.

Whether preoperative TNF-α antibodies and steroids are risk factors for postoperative surgical complications is a matter of controversy. In adults, TNF-α antibodies as well as large doses of pre-
disolone (>20 mg for 6 week or more) may increase the complications after ileocolonic anas-
tomoses. Therapeutic concentrations of TNF-α antibodies persist for 8 weeks after infusion. Pre-
operative weaning from steroids and TNF-α antibo-
dies may be beneficial in reducing surgical complications (Dignass et al. 2010). In patients
who are malnourished or cannot be weaned from high doses of steroids, staged procedures with
enterostomy should be considered.

Preoperative discussion with patients and the
parents should include all aspects and options of the surgical therapy. Reliable information should be
given on the goals of the planned surgery, postoperative complications, expected high prob-
ability of a recurrent disease, and the need of renewed surgery. Consultations with stoma nurse
and dietician should be arranged when necessary. In the case of colorectal surgery, preoperative
bowel preparation may be performed.
Operative Approach and Technique

Duodenum
Primarily duodenal CD is rare, but it may cause obstructive symptoms or ulcer-like hemorrhage. Symptoms are initially managed medically with anti-TNF agents and proton pump inhibitors, but eventually the majority of affected patients may need surgical intervention. Mild recurrent obstructive symptoms can be successfully treated with endoscopic balloon dilatation. In more severe symptoms, gastrojejunal bypass with or without duodenal stricturoplasty is recommended, whereas duodenal resections are associated with a high complication rate. A gastrojejunal bypass can be performed laparoscopically. A vagotomy is unnecessary because of proton pump inhibitors (Shapiro et al. 2008).

Fistulas from diseased intestine may target stomach and duodenum. Persistent fistulas are treated by resection of the diseased intestine and suture closure of the fistula opening in the stomach or duodenum (Dolgin 2007).

Small Intestine
Surgical approach in jejunal, ileal, or ileocolic resections may be open, or laparoscopic assisted (i.e., laparoscopic mobilization of the intestine with an extracorporeal intestinal anastomosis). In adults, the advantages of laparoscopy – shorter hospital stay, reduced complication rate, better cosmesis, and a reduced rate of intra-abdominal adhesions – have emerged as definite benefits of laparoscopy. In selected patients, laparoscopic assisted re-resections are possible. In patients with previous open surgery, fistulas, and abscess, an open approach is preferred. If long segments of small bowel are affected, it is advisable to only deal with the obstructive segments and leave diseased but nonobstructing lesions and skip lesions behind. Disease activity at the anastomotic margins does not compromise the outcome of the anastomosis. In adults, stapled side-to-side anastomosis carries a somewhat lower complication rate than hand-sewn end-to-end anastomosis, but whether the same is true in children is unclear. A wide anastomosis, irrespective of the anastomotic technique, is always recommended. In terms of disease recurrence at the anastomotic site, the anastomotic technique does not play a role (Dolgin 2007; Dignass et al. 2010). Electrosurgical vessel sealing devices are useful in dealing with the thickened mesenterium.

In selected patients, stricturoplasty may be successfully used in short jejunoileal strictures (<10 cm). Heineke-Mickulicz stricturoplasty is suitable for single short (<10 cm) strictures with a linear diameter of 2 cm or less. In single or multiple adjacent ileal or ileocecal strictures, a side-to-side isoperistaltic stricturoplasty may be used instead of resection. A widening stricturoplasty may also be used in a stenosed ileocolic anastomosis.

Small bowel resection is indicated in patients with perforation, fistula formation, or extreme bowel wall thickening that precludes stricturoplasty, contiguous stricturing for 30 cm or more of intestinal length, and ileocecal involvement. Endoscopic dilatation is a valid technique in endoscopically accessible short strictures, especially for recurrence after ileocolic resection (Ono et al. 2012; Dignass et al. 2010).

An abdominal abscess, concomitant with CD of the small bowel, should be drained percutaneously when accessible. A delayed resection is recommended in the presence of obstructive symptoms. A coincidental ileitis during laparotomy for suspected appendicitis should not be resected unless there is strong evidence of obstructive symptoms, dilated proximal bowel, and an inflamed bowel wall typical of CD (Dignass et al. 2010).

