Ulcerative Colitis

30

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Introduction

Chronic inflammatory bowel diseases (IBD), which include Crohn's disease (CD), inflammatory bowel disease unclassified (IBDU) and ulcerative colitis (UC), are important causes of gastrointestinal disease in children and adolescents. The early age of disease onset in some children, variable clinical presentations, therapeutic challenges, as well as emotional needs of children and their parents pose difficult challenges to the gastroenterologist.

Epidemiology

UC has an increasing incidence and prevalence worldwide, especially in adolescents and young adults. The incidence of UC may vary from 0.5 to 31.5 per 100,000 people each year, depending on the studied population. In general, the disease has a high occurrence in Western countries such as those in North America and Northern/Western Europe compared to Asian countries. However, incidence rates have plateaued or even decreased in Western countries over time, and in contrast incidence has been steadily increasing in more developed countries in Asia as well as in Central and South America. In Asia in particular, the incidence of IBD is 1.4 cases per 100,000 people and climbing [1].

There is also a geographical gradient for the incidence of IBD, with higher rates in the north as compared to the south [2]. Additionally, pediatric-onset IBD continues to increase steadily. As IBD is a chronic disease with relatively low mortality that is diagnosed primarily in young people, the prevalence of IBD increases over time such that new diagnoses add to the base population at a rate significantly higher than the loss of patients from a clinical practice [1].

According to a single-center prospective study by Capone et al. there was an increase in the prevalence of IBD for first-degree relatives and all relatives at 20 years from the time of diagnosis by 12.9% and 13.7%, respectively. Additionally, positive family history at diagnosis was associated with a 2-fold greater likelihood of subsequent positive family history at 20 years. This suggests an increased role of environmental factors and lifestyle effects on the pathogenesis of UC [3].

The female to male ratio for UC differs between 0.51 and 1.58, indicating that UC is not sex specific. Any age group from infants to the elderly can be affected, but the peak age of onset is between 15 and 30 years with a second but smaller peak between 50 and 70 years. About 20 to 30% of patients with UC and CD have the onset of their symptoms below the age of 18 years, and about 5% of cases occur before age 10 years [4].

Pathogenesis

UC can be considered an immune-mediated disorder that develops in genetically predisposed individuals because of dysregulated immune responses against environmental and intraluminal antigens [5]. More recently the focus of research has shifted to examining the interplay between the environment (mainly the intestinal flora) and the defense mechanisms of the intestinal barrier (mainly the mucosal layer and the mucosal immune system). These aberrant immune responses to commensal microbes likely result in lesions of the intestinal mucosal layer involving extensive epithelial damage, immune infiltration, crypt abscesses, and chronic inflammation, which are hallmarks of UC [6].

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S. Guandalini, A. Dhawan (eds.), *Textbook of Pediatric Gastroenterology, Hepatology and Nutrition*,
https://doi.org/10.1007/978-3-030-80068-0_30

Genetics

In a recent meta-analysis of genome-wide association studies (GWAS) for CD and UC, more than 200 IBD-associated loci were identified. Many of them are associated with both UC and CD. These regions contain candidate genes for a variety of functions like autophagy, microbe recognition, lymphocyte signaling, response to endoplasmic reticulum stress, and cytokine signaling, among others. While GWAS has uncovered many new pathogenesis pathways, each locus only has a very small to modest effect size, with the exception of a strong association for the human leukocyte antigen (HLA) loci on chromosome 6 that has consistently shown a large effect on UC susceptibility [7].

UC is more common in the Jewish population. The lower concordance rate in monozygotic twins of 15% and in dizygotic twins of 5% in UC, compared with 50% in monozygotic twins and 20% in dizygotic twins in CD, indicates that genetic contribution in UC is weaker than in CD [8]. In the case of "very early onset" or VEO-IBD, mutations of the genes *IL-10RA*, *MSH5*, and *CD19* are associated with disease development [9].

Environmental Factors

Increasing incidence particularly in industrialized countries indicates environmental influences in the development of UC. In fact, cesarean delivery, lack of exposure to breast milk [10], increased dietary fat intake (i.e. a "western diet"), and early exposure to antibiotics have all been implicated as risk factors for IBD. Patients with newly diagnosed UC are more likely than age-matched controls to have a history of gastroenteritis [11]. Interestingly, early appendectomy prior to the age of 20 years is associated with decreased risk of UC [12]. In a meta-analysis of 13 studies examining the relationship between UC and smoking, there was an association between former smoking and the development of UC, with current smoking having a protective effect on the development of UC compared to controls [13, 14].

Children of persons who emigrated from an area of low prevalence to one of high prevalence show an increased risk of UC than the immigrants themselves, suggesting that environmental factors in early life that affect the developing immune system and microbiome are essential to UC pathogenesis [5, 15]. The natural geographic distribution of IBD, with higher rates seen in the north and lower rates seen in the south, introduces the question of whether vitamin D and sunlight are protective factors.

