# Inflammatory Bowel Disease

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Inflammatory bowel disease (IBD) includes two classic entities, Crohn's disease (CD) and ulcerative colitis (UC), and a third undetermined form (IBD-U), characterized by a chronic relapsing course resulting in a high rate of morbidity and impaired quality of life. In this chapter, we will describe the current knowledge in management options for children with IBD, emphasizing the unique aspects of the pediatric condition.

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## 23.1 Ulcerative Colitis

### 23.1.1 Introduction

Ulcerative colitis is an idiopathic IBD affecting primarily the mucosal layer of the colon. UC is more frequent between ages 15 and 35 (20 % of patients are younger than 20 years old), even if it has been reported in every decade of life. The disease extent is variable; inflammation can be restricted either to the distal rectum or to the entire colon. Usually, early-onset disease (<5 years old) is more aggressive than adolescence or adult onset. Pediatric onset of disease is characterized by delayed skeletal maturation and a delayed onset of puberty. Hence, as well as gastrointestinal and extraintestinal complications, growth and nutrition are key priorities in the management of adolescents with UC, together with psychosocial implications [1].

### 23.1.2 Epidemiology and Pathogenesis

The incidence of UC in children has remained almost constant over the past five decades. Incidence rates are noted to be increased recently in countries where IBD was previously uncommon. According to Scandinavian, North American, and UK studies, UC incidence in children ranges from 2.1 to 4.2 cases/year/100,000 population. This disease is more common in


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industrialized countries and in urban population. This peculiar distribution suggests that environmental factors may be fundamental to the development of such disease. Of course, genetic predisposition is crucial: higher rates are reported in Jewish population than non-Jewish, and they are even higher in the same ethnic population moved from low-risk geographic region to high-risk one. Concordance rates among monozygotic twins are about 16.5 % and among dizygotic twins about 2 %. Therefore, the pathogenesis of such disease seems to imply genetic, environmental, and immunologic factors. Precisely, the interaction between the intestinal microflora and the host innate immune system may lead to a deregulated immune response and consequently to inflammation. Antibiotic usage, especially early in childhood, and dietary habits may trigger UC by modifying microbiome. However, there is no data to support whether microflora alteration is the cause or the result of intestinal inflammation [2].

### 23.1.3 Clinical Features

UC is a chronic inflammatory bowel disease characterized by flare-ups and remissions. Clinical presentation of pediatric UC depends on disease extension, severity, and patient age. Most common symptoms include rectal bleeding, abdominal pain, and diarrhea. If the disease involves the rectum only (proctitis), common symptoms are tenesmus and urgency, together with bloody stools. Otherwise, left-sided colitis and pancolitis generally present with abdominal pain and diarrhea with blood and mucus. Systemic symptoms, such as low-grade fever, weight loss, anemia, lethargy, and growth retardation, may be present. Several studies have reported more extensive colonic involvement in childhood-onset compared to adult-onset disease. Furthermore, about 35 % of children with UC required immunomodulators within 12 months of diagnosis, and the median time to first surgery was shorter in patients with childhood-onset than in adult-onset patients. Although most of pediatric patients will present with a mild form of the disease, about 10–15 % of them will present with an acute and severe one (fulminant colitis). In adults this pattern is defined as the presence of six or more bloody stools per day along with one of the following: anemia, tachycardia, fever, and elevated ESR. This classification has never been validated in children, because of age-dependent hemoglobin values and pulse rate; moreover, fever is not so common in children with severe colitis. Therefore, a noninvasive, continuous scoring for pediatric UC activity evaluation has been proposed, which is the pediatric UC activity index (PUCAI). It is based on six variables, which are abdominal pain, rectal bleeding, stool consistency, nocturnal stools, number of stools each 24 h, and interruption to normal activities, and it is adequate to quantify the degree of disease severity. Cutoff scores for remission and mild, moderate, and severe disease have been identified and validated: PUCAI 0–9 indicates remission, 10–34 mild activity, 35–64 moderate activity, and 65–85 severe activity. PUCAI has been proven to correlate closely with physician's global assessment and endoscopic score. Acute severe UC is considered as a life-threatening condition, with risk of various complications. The mortality rate is about 1 %, and most common severe complications are massive hemorrhage, toxic megacolon, perforation, and intestinal infections. Potential complications of long-standing UC include dysplasia, colon cancer (CRC), and rarely strictures. A meta-analysis reported that the cumulative risk of CRC in patients with UC was 2 % at 10 years, 8 % at 20 years, and 18 % at 30 years. The risk is increased by specific factors, such as disease duration, extensive mucosal involvement, concomitant primary sclerosing cholangitis, family history of CRC, and early onset of UC. ECCO guidelines published in 2013 recommend a screening colonoscopy 8 years after the onset of colic symptoms. Ongoing surveillance should be repeated every 1, 3, or 5 years depending on the risk factors.

### 23.1.4 Extraintestinal Manifestations

Extraintestinal manifestations of UC may occur in 25–30 % of children with CU. It may present at diagnosis in about 6–23 % of children, with higher frequency in those >6 years. Many symptoms seem to be independent on disease activity, such

as pyoderma gangrenosum, uveitis, axial arthropathy, autoimmune hepatitis, and primary sclerosing cholangitis. In particular, the latter affects 3–7.5 % of children with UC, and it is responsible for the destruction of biliary ducts that is most of the cases irreversible and refractory on medical treatment and often leads to liver transplantation. Symptoms such as peripheral arthritis, episcleritis, erythema nodosum, and aphthous stomatitis, on the contrary, usually come out or exacerbate parallel to intestinal inflammatory activity and extension. Several studies have reported an increased risk for venous thromboembolism (VTE) in IBD population, especially during flare-ups. For this reason, it is useful to verify the presence of additional risk factors for VTE, such as thrombophilia, chronic presence of antiphospholipid antibody, obesity, smoking, the use of oral contraceptives, and other medications with increased risk of thrombosis, in patients with UC.