Large Intestine
Isolated colonic CD is identified in 18–42% of children at the time of surgery and it is the most common presentation in children aged 8 years or less. Colonic involvement is often extensive and aggressive and after segmental resections recurrent disease occurs almost invariably. In severe Crohn’s colitis with anorectal involvement, the lowest recurrence rate is achieved with total proctocolectomy and permanent ileostomy. However, the majority of children and adolescents are reluctant to approve permanent ileostomy.
Expert opinions’ divide on whether local colonic disease should be treated with segmental resections including modifications of left and right colectomies with appropriate stapled wide ileocolostomy or colo-colostomy. After segmental resections, the reoperation rate exceeds 80% and a significant percentage of patients eventually undergo colectomy, whereas the rate of permanent ileostomy is similar to that after subtotal colectomy. Decisions should take individual preferences of the patient and surgeon into account (Moir 2007; van Assche et al. 2010).

In case of extensive colonic involvement, subtotal colectomy with ileorectal anastomosis is a valid option. Despite a high rate of clinical recurrence, the 10-year rectal sparing rate is 75–86%. In case of severe rectal inflammation, an ileostomy and a staged ileorectal anastomosis is performed after the rectal inflammation is medically controlled. Because of a relative high risk of anastomotic leakage with the ileorectal anastomosis, a temporary diverting ileostomy is advisable (Alves et al. 2002). In an emergency operation because of megacolon, bleeding or perforation in a debilitated patient a three-staged operation (subtotal colectomy and end-ileostomy followed by ileorectostomy with a protective ileostomy and finally, closure of the protective ileostomy) may be the safest option.

Anorectal involvement of CD considerably increases the risk of recurrence after segmental resections or ileorectostomy. However, as an option for proctectomy and permanent ileostomy, medically controlled rectal or perianal involvement or fistulizing perianal disease are not absolute contraindications to a staged ileorectostomy. Until recently, 20% of patients with severe anorectal involvement underwent a primary proctocolectomy and eventually 60% ended up with a permanent ileostomy, with or without completion proctectomy. According to a recent study, biological medication may significantly increase the rate of rectal preservation and reduce the need for permanent ileostomy (Coscia et al. 2013).

Dysplasia associated with Crohn’s colitis may be multifocal. If dysplasia is found in biopsies from one site of the colon, total proctocolectomy and permanent ileostomy are recommended (Kiran et al. 2012). Proctocolectomy may be complicated by dehiscence and fistulization of the perineal wound and recurrent ileal disease may occur (Moir 2007).

Ileal pouch anastomosis is not recommended because of a high rate of fistulization and pouch failure. In a stricturizing colonic CD, stricturoplasties are associated with an increased risk of colonic cancer and thus not recommended (Moir 2007).

**Fistulating Nonperianal Disease**

Fistulae communicating between loops of intestine (entero-enteral), intestine, and abdominal wall (enterocutaneous) or between intestine and viscera (urinary bladder, vagina) may resolve with medical treatment. If surgery is needed, the surgeon should resect the diseased intestine from which the fistula arises and oversew the fistula opening in the healthy target organ. In enterocutaneous fistulas, every effort should be made with medical and nutritional therapy. The surgeon should also avoid early re-operations because of a high rate of recurrence and complications in a malnourished patient. Low anal-vaginal introitus fistulae may not need surgical treatment. In rectovaginal fistulae with persistent and unacceptable symptoms, surgery with a diverting enterostomy and advancement flap or gracilis plasty may be attempted (van Assche et al. 2010).

**Postoperative Management**

Patients are treated with antibiotics and nil by mouth status until the return of bowel function. Older children should receive prophylaxis against deep venous thrombosis with compression stockings, combined with low-molecular-weight heparin in those undergoing emergency colectomy. The patency of the ileorectal anastomosis should be ascertained with water-soluble rectal contrast enema 6–8 weeks postoperatively. At the planned closure of the diverting ileostomy 2–3 months postoperatively, the anastomosis is viewed with
an endoscope under general anesthesia and if necessary an endoscopic balloon dilatation is performed.

For children, no definitive recommendations exist for postoperative medical therapy and recommendations in adult patients have been extrapolated into children. All children who retain extensive CD after local resection should have maintenance therapy. After small bowel resection maintenance therapy with thiopurines and after isolated ileal resection optionally, high dose mesalazine is recommended. Imidazole antibiotics have been shown to be effective after ileocolic resection, but are less well tolerated. Although some specialists favor postoperative anti-TNF therapy, controlled data is lacking.

Endoscopic follow-up should be arranged and the first ileocolonoscopy should occur within 1 year of the resection. Alternatively, a MRE may be performed (Assche et al. 2010).