UC and the Microbiome

The IBD gut is characterized by reduced microbiome diversity and a depletion of protective bacteria such as short-chain fatty acid (SCFA)-producing Ruminococcaceae and Lachnospiracaea that coincides with an expansion of pro-inflammatory microbes such as Enterobacteriaceae, including *Escherichia coli* and Fusobacteriaceae [6]. SCFAs including butyrate are a major fuel source for colonic epithelium and are associated with better gut health; notably, oxidation of butyrate is impaired in UC patients [16]. Blooms of *Ruminococcus gnavus* strains and an increase in facultative anaerobes co-occur with more severe IBD activity. Microbes also show protective effects in mouse models, and *Bacteroides fragilis* mono-colonization has been shown to protect against induced colitis. Depletion of butyrate-producing *Faecalibacterium prausnitzii* in IBD has been reported previously in the literature, and animal studies have shown that *F. prausnitzii* inhibits IL-17 and suppresses Th17 activity, suggesting an association between this bacterium and reduced mucosal inflammation. Topical butyrate is effective as an adjunct therapy for UC, and butyrate enemas have been shown to reduce mucosal inflammation in distal UC, indicating a benefit of increased butyrate levels. The anti-inflammatory activity of butyrate in UC has been associated with inhibition of NF-kB activation in lamina propria macrophages, reducing cytokine secretion and inflammation [6]. Early onset dysbiosis may cause immune disruptions that result in microbiome intolerance by the host. Factors that cause early-life dysbiosis, including antibiotic usage, have gained more attention as the incidence of pediatric IBD has increased dramatically [17].

Clinical Manifestations

UC always affects the rectum and extends proximally in a symmetric fashion involving variable lengths of the colon. Involvement could be limited to the rectum (proctitis), or can extend to the distal colon (up to splenic flexure or left-sided colitis) or the entire colon (pancolitis). Children tend to have a higher likelihood of pancolitis at presentation as well as proximal extension of disease over time compared to adults [18]. In fact, 60–90% of pediatric UC presents with pancolitis, which is twice as often as adult UC. Additionally, pediatric UC carries a 30–40% colectomy rate at 10 years, compared to 20% in adult UC. Childhood-onset disease is also characterized by a higher risk of corticosteroid dependency and earlier immunosuppressive therapy introduction [19].

Intestinal Manifestations UC is usually diagnosed earlier after the onset of symptoms than CD, as rectal involvement leads to the presence of gross blood in the stools alerting parents and physicians to a gastrointestinal problem. The most consistent feature of UC is the presence of blood and mucus mixed with stool, accompanied with lower abdominal cramping that is most intense during the passage of bowel movements. Patients may also experience tenesmus, which a sensation of needing to evacuate stool. The location of abdominal pain depends on the extent of colonic involvement. Pain in the left lower quadrant is associated with distal disease and extends to the entire abdomen with pancolitis. Systemic symptoms including fever, anorexia, weight loss, and anemia may occur with fulminant colitis [11].

Nevertheless, the diagnosis of pediatric-onset UC may be more challenging due to the existence of atypical phenotypes. "Atypical UC" is suggested when features not characteristic of classic UC are present, but common enough in UC to preclude the diagnosis of CD. In particular, six different atypical phenotypes have been recently identified in the revised criteria from the Pediatric IBD Porto Group of the European Society of Pediatric Gastroenterology, Hepatology, & Nutrition (ESPGHAN) for the diagnosis of pediatric UC: rectal sparing, short segment disease, cecal patch, upper gastrointestinal (UGI) findings, acute severe colitis (ASC), and "backwash ileitis" [19]. The presence of ileitis may complicate the potential diagnosis of UC, and although UC is restricted to the colon by definition, nonspecific mucosal inflammation in the terminal ileum (called "backwash ileitis") may be found in up to 20% of UC patients [20]. According to the Porto criteria, backwash ileitis should entail a "short segment of nonstenotic erythema or edema in the presence of pancolitis including the ileocecal valve, without granulomata or deep ulcers" which would suggest CD [21].

Extraintestinal Manifestations

As IBD is a systemic disease that can involve multiple organs, patients with IBD often exhibit extraintestinal manifestations (EIM). In up to 28% of pediatric patients, EIMs are present at diagnosis [18]. In fact, rates of EIM at IBD onset are higher in children compared to adults [22]. EIMs are more commonly seen in CD compared to UC (30–71% vs. 21–22%). EIM's are usually related to disease activity but may precede, develop concurrently, or may also occur after a colectomy [18]. Data from the PediIBD Consortium Registry including 1649 children with IBD show a cumulative incidence of EIMs of 9% at 1 year, 19% at 5 years, and 29% at 15 years after diagnosis. Thus, in 29% of pediatric IBD patients who do not have EIMs at the time of diagnosis, at least one EIM will develop within 15 years [23]. Since up to 35% of pediatric IBD patients may manifest EIM prior to intestinal symptoms, IBD should be suspected in children with EIMs to prevent delays in diagnosis and treatment [18]. EIMs predominantly involve four organ systems: skin, joints, biliary tract, and eyes. Skin-related EIMs include erythema nodosum, pyoderma gangrenosum, psoriasis, and aphthous stomatitis. Eye-related EIMs include episcleritis and uveitis. Other EIMs include peripheral arthritis, axial arthropathy, osteoporosis, primary sclerosing cholangitis, and chronic active hepatitis [5].

Arthralgia and Arthritis

Arthralgia and arthritis occur frequently in about 5–20% of children with UC and may occasionally precede intestinal manifestations of IBD [24]. They usually coincide with disease activity and improve with medical treatment of underlying intestinal inflammation. They can be classified into two forms: peripheral arthropathy and axial arthropathy (AS) [25]. Peripheral arthropathy or arthralgia is usually pauciarticular affecting large joints, such as knees, ankles, hips, wrists, and elbows in decreasing order of frequency. Joint deformities are usually not seen.