## 23.1.5 Diagnosis

The diagnosis of UC relies on exhaustive anamnesis, the presence of gastrointestinal and extraintestinal manifestation, family history, and physical examination, together with endoscopic and histological characteristic features. It is essential to exclude other causes of intestinal inflammation, such as Crohn's disease and infectious colitis. In infancy, a common cause of bloody diarrhea with cramping is allergic colitis. In infancy, other causes of bloody diarrhea should be considered, such as necrotizing enterocolitis, Hirschsprung's enterocolitis, and intussusception. Differential diagnosis for early-onset colitis includes immunodeficiency; the most common are chronic granulomatous disease and IL10 receptor deficiency. In older children, polyps and Meckel's diverticulum should be considered. Physical examination consists primarily of abdomen and perianal region examination. Signs of abdominal distention, tenderness, and mass should be checked. Perianal abnormalities include fissures, skin tags, fistulas, or abscess. Eventual extraintestinal manifestations of IBD should be documented. Then, assessment of height, weight, and nutrition is useful [1].

### 23.1.5.1 Laboratory Assessment

The initial work-up consists in collection of multiple stool samples for microscopy and culture in order to exclude an enteric infection. Most frequent microbic agents that can mimic UC are *Shigella*, *Salmonella*, *Campylobacter*, *Enteropathogenic Escherichia coli*, *Yersinia*, and *Clostridium difficile*. Exclusion of enteric infection is fundamental, but we have to take into account that infective agents may trigger a first episode of flare of UC. Hence, the identification of an enteric infection does not necessarily exclude a diagnosis of UC. Stool inflammatory markers are helpful to assess bowel inflammation: fecal calprotectin and lactoferrin are generally increased in active UC. Fecal biomarkers may be useful as screening test, because they are noninvasive and they have a high sensitivity; however, they are largely nonspecific, since they cannot distinguish UC from CD or from any other inflammatory bowel conditions, including enteric infections. Routine laboratory studies may reveal a nonspecific inflammatory state with leukocytosis, thrombocytosis, hypoalbuminemia, and elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Nevertheless they have low specificity and sensitivity for gut inflammation, because in most cases (about 54 % of children with mild disease) they are quite normal at the time of diagnosis.

Even if results are often negative, two serological markers may be useful in differential diagnosis between CD and UC: the presence of antineutrophil cytoplasmic antibodies (ANCA) is more common in UC (60–70 %) than in CD (20–25 %), whereas anti-*Saccharomyces cerevisiae* antibodies (ASCA) are more frequently found in CD (50–70 %) than in UC (10–15 %). These markers may be useful to orientate the diagnosis in cases of chronic colitis not referable to UC nor CD despite extensive work-up.

### 23.1.5.2 Endoscopic and Histologic Evaluation

Colonoscopy and ileoscopy with biopsies play a pivotal role in the diagnostic process of UC. Typical endoscopic appearance of UC is diffuse uniform inflammation extending proximally from the rectum for a variable length. Common findings are erythema, granularity and increased

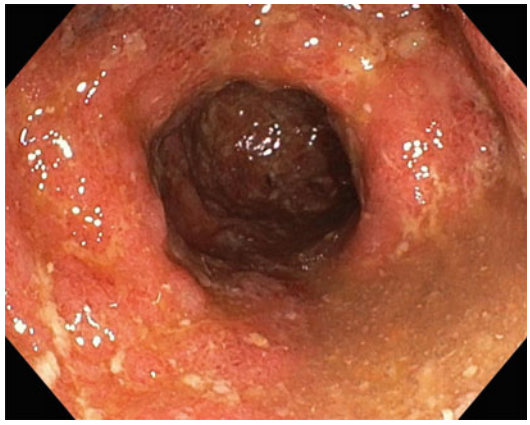

**Fig. 23.1** Typical endoscopic findings of ulcerative colitis characterized by friability of colonic mucosa and the presence of erosions and minute ulcers

friability of colonic mucosa, loss of normal vascular pattern, and the presence of erosions and minute ulcers (Fig. 23.1). In case of severe disease, deeper ulcerations may be present, and, rarely, strictures have been described. Pseudopolyps are characteristic of a long-standing disease. If pancolitis is present, the inflammation may involve the terminal ileum that may exhibit a nonerosive erythema and edema of the mucosa ("backwash ileitis"). Ileal inflammation correlates with the degree of inflammation of the right colon. Typical histological findings of UC are a continuous pattern of acute and chronic inflammation limited to mucosal layer, with basal plasmacytosis, crypt distortion, crypt abscesses, and goblet cell depletion. Generally, inflammation progressively decreases from distal to proximal colon. The absence of granulomas helps to exclude CD. The adult-based Montreal disease classification system for IBD includes three types of UC: proctitis (E1), left-sided disease (E2), and disease proximal to the splenic flexure (E3). Recently, Paris classification has modified the Montreal system for pediatric UC by the addition of E4 (disease proximal to hepatic flexure) and S1 (severe UC).

In children five atypical features of UC have been reported:

1. Rectal sparing: 5–30 % of untreated pediatric patients exhibit a macroscopic, though not microscopic, normal rectal mucosa. This feature is more frequent in younger children.
2. Short duration: in young children with short duration of disease, biopsies may show a focal inflammation or absence of typical architectural distortion.
3. Cecal patch: about 2 % of children with left-sided colitis exhibit an area of cecal inflammation. Histopathologic examination reveals a nonspecific inflammation without granulomas.
4. Upper gastrointestinal endoscopy: 4–8 % of children present an upper gastrointestinal involvement, with diffuse or focal inflammation and mild ulcerations.
5. Acute severe colitis: children with acute pancolitis may have histopathology findings similar to CD, such as transmural inflammation and deep ulcers. However, lymphoid aggregates are absent, and ulcers are typically V-shaped, differently from CD.

Hence, in addition to ileocolonoscopy, the ESPGHAN Revised Porto Criteria for IBD recommend to perform esophagogastroduodenoscopy with biopsies in all children, when IBD is suspected, irrespective of the presence or absence of upper gastrointestinal symptoms.