Complications

Anastomotic leak, hemorrhage, abscess, obstructions, and enterocutaneous fistulae are the most common complications occurring in 15% of patients after stricturoplasty and resection. Percutaneous radiologic-guided or open drainage of abscesses may be adequate therapy, whereas in complicated cases diverting enterostomy may be needed (Dolgin 2007). In the laparoscopic approach, the perioperative complication rate is comparable with open operations. The rate of bowel obstruction after laparoscopic subtotal colectomy (16%) is similar to that in an open approach (Diamond et al. 2010). Postoperative enterocutaneous fistulae of the small bowel may initially be treated with a period of parenteral nutrition, antibiotics, and administration of subcutaneous somatostatin rather than early re-resections. Recurring anastomotic strictures or ulcers may eventually require re-resection (van Assche et al. 2010).

Intestinal failure is a devastating complication of CD. An active and stricturing CD, first surgery at an early age, perioperative complications and repeated operations for enterocutaneous fistulae, strictures or enterostomy complications are the most significant risk factors contributing to intestinal failure (Gearry et al. 2013).

Outcomes of Surgery for CD

The rate of postoperative recurrence in children is very high. In a study including 27 patients who underwent either resection or stricturoplasty with postoperative azathioprine maintenance therapy, the 1-year relapse rate was 55% and 18% underwent re-resection (Pacilli et al. 2011). Another recent study, which included 36 children who underwent surgery for CD, reported a 94% rate of postoperative relapse a median of 1.8 years after the primary surgical resection and a 54% rate of re-resection in the follow-up period of 10 years. The median time from first surgery to re-resection was 2 years, whereas the median time without re-resection was 7 years. Of the 7 (19%) of patients who ended up with a permanent ileostomy, three had initially been diagnosed with UC and had undergone ileal J-pouch anastomosis. Despite a high recurrence rate, bowel function was acceptable and quality of life was comparable between patients and their peers (Piekkala et al. 2013). Colectomy, repeated abdominal operations and pelvic infections and fistulae may have a negative effect on sexual function (van Balkom et al. 2012) and cause subfertility in females.

Conclusion and Future Directions

CD is an increasing problem in children, especially in the developed world. In children, CD is usually more widespread and severe than in adults. CD commonly presents with significant general symptoms and affects growth and development of the child. The etiology of CD is unknown and there is no permanent cure. The management of CD is predominantly medical, and surgery is reserved for complications or recalcitrant and refractory disease. There are a number of management options in CD, but it is not known if the modern therapeutic modalities such as immunomodulatory and biological drugs have
permanently improved the prognosis of CD or decreased the need of surgery.

In the future, it is likely that CD will also increase in developing countries as the standard of living increases. This will mean a huge number of new patients with CD. It is also likely that medical therapies develop and treatment strategies more specific to CD will emerge. This will require research to reveal the basic etiological and pathophysiological mechanisms of CD. Surgery remains an adjunct to medical treatment modalities, but it is unlikely that the need for surgery will be completely abolished or even significantly decreased.

References

Alves A, Panis Y, Trancart D, Regimbeau JM, Pocard M, Valleur P. Factors associated with clinically significant anastomotic leakage after large bowel resection: multivariate analysis of 707 patients. World J Surg. 2002;26 (4):499–502.

Amil-Dias J, Kolacek S, Turner D, 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.

Auvin S, Molinié F, Gower-Rousseau C, Brazier F, Merle V, Grandbastien B, Marti R, Lerebours E, Dupas JL, Colombel JF, Salomez JL, Cortot A, Turck D. Incidence, clinical presentation and location at diagnosis of pediatric inflammatory bowel disease: a prospective population-based study in northern France (1988–1999). J Pediatr Gastroenterol Nutr. 2005;41:49–55.

Cameron DJ. Upper and lower gastrointestinal endoscopy in children and adolescents with Crohn’s disease: a prospective study. J Gastroenterol Hepatol. 1991;6:355–8.

Castellaneta SP, Afzal NA, Greenberg M, Deere H, Davies S, Murch SH, Walker-Smith JA, Thomson M, Srivistrava A. Diagnostic role of upper gastrointestinal endoscopy in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2004;39:57–61.

Coscia M, Gentilini L, Laureti S, Gionchetti P, Rizzello F, Campieri M, Calabrese C, Poggioli G. Risk of permanent stoma in extensive Crohn’s colitis: the impact of biological drugs. Color Dis. 2013;15(9):1115–22.

de Bie CI, Escher JC, de Ridder L. Antitumor necrosis factor treatment for pediatric inflammatory bowel disease. Inflamm Bowel Dis. 2012;18:981–98.

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;57:401–12.

Debruyne JC, Soon IS, Hubbard J, Wrobel I, Panaccione R, Kaplan GG. Nationwide temporal trends in incidence of hospitalization and surgical intestinal resection in pediatric inflammatory bowel diseases in the United States from 1997 to 2009. Inflamm Bowel Dis. 2013;19(11):2423–32.