Ankylosing spondylitis (AS) is more common with UC and is associated with HLA B27 in 50 to 80% of cases. Progression is variable and does not appear to correlate with severity of bowel symptoms. Colectomy does not affect the course of AS. Sacroileitis is usually asymptomatic and may be detected on bone scans.

Chronic recurrent multifocal osteomyelitis (aseptic inflammation of the long bones and clavicles) and hypertrophic osteoarthropathy (digital clubbing, painful swelling of limbs, arthralgia, joint effusions) are uncommon but have been described. Both of these conditions are managed by treating the underlying colitis [26].

Mucocutaneous Lesions

Oral aphthous ulcers occur less commonly with UC (5%) as compared to CD. Ulcers usually cause minimal discomfort although they may occasionally cause debilitating pain. They tend to parallel disease activity and treatment is directed towards the underlying disease.

Pyoderma gangrenosum (PG) is a deep severe ulceration of the skin and is an unusual manifestation with UC (<1%). Lesions can be multiple in number and are typically located below the knees. Biopsy of the lesion shows neutrophilic infiltration with abscess surrounded by a lymphocytic vasculitis. PG usually parallels active colonic disease but on occasion may be refractory to treatment and may require intensive

local therapy, corticosteroids (CS), minocycline, dapsone, clofazimine, cyclosporine, or infliximab.

Erythema nodosum is characterized by the development of painful, indurated, purplish red, ovoid nodules 1 to 3 cm in diameter, most commonly seen over extensor surfaces. Erythema nodosum is less common in UC, and improvement coincides with the treatment of the bowel disease [27].

Ophthalmologic Disease

Eye abnormalities are described in approximately 1.6 to 4.6% of children with UC [28]. Iritis and uveitis are associated with the presence of the human leukocyte antigen HLA-B27 and typically run a course independent of the bowel disease. They present with eye pain, headache, and blurred vision or may be asymptomatic and detected by slit lamp examination. Treatment consists of pupillary dilatation, covering the eye to decrease pain and photophobia and local or systemic corticosteroids. Episcleritis usually is related to disease activity and presents with scleral and conjunctival erythema with a burning sensation and photophobia. Local corticosteroid drops are usually effective.

Hepatobiliary Disease

Primary sclerosing cholangitis (PSC) is usually seen in association with UC. PSC is a chronic progressive cholestatic disease characterized by inflammation and fibrosis of the intrahepatic and extrahepatic biliary tree resulting in multifocal strictures. It is diagnosed based on a cholestatic biochemical pattern and a characteristic "beaded" appearance on cholangiography, which defines large duct, or "classic" PSC. In contrast, "small duct" PSC is only identifiable by liver biopsy without the presence of cholangiographic abnormalities. It is a less common variant with a more benign course. PSC may be asymptomatic and is detected because of elevated alkaline phosphatase and γ-glutamyltransferase (GGT) during routine blood screening. Patients may occasionally present with pruritis and PSC prior to the development of UC. The course of PSC appears to be unrelated to underlying bowel disease and may progress even after a colectomy. Peripheral antineutrophilic cytoplasmic antibodies (pANCA) are positive in most patients with PSC and may be a marker for genetic susceptibility for this disease.

Colorectal cancer (CRC) has been associated with concomitant PSC and IBD, with patients having a higher risk of CRC at a younger age when compared to non-IBD PSC patients [29, 30].

Autoimmune hepatitis (AIH) is also seen in association with UC. Diagnosis is made following a liver biopsy, which shows lobular inflammation with piecemeal necrosis. Treatment includes CS and immunosuppressive medications. As with PSC the course of AIH can be independent of UC.

Diagnostic Criteria

The diagnosis of UC is based on clinical presentation and then confirmed by laboratory screening tests, radiologic examination, endoscopic appearance, histopathology, and serological findings. Additionally, it is extremely important to exclude the presence of enteric pathogens before confirming the diagnosis of UC. Lennard-Jones suggested the following criteria for the diagnosis of UC: contiguous mucosal inflammation without granulomata, always involving the rectum and extending continuously in various degrees to a part or the whole colon [31]. However, universally accepted well-defined criteria or a point score for classification of UC do not exist. Abnormalities like complex or fistulizing anal lesions, involvement of the upper gastrointestinal (UGI) tract, skip lesions, or granulomata are highly suggestive of CD [5].

Endoscopic and Histological Features

All patients should undergo endoscopic evaluation (colonoscopy and esophagogastroduodenoscopy) with biopsies taken from all segments of the intestine as part of medical workup. Endoscopic features of UC include continuous mucosal ulcerations starting from the rectum with erythema, friability, and loss of typical mucosal vascular pattern. The Ulcerative Colitis Endoscopic Index of Severity (UCEIS) is a method in which to grade endoscopic severity of disease that includes three descriptors: vascular pattern, bleeding, and erosions or ulcerations. The final UCEIS score ranges from 0 to 8, with higher scores denoting increasing disease activity (See Fig. 30.3) [32].

Histological, UC is characterized by diffuse inflammatory cell infiltration of the mucosa with basal plasmacytosis, crypt architectural distortion, cryptitis/crypt abscesses, and a reduction of mucus-secreting goblet cells (See Figs. 30.1 and 30.2) [5, 33] (Figs. 30.3 and 30.4).