#### 23.1.5.3 Small Bowel Imaging

Small bowel evaluation is essential if IBD is suspected. The ESPGHAN Revised Porto Criteria for IBD recommend to perform it during the diagnostic work-up, in order to evaluate the extent or the presence of small bowel CD and to aid the diagnosis in patients with atypical UC; it can be delayed in patients with typical UC. Magnetic resonance imaging is an accurate radiation-free test useful to ascertain the extent and the degree of the disease. In order to better evaluate the lumen, distention of intestinal loops may be produced by polyethylene glycol solution administration, given by mouth or by nasogastric tube. Ultrasound may also be useful in IBD evaluation because it is a noninvasive, low-cost, widespread available tool. However interobserver variability is very high. Small intestine contrast US, consisting in using of an oral anechoic contrast, increases

its sensitivity and reduces interobserver variability.

Alternative methodologies in the assessment of small bowel disease are capsule endoscopy (CE) and balloon-assisted enteroscopy (BAE). The first is a high-sensitivity and well-tolerated tool, although it does not consent to take biopsies, and has a high number of false-positive features. If stricture is suspected, patency capsule should precede CE, because of the risk of retention. BAE may be very useful in small bowel evaluation, because of the possibility to biopsies taken. However, it is indicated in selected cases. Radiological tools, such as plain abdominal radiograph and abdominal/pelvic CT scans, may be useful to detect UC complications, like toxic megacolon and perforation [3].

## 23.1.6 Management

Management of children with UC consists not only in inducing and maintaining remission; considering that chronic diseases influence growth and psychological aspects of children, in this population, it is necessary to optimize growth and to ensure pubertal development and physiologic well-being. Treatment options depend on the extent and severity of disease. Medical treatment should be proposed first. Surgery should be reserved to patients with severe and/or refractory disease or with serious pharmacological side effects.

### 23.1.6.1 Mild-to-Moderate Colitis

The first-line therapy in children with mild-to-moderate colitis is oral aminosalicylates, which can be combined with topical aminosalicylates to increase remission rate, if tolerated. Aminosalicylates are used in induction and maintenance treatment of UC. The aminosalicylates of choice are mesalazine and sulfasalazine. Their effectiveness is quite similar, but sulfasalazine is considered superior to mesalazine in patients with associated arthropathy, although dose-dependent adverse events (headaches, nausea, and fatigue) are more frequent. Oral mesalazine dosage for pediatric population is 60–80 mg/kg/day in one or two daily doses with a maximal dose of 4, 8 g/daily. Rectal mesalazine is dosed 25 mg/kg up to 1 g once daily. Sulfasalazine is dosed 40–70 mg/kg/day in one or two daily doses up to 4 g/day. To minimize side effects, sulfasalazine may be started at a dose of 10–20 mg/kg/day with a gradual dose increase over a 2-week period. In addition, sulfasalazine impairs folic acid absorption, so its supplementation is recommended to prevent anemia. Maintenance dose of mesalazine is the same as used for induction therapy. Because of their safety profile, they could be continued indefinitely. Dosage may be reduced after a long period of complete remission. Serious side effects are uncommon, and they usually resolve when the medication is stopped. Acute intolerance to aminosalicylates may mimic a flare of colitis, and it precludes any further usage of that drug. Patient's response to medication may be evaluated 2 weeks after onset of therapy. If no response is seen then, rectal therapy (if not started already) or oral steroids should be offered.

### 23.1.6.2 Proctitis/Left-Sided Colitis

Left-sided colitis and proctitis are usually managed with topical mesalazine or topical steroids. Mesalazine is available as enema and suppositories. They can be used for induction and maintenance remission. Suppositories are useful for proctitis, while left-sided colitis is treated with enemas, as long as they can reach the left colon. Corticosteroids enema or suppositories are useful for induction therapy, but prolonged treatment may cause systemic side effects. Often, oral aminosalicylates are added to the topical therapy in patients with moderate left-sided colitis.

### 23.1.6.3 Moderate Colitis

Oral steroids are useful in inducing remission in pediatric patient with moderate colitis and systemic symptoms. Because of their well-known side effects (e.g., weight gain, fluid retention, growth retardation, mood disorders, osteopenia, aseptic necrosis, glaucoma, cataracts), corticosteroids should be tapered shortly after remission is achieved. Standard corticosteroids therapy involves oral prednisone or prednisolone, which are dosed 1 mg/kg up to 60 mg/day once daily. Beclomethasone dipropionate is an alternative

steroid that may be used orally or rectally in mild-to-moderate colitis, with fewer systemic steroids side effects.

#### 23.1.6.4 Severe Colitis

Severe acute colitis is a potentially life-threatening condition, defined by PUCAI greater than 65. It requires hospitalization for further evaluation and management. Assessment of vital sign and key blood test evaluation are essential. Stool samples should be collected for culture and *Clostridium difficile* toxin detection. Severe UC first-line therapy is intravenous corticosteroids. Methylprednisolone is dosed 1–1.5 mg/kg/day up to 60 mg/day in one or two doses daily. In addition, supportive treatment may be required: fluid rehydration, correction of electrolytes imbalance, blood transfusion, and albumin infusion. PUCAI score should be evaluated daily. A score of greater than 45 on day 3 of admission is predictive of lack of response to corticosteroids. A score of greater than 70 on day 5 guided the start of rescue therapy. There is no agreement about intravenous corticosteroid therapy duration; 7–14 days of therapy are usually enough to obtain a good clinical response. Recently, a consensus statement for managing acute severe ulcerative colitis in children from ECCO, ESPGHAN, and the Porto IBD Group of ESPGHAN has been published. Key points of this document are the following:

1. Stool evaluation should include standard culture and specific screening for *C. difficile*.
2. In children with steroid-resistant disease, CMV infection should be excluded endoscopically.
3. Disease activity should be monitored frequently during admission, with regular assessment of vital signs, daily PUCAI score evaluation, and monitoring of key blood tests (ESR, full blood count, albumin, and electrolytes) at admission and at subsequent intervals.
4. First-line therapy is intravenous corticosteroids with methylprednisolone.
5. Antibiotics are not recommended routinely but should be considered when infection is suspected or when toxic megacolon is present.
6. There is no evidence for the routine use of prophylactic heparin to prevent thromboembolic events.
7. Aminosalicylate therapies should be interrupted at admission, and in naive patients, its introduction should be delayed.
8. Regular diet should be continued. If oral intake seems inadequate, nutritional support (enteral or parenteral) should be considered. Oral intake should be ceased when surgery appears imminent and it is contraindicated in toxic megacolon.
9. Children with increasing or severe abdominal pain should be investigated for complication onset, such as perforation or toxic megacolon. Narcotics or nonsteroidal anti-inflammatory drugs are not recommended in the setting of acute severe colitis.
10. PUCAI scores can be used to monitor response and the need for secondary therapy. A score greater than 45 points at day 3 indicates poor response to corticosteroids and a need to prepare for rescue therapy. A score greater than 65 on day 5 indicates a need to a rapid switch to rescue therapy. If PUCAI scores is between 35 and 60 at day 5, steroids can be continued for a further 2–5 days before secondary therapy should be considered. Children with scores of less than 35 points on day 5 are unlikely to require rescue therapy.
11. Plain radiographs of the abdomen should be obtained in any child with clinical signs of toxicity and subsequently as indicated. The diagnostic criteria for toxic megacolon consist of radiological evidence of transverse colonic dilatation ($\geq$56 mm) along with systemic signs. In children less than 10 years old, a radiological evidence of transverse colonic dilatation greater than 40 mm with signs of systemic toxicity is sufficient to diagnose a toxic megacolon. Urgent surgical consultation is required in all children with toxic megacolon. If the child has stable vital signs and there are no signs of sepsis, conservative management may be appropriate. If signs of toxicity worsen or they do not resolve within 48–72 h, immediate colec-

tomy should be performed. Rescue medical therapies are not indicated in the setting of toxic megacolon.
12. Rescue therapies include medical (infliximab or calcineurin inhibitors) and surgical (colectomy) options.
13. Sequential medical rescue therapy is not recommended in children.
14. If colectomy is required in acute severe colitis in children, subtotal colectomy and ileostomy is recommended. Pouch formation can subsequently be considered.
15. Surgical complications can be reduced by avoiding delays in colectomy, improving nutrition, and using perioperative broad-spectrum antibiotic coverage. Preoperative steroid administration is related to an increased risk of anastomotic leak and infectious complications, although surgery should not be delayed to taper steroids.

#### 23.1.6.5 Salvage Therapy

A second-line medical therapy is usually preferred than surgery in children. However, colectomy may be required in several circumstances, such as patients with severe colitis unresponsive to medical therapy, patients with complications (toxic megacolon and/or perforation), and if precancerous lesions are identified. Colectomy could be discouraged in children younger than 5 years old, in whom it could be difficult to distinguish between UC and CD.

The most common medical rescue therapy in steroid-refractory acute severe UC is calcineurin inhibitors (cyclosporine, tacrolimus) and biological agents (infliximab, adalimumab). Several studies reported a high rate of short-term success, though there is a low rate of long-term success of calcineurin inhibitors. Because of its long-term renal toxicity, cyclosporine should only be administered as a "bridge" to thiopurine treatment (azathioprine), which is typically effective after 3–4 months. Although not structurally related to cyclosporine, tacrolimus has a similar mechanism of action and efficacy, though there is a more tolerable side effect profile. Calcineurin inhibitors may also be used as a steroid-sparing "bridge" to surgery. There aren't any comparative prospective trials between cyclosporine and infliximab in children. Infliximab is a monoclonal antibody to tumor necrosis factor-alpha. The recommended dose is 5 mg/kg at 0.2 and 6 weeks, followed by maintenance therapy every 8 weeks. Unlike cyclosporine, infliximab can be continued as long-term maintenance therapy. Infliximab seems to be more effective in obtaining mucosal healing than immunomodulators. Combination therapy with infliximab and azathioprine should be discouraged because of the potential risk or lymphoma, even if combination therapy has reported a good response in many adult studies.

Adalimumab is a fully human monoclonal antibody to tumor necrosis factor-alpha. Extrapolating from the adult literature and pediatric case series, adalimumab should be started at 100 mg/m$^2$ up to 160 mg, followed by 50 mg/m$^2$ up to 80 mg after 2 weeks and then 25 mg/m$^2$ up to 40 mg every other week; dose individualization may be needed. It is generally used in children who either fail to tolerate or become intolerant to infliximab. Adalimumab is an effective and safe treatment that should be considered as the rescue treatment before colectomy in children [1, 4–7].

### 23.1.7 Surgical Management of UC

Although the primary therapy of ulcerative colitis is medical, surgery may be required in patient who develops severe complications or becomes refractory to medical therapy.

*Indications for urgent surger*y:

- Massive colorectal bleeding: uncontrolled, life-threatening hemorrhage occurs in a small portion of patient, but it requires immediate surgery.
- Toxic megacolon, which is characterized by systemic toxicity and segmental or total colonic dilatation.
- Perforation: this complication is rare but these patients require colectomy.
- Severe colitis, which has failed to respond to aggressive medical therapy within 2 weeks.

*Indications for elective surgery*:

- Unresponsive patients: patients who do not respond to medical therapy or cannot be weaned from glucocorticoids or immunomodulatory therapy should be offered a surgical option.
- Side effects: when medical therapy influences the physiologic development (growth failure from steroids), this constitutes an indication to colectomy.
- Cancer risk: bioptic findings at risk for cancer require colectomy [4, 7].

#### 23.1.7.1 Technique

The gold standard technique is *ileal pouch-anal anastomosis* (*IPAA*) firstly described in 1978 by Parks and Nicholls [8]. It consists of colectomy and rectal mucosectomy with an endorectal ileoanal pull-through, creation of a distal reservoir and ileorectal anastomosis (Fig. 23.2). If urgent surgery is required, the treatment of choice is to perform a colectomy and ileostomy leaving a rectal stump.