Di Nardo G, Aloisi O, Civitelli F, Cesciani E, Cucchiara S. Investigation of small bowel in pediatric Crohn’s disease. Inflamm Bowel Dis. 2012;18:1760–76.

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

Dignass A, Van Assche G, Lindsay JO, Lémann M, Söderholm J, Colombel JF, Danese S, D’Hoore A, Gassull M, Gomollón F, Hommes DW, Michetti P, O’Morain C, Oresland T, Windsor A, Stange EF, Travis SP, European Crohn’s and Colitis Organisation (ECCO). 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.

Dolgin SE. Surgical management of upper gastrointestinal tract and small bowel Crohn’s disease. Semin Pediatr Surg. 2007;16(3):172–7.

Dotson JL., Hyams JS, Markowitz J, LeLeiko NS, Mack DR, Evans JS, Pfefferkorn MD, Griffiths AM, Otley AR, Bousvaros A, Kugathasan S, Rosh JR, Keljo D, Carvalho RS, Tomer G, Manula P, Kay MH, Kerzner B, Oliva-Hemker M, Langton CR, Crandall W. Extra-intestinal manifestations of pediatric inflammatory bowel disease and their relation to disease type and severity. J Pediatr Gastroenterol Nutr. 2010;51:140–5.

Gearry RB, Kam MA, Hart AL, Bassett P, Gabe SM, Nightingale JM. Predictors for developing intestinal failure in patients with Crohn’s disease. J Gastroenterol Hepatol. 2013;28(5):801–7.

Giles E, Barclay AR, Chippington S, Wilson DC. Systematic review: MRI enterography for assessment of small bowel involvement in paediatric Crohn’s disease. Aliment Pharmacol Ther. 2013;37(12):1121–31.

Hildebrand H, Finkel Y, Grahnquist L, Lindholm J, Ekborn A, Askling J. Changing pattern of paediatric inflammatory bowel disease in northern Stockholm 1990–2001. Gut. 2003;52:1432–4.

Hojsak I, Pavić AM, Mišak Z, Kolacek S. Risk factors for relapse and surgery rate in children with Crohn’s disease. Eur J Pediatr. 2014;173:617–21.

Hukkinen M, Pakarinen M, Piekkaala M, Koivusalo A, Rintala R, Kolho KL. Treatment of complex perianal fistulas with seton and infliximab in adolescents with Crohn’s disease. J Crohns Colitis. 2014;8:756–62.

Jostins L, Ripke S, Weersma RK, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature. 2012;491:119–24.

Kiran RP, Nisar PJ, Goldblum JR, Fazio VW, Remzi FH, Shen B, Lavery IC. Dysplasia associated with Crohn’s
Crohn’s Disease

Knights D, Lassen KG, Xavier RJ. Advances in inflammatory bowel disease pathogenesis: linking host genetics and the microbiome. Gut. 2013;62:1505–10.

Kostakis ID, Cholioudi KG, Vaiopoulos AG, Vlachos IS, Perrea D, Vaos G. Fecal calprotectin in pediatric inflammatory bowel disease: a systematic review. Dig Dis Sci. 2013;58:309–19.

Kucharska M, Daniluk U, Kwieatk–Średzińska KA, et al. Hepatobiliary manifestations of inflammatory bowel disease in children. Clin Exp Hepatol. 2019;5(3):203–9.

Levine A, Griffiths A, Markowitz J, Wilson DC, Turner D, Russell RK, Fell J, Ruemmele FM, Walters T, Sherlock M, Dubinsky M, Hyams JS. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. Inflamm Bowel Dis. 2011;17:1314–21.

Levine A, Koletzko S, Turner D, Escher JC, Cucchiara S, de Ridders L, Kolho KL, Veres G, Russell RK, Paerregaard A, Buderus S, Greer ML, Dias JA, Veereeman-Wauters G, Lionetti P, Sladek M, Carpi JM, Staiano A, Ruemmele FM, Wilson DC. The ESPGHAN revised Porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. J Pediatr Gastroenterol Nutr. 2013;58:795–806.

Mack DR, Langton C, Markowitz J, LeLeiko N, Griffiths A, Bousvaros A, Evans J, Kugathasan S, Oteley A, Pfefferkorn M, Rosh J, Moyer S, Oliva-Hemker M, Rothbaum R, Wyllie R, delRosario JF, Keljo D, Lerer T, Hyams J. Pediatric Inflammatory Bowel Disease Collaborative Research Group. Laboratory values for children with newly diagnosed inflammatory bowel disease. Pediatrics. 2007;119:1113–9.