Laboratory and Serological Markers

Laboratory findings are important screening tests in the diagnosis and monitoring of UC; however, there are no disease-specific markers yet identified. Common laboratory findings include an elevated white blood cell count, thrombocytosis, elevated inflammatory markers (CRP, ESR, and fecal calprotectin), and measures of deficiencies due to

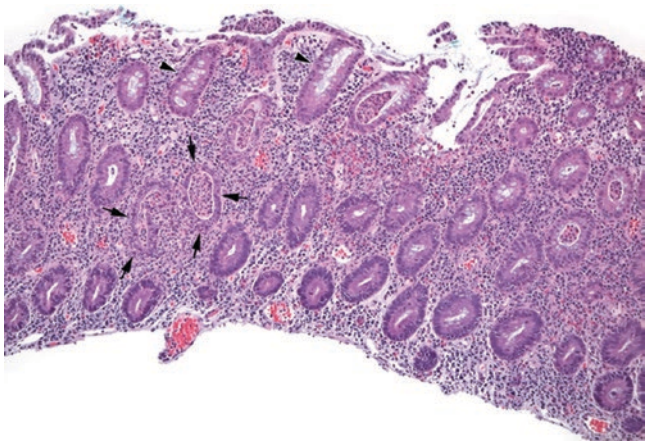

Fig. 30.1 Representative acute inflammatory features. In contrast to relatively well-preserved crypts (arrowheads), crypt abscesses (arrows) are dilated, lined by attenuated damaged epithelium, and contain acute inflammatory cells in the epithelium and the lumen of the crypt (hematoxylin and eosin). (Reprinted with permission from Boyle et al., "Histologic Correlates of Clinical and Endoscopic Severity in Children Newly Diagnosed With Ulcerative Colitis")

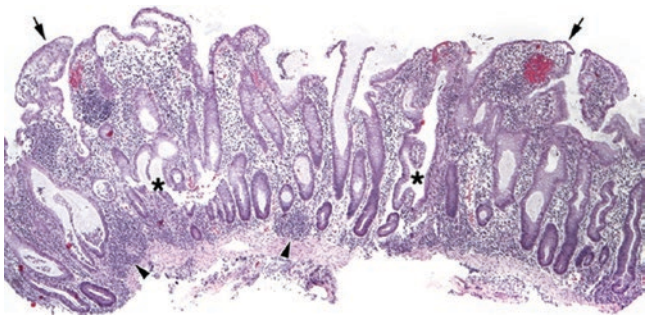

Fig. 30.2 Representative architectural and nonarchitectural features. Surface villiform changes are evident (arrows), elongated crypts are easily identified, crypts with abnormal shapes are seen (asterisk), as are subcryptal lymphoid aggregates (arrowheads) (hematoxylin and eosin). (Reprinted with permission from Boyle et al., "Histologic Correlates of Clinical and Endoscopic Severity in Children Newly Diagnosed With Ulcerative Colitis")

increased losses from diarrhea (iron deficiency anemia, hypoalbuminemia) [34].

On presentation, serum inflammatory markers (CRP, ESR) are usually higher in CD compared to UC. In a cohort of 512 children with the new diagnosis of UC, 54% of those with mild disease had normal results on four common laboratory assays (hemoglobin, albumin, platelet count, and ESR), compared with 21% of children with mild CD [35]. ESR and CRP are fairly correlated with colonic inflammation, with a slight superiority of CRP [34]. Fecal calprotectin levels above the cutoff of 100 μg/g have been shown to correlate with mucosal inflammation in UC and are considered to be superior to inflammatory markers in the blood, which may be nonspecific. Fecal calprotectin is also useful for long-term follow-up and in differentiating IBD from functional causes [34].

Generally, serological antibodies related to IBD encompass either autoantibodies or antibodies targeting microbial antigens. Particular microbial antibodies include antibodies directed against the yeast *Saccharomyces cerevisiae* (ASCA), *Escherichia coli* outer membrane porin C (Omp-C), and flagellin (cBir1), which suggests that commensal flora may be triggering a deleterious immune response in patients with IBD [36].

The most frequently studied serological markers in IBD are perinuclear antineutrophil-cytoplasmic antibodies (pANCA) and antibodies against *Saccharomyces cerevisiae* (ASCA). pANCA can be found in 50–70% of UC patients and in less than 10% of CD patients, mainly in those that have a "UC-like" phenotype. pANCA positivity and a negative test for CD-specific ASCA indicate that UC is more likely than CD. In patients with IBD-U, the results of both pANCA and ASCA can aid in making a definitive diagnosis [37].

Previous studies have shown that pANCA titers can be used to stratify patients into distinct subgroups. In a pediatric study from 1998, Ruemmele et al. observed differences in pANCA titers within subgroups of IBD, with equally high titers in both UC-like CD with pancolitis (median of 68.2 EU/mL) and in UC (median of 57.7 EU/mL) [38]. In adults, a preoperative pANCA titer greater than 100 was shown to be a risk factor for the development of chronic pouchitis after ileal pouch-anal anastomosis [39]. An association between high pANCA titers and both pancolitis and backwash ileitis has also been reported [40].

Beyond phenotypic predictions, pANCA titers have been linked to response to therapy. A retrospective study of 56 UC patients with left-sided disease showed that patients who were pANCA-positive were more likely to have treatment-refractory disease than patients with negative pANCA (90% vs 62%) [41]. In a 2007 study of 100 IBD patients starting infliximab, patients who were pANCA+ and ASCA− had lower early clinical response to infliximab (55% vs 76%). In a pediatric study from 2010, Dubinsky et al. reported that pANCA positivity was independently associated with a primary nonresponse to anti-TNF-α therapy in both CD and UC [42].