IPAA can be performed in one, two, or three stages:

- One-stage IPAA: following the proctocolectomy, an ileal pouch is anastomosed to the anus. Single-stage surgery is feasible, but it seems to be associated to a higher risk of major complication such as anastomotic dehiscence and late pouch failure [9].
- Two-stage IPAA: following the proctocolectomy and the ileal pouch-anal anastomosis, a loop ileostomy is made to protect to lower anastomosis from the fecal stream. The ileostomy is reversed in a second procedure.
- Three-stage IPAA: during the first stage, a colectomy and ileostomy are performed leaving a rectal stump. During the second procedure, the proctectomy is completed, and ileal pouch-anal anastomosis is performed leaving a loop ileostomy which is reversed during a third procedure.

Total *abdominal colectomy with ileorectal anastomosis* is another applicable technique (Fig. 23.3). It consists of colonic removal and ileal anastomosis to the rectum. The rectum serves as native reservoir ensuring continence but local disease persists. Eligible patients for this technique are those who are not suitable for IPAA but refuse a permanent ileostomy, patients with indeterminate colitis in whom Crohn's disease cannot be excluded, and young women who desire preservation of fecundity [10]. In fact some authors reported improved fertility in ileorectal anastomosis, thus avoiding pelvic adhesions. This advantage has to be balanced with the need for endoscopic surveillance and a possible failure of medical control of the residual disease.

*Laparoscopic IPAA* is increasingly being performed in adults, while the application of this technique to pediatric practice has been slower. Laparoscopic approach offers advantages in terms of wound infection, intra-abdominal abscess, length of stay, and reduced incidence of small bowel obstruction at 1-year follow-up [11, 12].

#### 23.1.7.2 Complications

The major complication of IPAA is inflammation of the pouch (pouchitis). Main symptoms are diarrhea, rectal bleeding, abdominal pain, and malaise. Therapy is based on broad-spectrum antibiotics or glucocorticoid enemas. Other long-term complications are incontinence and a reduction in fertility in females.

## 23.2 Crohn's Disease

### 23.2.1 Introduction

The incidence of CD in children is increasing worldwide, ranging from 2.5 to 11.4 per 100,000, with an estimated prevalence of 58/100,000 which is rising in both developed and developing countries. The cause of CD is still poorly understood, but evidence demonstrated that the disease is based on abnormal response to the intestinal microbiota in a genetically susceptible host; in particular in pediatric-onset CD, the genetic component is more dominant, and therefore recurrence within the family is more prevalent than in

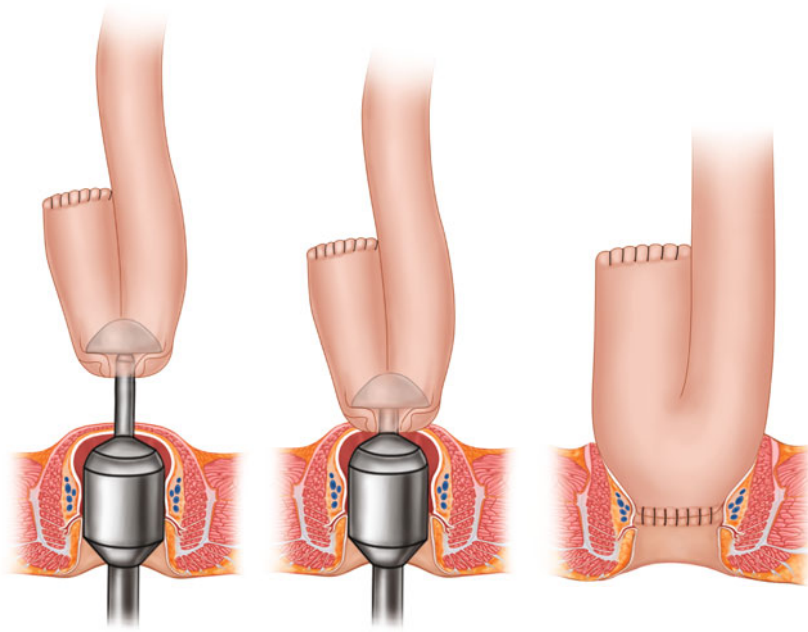

**Fig. 23.2** After total colectomy and ileal pouch are performed, circular staple is used to perform ileoanal anastomosis (**a**, **b**). At the end of the procedure, no rectal mucosa should be present (**c**)

adults. Some features are typical of pediatric age; pediatric CD is more often extensive; is associated with a more aggressive disease course, including a greater propensity for disease extension and early use of immunomodulators; presents various phenotypes; and is influenced by nutritional treatment. The cumulative risk of progression to complicated CD (i.e., fistulizing or stricturing disease) is similar to adults, but children are more likely to have undergone surgery by young adulthood [13–15].

### 23.2.2 Epidemiology

In the last years, CD has shown an increase of incidence, which determinates an increase in the overall mean annual incidence of pediatric IBD. CD highest rates occur in Western and Northern countries, with a decreasing gradient from North to South and from West to East. In Europe data suggest a mean annual incidence rate of 2.6 for pediatric CD. US studies reported a prevalence of 43/100,000. Factors contributing to the increase of CD could be a greater case of diagnosis, the widening case definition, earlier onset, and a greater access to medical care associated to a real increase in the number of affected children. CD is more frequent than UC in childhood with a male predominance. In pediatric CD, most patients have an extensive disease, ileocolonic or colonic, and also an upper gastrointestinal involvement. Pediatric CD usually presents as an inflammatory or nonstricturing, nonpenetrating disease, although complicated disease is fairly unusual at presentation [2].