Mackner LM, Crandall WV. Long-term psychosocial outcomes reported by children and adolescents with inflammatory bowel disease. Am J Gastroenterol. 2005;100:1386–92.

Moir CR. Surgical management of Crohn’s colitis. Semin Pediatr Surg. 2007;16(3):178–84.

Morgan XC, Tickle TL, Sokol H, Gevers D, Devaney KL, Ward DV, Reyes JA, Shah SA, LeLeiko N, Snapper SB, Bousvaros A, Korzenik J, Snapper SB, Keljo D, Lerer T, Hyams J, Pediatric Inflammatory Bowel Disease Collaborative Research Group. Laboratory values for children with newly diagnosed inflammatory bowel disease. Pediatrics. 2007;119:1113–9.

Murakawa K, Ozaki H, Kusunoki M, et al. Long-term outcomes after surgery on pediatric patients with Crohn disease. J Pediatr Gastroenterol Nutr. 2013;56(3):271–6.

Sandborn WJ, Phillips SF. Pathophysiology of symptoms and clinical features of inflammatory bowel disease. In: Kirsner JB, Shorter RG, editors. Inflammatory bowel disease. 4th ed. Baltimore: Williams & Wilkins; 1995. p. 407–28.

Santos MPC, Gomes C, Torres J. Familial and ethnic risk in inflammatory bowel disease. Ann Gastroenterol. 2018;31(1):14–23.

Sawczenko A, Sandhu BK, Logan RF, Jenkins H, Taylor CJ, Mian S, Lynn R. Prospective survey of childhood inflammatory bowel disease in the British Isles. Lancet. 2001;357:1093–4.

Shapiro M, Greenstein AJ, Byrn J, Corona J, Greenstein AJ, Salky B, Harris MT, Divino CM. Surgical management and outcomes of patients with duodenal Crohn’s disease. J Am Coll Surg. 2008;207(1):36–42.

Sherlock ME, Griffiths AM. Medical therapy for pediatric inflammatory bowel disease. Curr Gastroenterol Rep. 2012;14:166–73.

Shivananda S, Lennard-Jones J, Logan R, Fear N, Price A, Carpenter L, van Blankenstein M. Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). Gut. 1996;39(5):690–7.

Turunen P, Kolho KL, Auvinen A, Iltanen S, Huhtala H, Ashorn M. Incidence of inflammatory bowel disease in Finnish children, 1987–2003. Inflamm Bowel Dis. 2006;12:677–83.

Van Asche G, Dignass A, Reinsch W, van der Woude CJ, Sturm A, De Vos M, Guslandi M, Oldenburg B, Dotan I, Marteau P, Arizzzone A, Baumgart DC, D’Haens G, Gionchetti P, Portela F, Vucelie B, Söderholm J, Escher J, Koletzko S, Kolho KL, Lukas M, Mottet C, Tilg H, Vermeire S, Carbonnel F, Cole A, Vodovec G, Reinschlag M, Tsianos E, Herrlinger K, Oldenburg B, Bouthin Y, Kiesslich R, Stange E, Travis S, Lindsay J. The second European evidence-based consensus on the diagnosis and management of Crohn’s disease: special situations. J Crohns Colitis. 2010;4:63–101.

van Balkom KA, Beld MP, Visschers RG, van Gemert WG, Breukink SO. Long-term results after restorative proctocolectomy with ileal pouch-anal anastomosis at a young age. Dis Colon Rectum. 2012;55:939–47.

Van Limbergen J, Russell RK, Drummond HE, Aldhous MC, Round NK, Nimmo ER, Smith LH, Gillett PM,
McGrogan P, Weaver LT, Bisset WM, Mahdi G, Arnott ID, Satsangi J, Wilson DC. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. Gastroenterology. 2008;135:1114–22.
Vernier-Massouille G, Balde M, Salleron J, Turck D, Dupas JL, Mouterde O, Merle V, Salomez JL, Branche J, Marti R, Lerebours E, Cortot A, Gower-Rousseau C, Colombel JF. Natural history of pediatric Crohn’s disease: a population-based cohort study. Gastroenterology. 2008;135:1106–13.
Yu YR, Rodriguez JR. Clinical presentation of Crohn’s, ulcerative colitis, and indeterminate colitis: symptoms, extraintestinal manifestations, and disease phenotypes. Semin Pediatr Surg. 2017;26(6):349–55.
Zimmerman L, Bousvaros A. The pharmacotherapeutic management of pediatric Crohn’s disease. Expert Opin Pharmacother. 2019;20:2161–8.