Another serological marker specific for UC are antigoblet cell antibodies (GAB) occurring in 15–28% of UC patients. Using appropriate assays, GAB are highly specific (and may be pathognomonic) for UC [5]. Recently PR3-ANCA, which is a marker for granulomatosis with polyangiitis, was found in certain subsets of UC patients and appeared to be associated with liver involvement, PSC, and more extensive disease. However, further studies are needed to confirm these findings [43].

In the multicenter pediatric PROTECT study, anti-CBir1 positivity was found in 19% of patients with UC. Additionally, anti-CBir1 positivity was associated with rectal sparing,

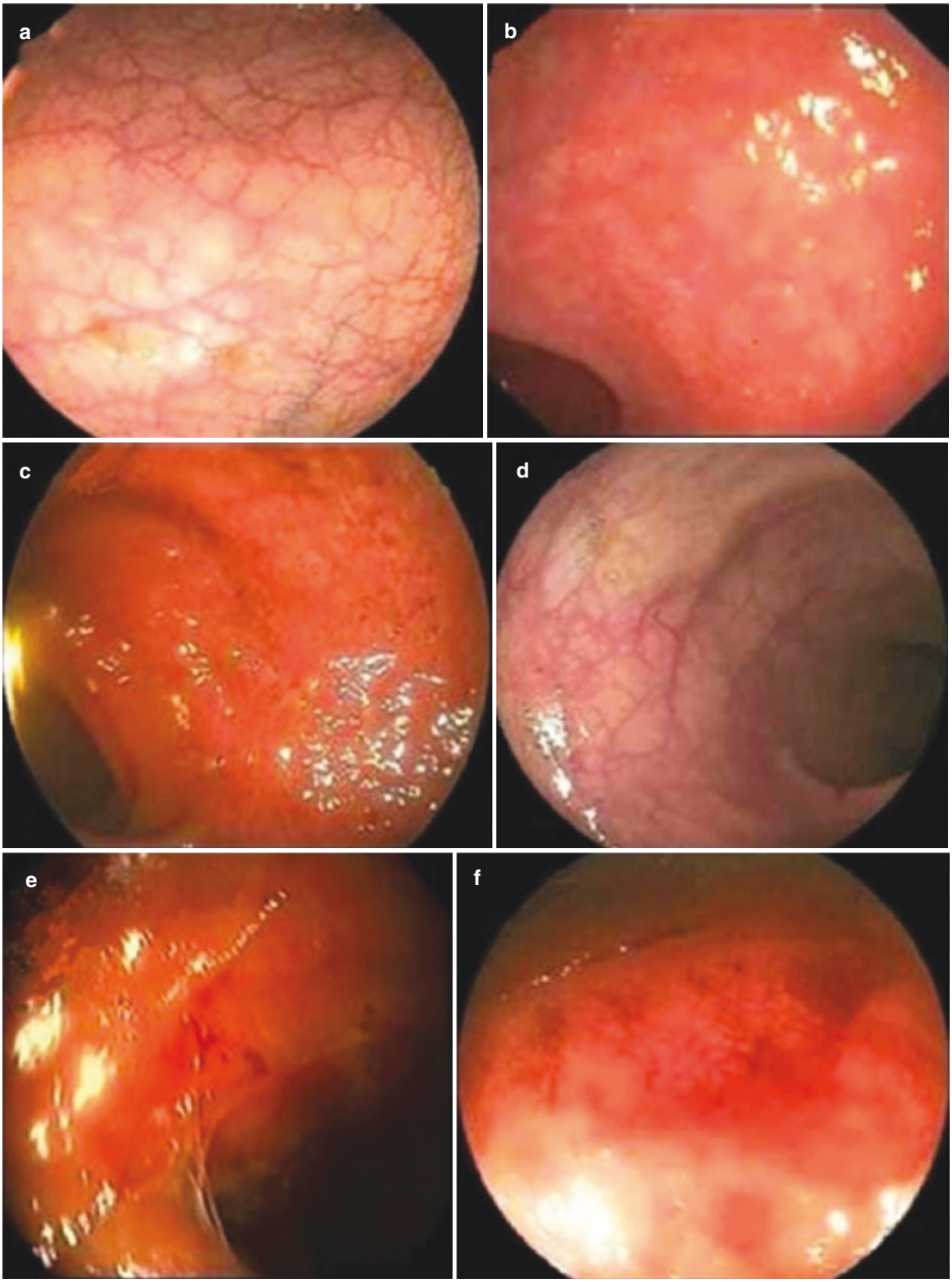

Fig. 30.3 Endoscopic images demonstrating the UCEIS scoring system for: vascular pattern (1–3): (**a**) 1, (**b**) 2, and (**c**) 3; bleeding (1–4): (**d**) 1, (**e**) 2, (**f**) 3, and (**g**) 4; erosions and ulcerations (1–4): (**h**) 1, (**i**) 2, (**j**) 3, and (**k**) 4. (Image courtesy of De Jong et al., "Validation and Investigation of the Operating Characteristics of the Ulcerative Colitis Endoscopic Index of Severity")