### 23.2.3 Etiopathogenesis

In genetically predisposed children, an interaction between luminal contents and the mucosa leads to a dysregulated inflammation, which is the most recognized mechanism of pediatric CD. Different microorganisms are studied to find the pathogen of CD; strains of adherent-invasive *E. coli* have been described both in adults and in children with CD. However no data

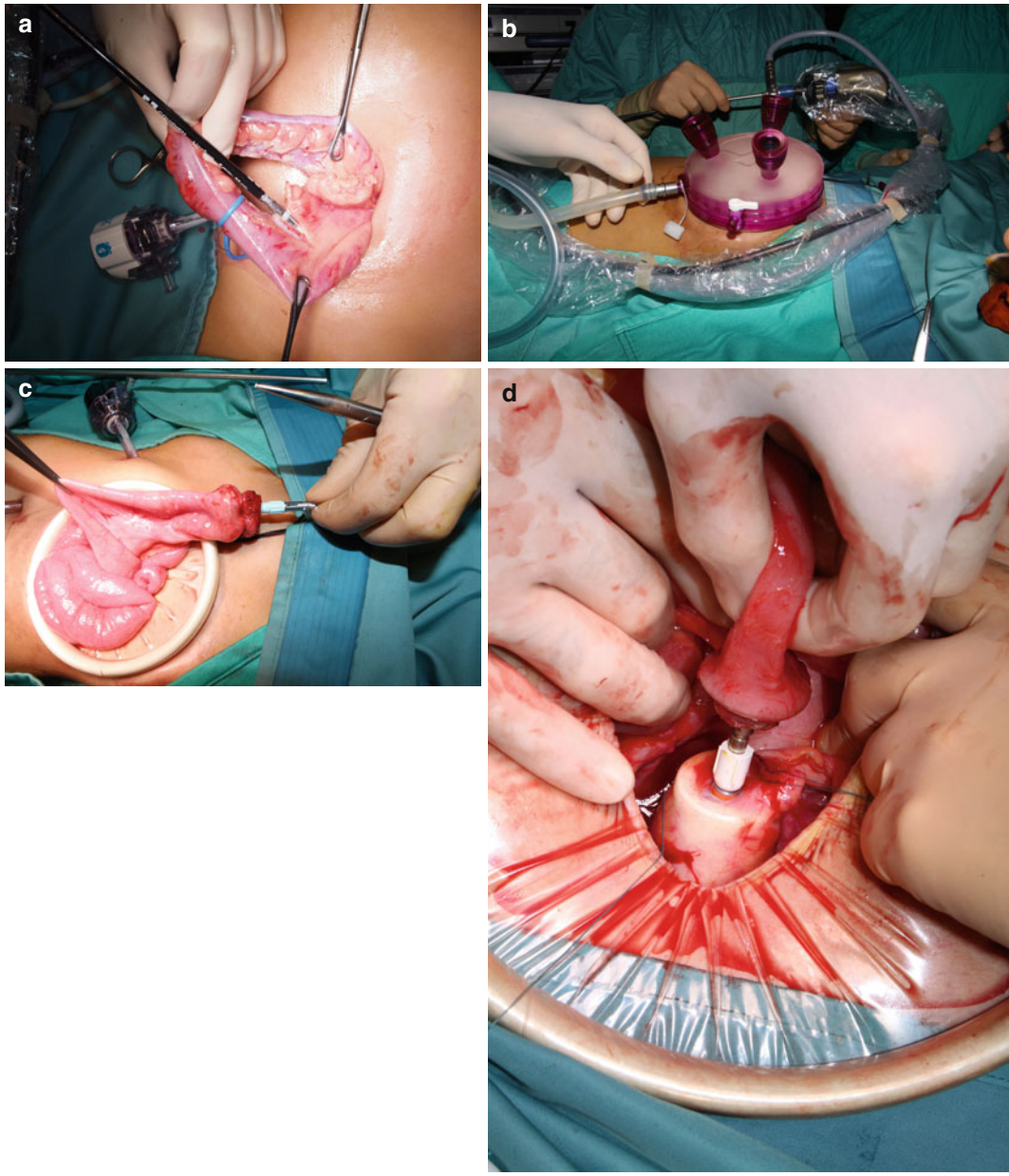


**Fig. 23.3** Colectomy can be performed with a video-assisted technique exteriorizing the colon through the umbilical wound during a fist surgical stage (**a**); when intestinal recanalization has to be done, the ileostomy site can be used to free intestinal loop laparoscopically (**b**, **c**) and finally perform an ileorectal anastomosis (**d**)

support the role of any microorganisms as the causative pathogen of CD. Genetics has an important role in CD pathogenesis; monozygotic twins show a phenotype concordance of 50–70 % in CD patients, with an increased risk (800-fold) compared to general population. Several susceptibility genes are discovered: variants of NOD2, IL23 receptor, ATG16L1, and IRGM and mutations of IL10RA, and IL10RB. NOD2 gene defect has an impaired ability to recognize and process bacterial products, a condition which could determinate an abnormal immune

response. ATG16L1 and IRGM gene defect have an impaired ability to process cell degradation products and so a disability to eliminate pro-inflammatory factors. Impaired IL10 signaling is associated to a very early-onset CD, an aggressive treatment-resistant CD colitis with perianal involvement.

## 23.2.4 Clinical Presentation

Crohn's disease is a chronic, relapsing, inflammatory disorder which could develop in any part of the gastrointestinal tract. A percentage of 60 % of children with CD have an extensive ileocolonic involvement and 20–30 % an isolated colonic involvement. Terminal ileum is the most common affected area. Classical symptoms and signs are abdominal pain, diarrhea, weight loss, fever, and failure to thrive. Deficit or delay in sexual development could be present and could be the main presentation of the disease; thus, particular attention should be given to these symptoms. Growth failure has been reported in up to 40 % of children with CD and comes from several factors as malnutrition, increased gastrointestinal loses, malabsorption, and medical effects. Inflammation could have a negative effect upon some linear growth, contributing to growth retardation. Maintaining adequate nutrition, minimizing inflammation, and maximizing corticosteroid-free treatment are goals to achieve in the management of the disease.

## 23.2.5 Diagnosis

A definite diagnosis is not found by a single specific test, but results from the association of several factors, such as family and personal history, physical examination, laboratory test, imaging, and endoscopic studies. Infectious diseases (*Salmonella*, *Yersinia*, *Shigella*, *E. coli*) and vasculitides such as Henoch-Schonlein purpura and hemolytic-uremic syndrome should be excluded. Several conditions such as intestinal lymphoma could mimic CD, and this entity should be carefully carried out [14].