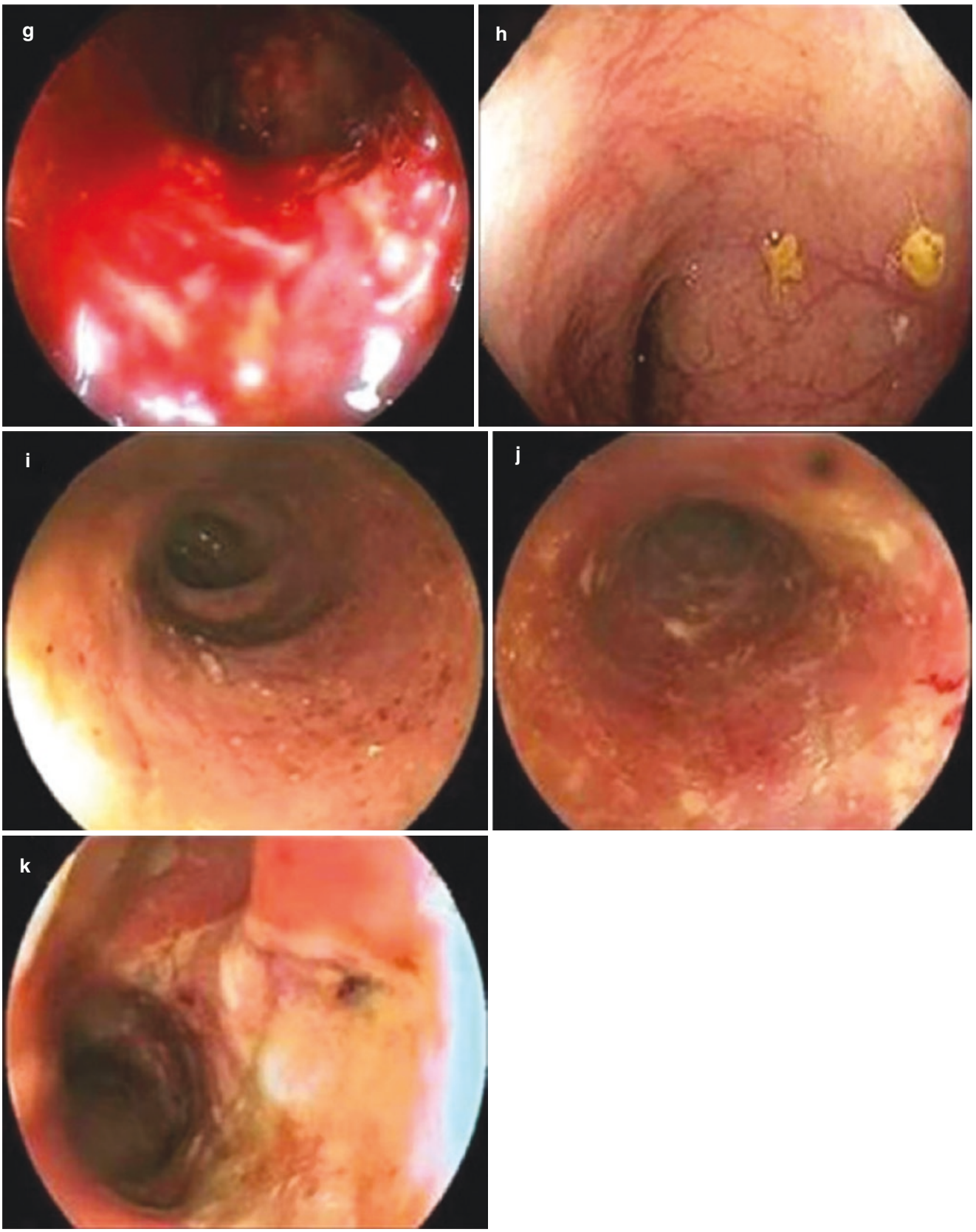

Fig. 30.3 (continued)