### 23.2.5.1 Serologic Test

These tests are the first line in the diagnosis of CD in children. Particular attention should be given to the acute reactants, C-reactive protein, whose levels correlate with clinical, endoscopic, and histologic disease activity. Studies demonstrate the potential role of *Saccharomyces cerevisiae* antibodies (ASCA) and perinuclear antineutrophil cytoplasmic autoantibodies (p-ANCA) as marker of IBD. In particular CD-positive ASCA counts correlated to younger at onset, ileal disease, aggressive behavior, and increased risk of early surgery.

*Pseudomonas fluorescens*-related protein was related to stenotizing IBD and necessity of surgery, and anti-*E. coli* outer membrane porin C has been associated to penetrating disease. Both the presence and the grade of immune response were correlated with more aggressive disease.

### 23.2.5.2 Fecal Markers

Calprotectin is a noninvasive test for the diagnosis and monitoring of activity of IBD. Calprotectin is a calcium-binding protein found in the feces, which could be quickly quantified by an enzyme-linked immunosorbent assay (ELISA). On the basis of the stability of the protein in stool specimens, the patient could simply collect a specimen at home without particular precautions. This protein is particularly useful to confirm tissue healing and predict disease relapses. Studies demonstrate a sensitivity of 89–90 % and specificity of 82–83 % for predicting disease relapse.

### 23.2.5.3 Imaging

Children affected by CD require frequent evaluations during follow-up, so radiation-free imaging test is an important alternative to endoscopy. Magnetic resonance (MR), ultrasound (US), and computed tomography (CT) could be the choice to define activity and complications of the disease. CT exposes the children to a large dose of radiation, so other techniques are preferable. MR with oral contrast (MRE) determinates a luminal distension which permits a better visualization of bowel wall and regularity associated to a detailed assessment of perianal disease. MRE is the imaging study of choice in IBD diagnosis and

follow-up in children. Abdominal US presents safety profile and low costs and permits high-resolution images with recent advances. A small intestine contrast ultrasonography (SICUS) is a technique performed after the administration of an oral contrast, which permits to visualize and assess the entire small bowel with higher sensitivity and specificity of standard US [3].

#### 23.2.5.4 Endoscopy

Ileocolonoscopy (IC) and esophagogastroduodenoscopy (EGD) should be recommended as the initial work-up for patients with suspected CD. Endoscopic features in CD are present throughout the entire GI tract. Endoscopic lesions in CD are discontinuous and segmental; frequent are deep serpiginous ulcers (Fig. 23.4) and cobblestoning. These exams are also useful in staging the severity of the disease and monitoring the response to therapies, to evaluate postoperative recurrence and to treat strictures. In selected patients, endoscopic dilation (Fig. 23.5) is a safe and effective alternative to surgery for the management of strictures and should be considered before surgery in short anastomotic strictures (<4 cm). Multiple biopsies should be executed in all areas of gastrointestinal tract, even in the absence of macroscopic lesions. Histologic features in CD are focal crypt distortion, ulcers, mucin depletion, focal cryptitis, focal lymphoplasmacellular infiltration of the lamina propria, granulation tissue-like inflammation, and epithelioid granulomas.

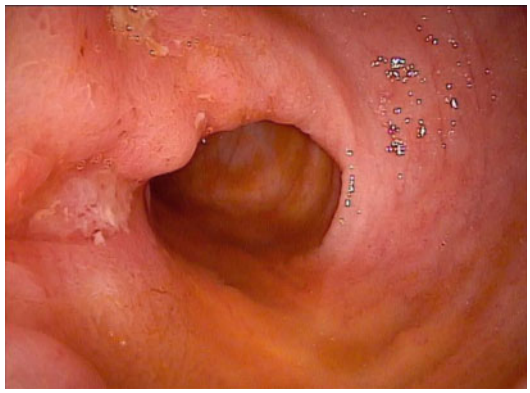

**Fig. 23.4** Deep serpiginous ulcer of the terminal ileum

Small bowel capsule endoscopy (CE) permits the study of small bowel lesions without the use of radiation. Advantages of this technique are the capacity to study the entire small bowel, simple preparation, and better tolerance by the children. Disadvantages are the incapacity of performing biopsies, no way to guide the capsule, obscured visualization due to luminal bubbles or debris, or delayed intestinal transit resulting in an inaccurate exam. CE is contraindicated in patients with strictures because of the risk of capsule retention. If stricture is suspected, patency capsule should precede CE. Balloon-assisted enteroscopy (BAE) is indicated in selected cases where biopsies and therapeutic procedures (i.e., stricture dilation) or CE retrieval are needed [1].

### 23.2.6 Therapy

Treatment of pediatric CD is finalized to achieve and maintain a stable remission with the minimum grade possible of drug toxicity. So the primary aim of CD therapy is to prevent relapses, to preserve growth and pubertal development, and to assure a good quality of life. Conventional therapy is based on the shift from drugs with a better safety profile but lower efficacy (mesalazine, sulfasalazine, antibiotics) to those with

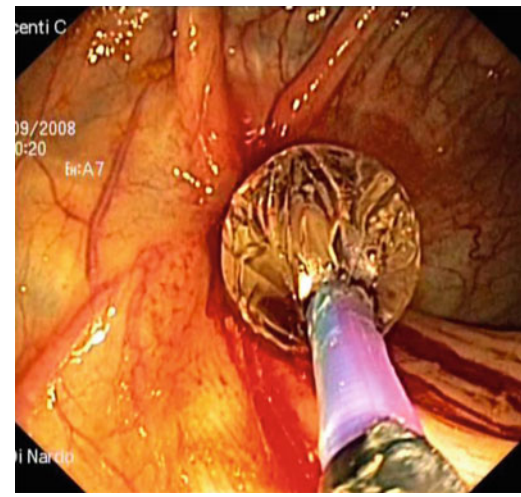

**Fig. 23.5** Endoscopic balloon dilation of a short anastomotic stricture

improved efficacy but a greater risk of side effects (steroids, immunomodulators, biologicals, surgery). This "step-up" approach determinates several advantages as reserving more toxic drugs for "particularly resistant" patients [16, 17].

#### 23.2.6.1 Conventional Therapy

Aminosalicylates are frequently used in the management of pediatric CD, although no randomized controlled studies were performed to evaluate the efficacy of these drugs in determining and maintaining the remission in children. No data support the use of this drug in ileal CD.

Corticosteroids are used to induce remission in moderate-to-severe CD. This drug is usually quickly weaned after the induction, on the basis of its understood adverse affects. Particular attention should be given to budesonide, an oral steroid preparation that is released in the distal ileum and proximal colon. This drug should be considered in patients with mild-to-moderate disease of those segments. Budesonide presents less systemic effect than other steroids, but quick withdrawal could determine adrenal insufficiency.

#### 23.2.6.2 Immunomodulators (Azathioprine, 6-Mercaptopurine, Methotrexate)

Thiopurines are usually used in maintenance therapy of pediatric CD. Their efficacy is shown in several studies in maintenance of remission in CD. These drugs are not used for induction of remission on the basis of their slow onset of action (2–3 months). The remission usually can be achieved 1 year after the beginning therapy. Methotrexate is often regarded as a second-line treatment in CD patient not responding or intolerant to thiopurines.

#### 23.2.6.3 Biological Agents

Infliximab, a chimeric monoclonal anti-TNF IgG1 antibody, has been introduced since 15 years ago in the management of pediatric IBD and is given intravenously. This drug has an important role in both inducing and maintaining remission in pediatric CD. The major effects of the use of infliximab are to induce mucosa healing and to reduce the necessity of corticosteroid, the hospitalization, and the surgery. It could also be used in cases with perianal involvement. Induction dose is 5 mg/kg at 0, 2, and 6 weeks, followed by 5 mg/kg maintenance infusion every 8 weeks. This program determinates a remission rate of 60 % at week 30 and of 56 % at week 54. The risk of using this drug is the development of opportunistic infections or a particular type of lymphoma, hepatosplenic T-cell lymphoma (HSTCL), which affects particularly the young male patients.

Adalimumab is a humanized anti-TNF-α drug effective both in induction and maintenance of remission for children with CD. It is useful in particular in patients intolerant or unresponsive to infliximab.

#### 23.2.6.4 Nutrition

Exclusive enteral nutrition (EEN) is used as a treatment to reach remission in children with acute CD. Nutritional therapy is based on the use of several products, such as elemental, semi-elemental, and polymeric formulas, as first treatment to achieve and maintain remission in CD, to improve growth, and to replenish micronutrient deficiency. Evidence of nutritional therapy as the first-line treatment is controversial. The most frequent theory, about its mechanism of action, is that the microbiota of the gut lumen changed under the use of enteral nutrition; the reduction in antigenic load associated to EEN could also contribute to bowel rest. However, the major limitation of EEN is the poor compliance; most parents are reluctant to commit their children to total enteral nutrition for 5–8 weeks as required, and few children are able to consume an adequate volume of formula by mouth, thus requiring the insertion of a nasogastric tube.

### 23.2.7 Surgical Management of CD

Surgery in Crohn's disease is reserved to those patients who do not respond to medical therapy, have a failure of growth, or develop complications such as fistulas, abscess, strictures,

bleeding, obstruction, and perforation. Although surgery cannot cure definitively CD and therapy is primarily medical, approximately 80 % of patients will need surgery during their clinical course [18].

The aim of surgery is to restore health and improve quality of life resecting as little bowel as possible since a large part of patients will have recurrence after intestinal resection.

Treatment of left-sided colitis continues to be debated as it has been shown to relapse early following segmental resection or develop complications. Despite this, segmental resection continues to be advocated, citing preservation of anorectal function and decreased postoperative symptoms [19].

Laparoscopy can offer benefits also in pediatric patients with CD. The main advantages include faster postoperative recovery, decreased risk of wound-related complications, formation of fewer intra-abdominal adhesions, and better cosmesis [20].

#### 23.2.7.1 Anastomotic Technique

After segmental resection, anastomosis can be performed with different techniques: end to end or side to side and handsewn or stapled. It's difficult to desume the best choice from the literature data. Simillis et al. concluded that side-to-side anastomosis is associated to a less postoperative complications rate, while an earlier meta-analysis did not show difference between the two techniques. Stapled anastomosis seems to be safer, but familiarity with this technique is mandatory to reduce complications [21, 22].

#### 23.2.7.2 Strictureplasty

Strictureplasty can be performed associated or not to segmental resection. The technique follows the Heineke-Mikulicz principle and involves creation of a longitudinal incision through the narrowed area while closing transversely, which widens the lumen.

Strictureplasty offers good results in chronic stenosis avoiding extensive resections but should not be performed in acutely inflamed bowel.

#### 23.2.7.3 Abdominal Abscess

Abdominal abscess should be treated with systemic antibiotic and percutaneous drainage that promote healing and should be used for >2 cm abscess [23]. The drainage is left in place till the outlet becomes <10 ml/day. Antibiotics against both nosocomial and community-acquired organisms are empirically selected till an antibiogram is obtained and subsequently adapted to the sensitivity of cultured organisms.

Patients with persistent or recurrent abscesses will have benefit from surgical drainage and resection of the affected tract.

#### 23.2.7.4 Intra-abdominal Fistulas

The aim of surgery is to interrupt fistula and resect the affected tract obtaining macroscopically free margins. The resection should be aimed at saving as bowel as possible considering that loss of colonic length is less dire than loss of small bowel.

#### 23.2.7.5 Perianal Disease

Perianal disease is characterized by the onset of perianal abscesses and fistulas. The principles of the management are a prompt identification and drainage of the septic focus, an appropriate medical therapy, and a conservative surgery if necessary. The most recommended surgical approach is the placement of a seton after drainage of purulent collections. Perianal setons promote drainage, prevent abscess recurrence, and provide pain relief but keep the fistula open until seton is removed. On the other hand, the impaired wound healing of patients affected by CD makes extensive perianal surgery quite hazardous. Fistulotomy can be performed in well medical-controlled patients with extra-sphincteric or short low intersphincteric fistula tracks.

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