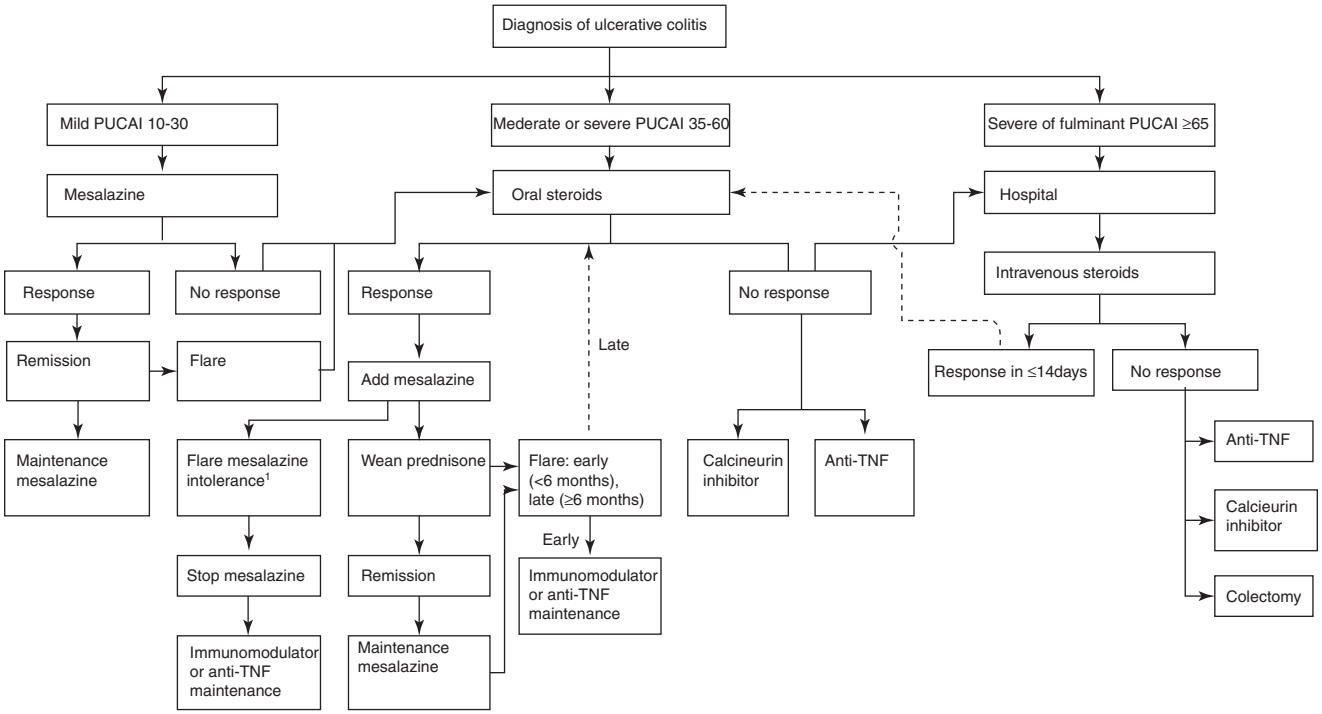

Fig. 30.4 Recommended treatment algorithm for pediatric UC per PROTECT cohort study. (Reprinted with permission from Hyams et al., "Factors associated with early outcomes following standardised therapy in children with ulcerative colitis (PROTECT): a multicentre inception cohort study")

more limited disease extent, less plasma cell infiltrate on rectal biopsy, and lower fecal calprotectin [44].

Activity Indices

There are several UC activity indices for classification and prognosis of UC. For clinical practice, it is sufficient to describe disease activity as mild (up to four bloody stools per day), moderate (four to six bloody stools per day and minimal toxicity), or severe (more than six stools per day and signs of toxicity, such as fever, tachycardia). Fulminant colitis is defined when there are more than 10 bloody stools per day with anemia requiring blood transfusion and colonic dilation on plain abdominal radiographs as a sign of toxic megacolon [5].

A commonly used classification for pediatric UC was developed by the Montreal Working Group. In the "Montreal Classification," disease extent for UC was divided into three categories. The first category (E1) describes patients with proctitis, the second category (E2) describes patients with left-sided disease distal to the splenic flexure, and the last category (E3) describes patients with extensive disease proximal to the splenic flexure. Disease extent was defined using macroscopic appearance rather than histopathologic or radiographic evidence. In 2008, Van Limbergen et al. compared a cohort of children with UC to an adult population with UC, demonstrating that 74.5% of pediatric patients had extensive colitis (E3) based on the Montreal classification, compared to 47% of adult patients [19, 45].

The Montreal classification was further adapted into the "Paris classification for pediatric IBD" in 2011, with greater subdivisions for disease location and age of diagnosis. Using the Paris classification, age groupings are subdivided to distinguish children under age 10 from adolescents between 10 to 17 years of age. The Paris classification includes additional subcategories for disease extent, including E3 (extensive disease distal to the hepatic flexure) and E4 (pancolitis proximal to the hepatic flexure) (See Table 30.1) [46]. E4 pancolitis is the most common phenotype in pediatric UC (57–75%), followed by E2 left-sided UC (10–59%), E1 ulcerative proctitis (5–18%), and E3 extensive disease distal to hepatic flexure (4–13%) [18].

Table 30.1 Differences between Montreal and Paris Classifications for pediatric ulcerative colitis

	Montreal	Paris
Extent	*E1:* Ulcerative proctitis	*E1:* Ulcerative proctitis
	E2: Left-sided UC (distal to splenic flexure)	*E2:* Left-sided UC (distal to splenic flexure)
	E3: Extensive (proximal to splenic flexure)	*E3:* Extensive (hepatic flexure distally)
		E4: Pancolitis (proximal to hepatic flexure)

Table 30.2 Pediatric Ulcerative Colitis Activity Index (PUCAI)

Item	Points
(1) Abdominal pain	
No pain	0
Pain can be ignored	5
Pain cannot be ignored	10
(2) Rectal bleeding	
None	0
Small amount only, in less than 50% of stools	10
Small amount with most stools	20
Large amount (>50% of the stool content)	30
(3) Stool consistency of most stools	
Formed	0
Partially formed	5
Completely unformed	10
(4) Number of stools per 24 hours	
0–2	0
3–5	5
6–8	10
>8	15
(5) Nocturnal stools (any episode causing wakening)	
No	0
Yes	10
(6) Activity level	
No limitation of activity	0
Occasional limitation of activity	5
Severe restricted activity	10
Sum of PULAI (0–85)	

Generally, a PUCAI score < 10 indicates remission, 10–34 mild disease, 35–64 moderate disease and ≥65 severe disease
Reprinted with permission from Siow et al. "*Management of acute severe ulcerative colitis in children*"

The Pediatric Ulcerative Colitis Activity Index (PUCAI) as developed by Turner et al. is a tool that is widely used in children, in part due to its feasibility, validity, and its potential use as a primary outcome measure to reflect disease activity (See Table 30.2). The PUCAI is a noninvasive tool for assessment of UC disease severity consisting of six clinical items: daily abdominal pain, rectal bleeding, stool consistency, number of stools, nocturnal stools, and activity level for a maximum score of 85. Scores under 10 represent remission while a score ≥65 signifies severe disease activity. Cut-off scores for remission, mild, moderate, and severe disease have been shown to have sensitivity and specificity of >90%. PUCAI is furthermore useful for assessing clinical response to treatment as a fall of >20 points signifies improvement due to medical therapy [47].

Cross-Sectional Imaging

Imaging modalities are of limited utility in the setting of acute colitis when a firm diagnosis of UC has been previously established (unless complications such as toxic megacolon are suspected). However, if the diagnosis of CD has yet to be ruled out, imaging of the entire GI tract should be performed to help distinguish between UC and CD [48]. This is also relevant for future surgical planning in children undergoing an elective colectomy to effectively rule out CD [49].

Small bowel follow-through (SBFT) was previously considered the standard of care in evaluation of the small bowel in IBD, but has fallen out of favor because of its limitations, including the length of time required to complete the test and increased radiation exposure. Furthermore, SBFT has been shown to have limited sensitivity for detecting small bowel disease when compared to newer radiographic methods. Enterography, which uses enteral contrast to optimally view the small bowel, is becoming more widely used and has proven to be highly sensitive for identifying inflammation and strictures. It encompasses computed tomography enterography (CTE) and magnetic resonance enterography (MRE). CTE is more commonly used in the adult population; however, given the high dose of radiation associated with this modality, its use has been limited in pediatrics. MRE is therefore replacing other imaging modalities as the preferred method in identifying small bowel disease in children [49].

Infectious Etiologies

Clostridium difficile (*C. difficile*)

Patients with IBD are more susceptible to *C. difficile* infection compared to the general population. Nylund et al. found that children with IBD were 11 times more likely to have a diagnosis of *C. difficile* compared to patients without IBD [50]. *Clostridium difficile* infection has been shown to worsen disease severity, prolong hospital stay, increase the need for parenteral nutrition and blood transfusions, as well as increase colectomy rates and colitis relapses.

Nucleic acid amplification tests (NAATs) such as PCR for *C. difficile* toxin genes have surpassed toxin A and toxin B enzyme immunoassays (EIA) as the preferred method for diagnosing *C. difficile,* having both high sensitivity and specificity [51].

In the setting of acute severe UC (ASUC), treatment with oral vancomycin (40 mg/kg per day orally divided into four doses for 10 days) is preferred due to several adult studies showing greater response rates to vancomycin compared to metronidazole in the setting of ASUC. However, if the patient has a coexisting ileus or toxic megacolon, intravenous metronidazole (30 mg/kg in four divided doses for 10 days) with Vancomycin delivered via enema is the recommended treatment [52].

Cytomegalovirus (CMV) Colitis

Several investigators have demonstrated that CMV infection is detected more often in patients with steroid-refractory UC and is associated with increased rates of colectomy. A CMV infection rate as high as 67% is seen in steroid-refractory UC compared to 33% in patients with steroid-responsive disease [53]. It is unclear whether CMV positivity is a causative factor contributing to disease severity or simply a marker of more severe disease. Serologic testing for CMV is not reliable and the diagnosis is usually made via polymerase chain reaction (PCR) or immunohistochemistry (IHC) of intestinal tissue biopsies. A consensus study recommends that children with steroid-resistant disease undergo flexible sigmoidoscopy and biopsy to exclude CMV infection. The decision to initiate antiviral therapy if CMV is detected should be made in conjunction with infectious disease specialists [52]. Recommended treatment is IV ganciclovir 5 mg/kg twice daily for 14 days, with remission rates as high as 67–100% with treatment [54]. A meta-analysis showed that the risk of colectomy was significantly lower in patients with corticosteroid-refractory UC treated with antivirals as compared to those who did not receive antivirals [55].

In a multicenter retrospective case-controlled study of 56 children with ASUC, CMV-positive patients were found to be more resistant to intravenous corticosteroids compared to CMV negative patients. There was also an increased 12-month risk of colectomy that was statistically significant ($p = 0.045$) in the CMV-positive patients [5, 56].

Complications

Toxic Megacolon

Toxic megacolon (TMC) is characterized by total or segmental nonobstructive colonic dilation with signs and symptoms of systemic toxicity. Although the exact incidence of toxic megacolon in pediatric IBD is not known, previous data reports the incidence around 1–5%. Mortality has been reported as 19–50% in adult patients with TMC; however, data is lacking in children. The most common diagnostic criteria for TMC in adults were introduced by Jalan et al. in 1969, which includes the presence of fever, dehydration, hypotension, an altered level of consciousness, hematologic and biochemical abnormalities, as well as radiographic evidence of a dilated colon [57].

Although radiographic evidence of colonic dilation alone is insufficient to diagnose TMC, one retrospective study noted that a transverse colon diameter of ≥56 mm (>40 mm in children less than 11 years old) was highly suggestive of TMC [58]. Importantly corticosteroids, which are commonly used in the treatment of acute colitis, may mask clinical signs of TMC or intestinal perforation. TMC should be treated quickly with intravenous broad-spectrum antibiotics (i.e., ampicillin, gentamicin, and metronidazole), correction of fluid and electrolyte imbalances, *nil* per os (NPO) status, and avoidance of gut-motility slowing agents (i.e., opioids and antidiarrheal medications). Children with toxic megacolon should be evaluated promptly by surgeons and conservative management should only be considered in stable clinical conditions and in highly specialized centers; urgent colectomy is recommended if there is no clinical improvement within 24 to 72 hours [52, 59].

Acute Severe Colitis

Approximately 25–35% of children with UC will require hospitalization for acute severe ulcerative colitis (ASUC) during a period of 3 years after the initial diagnosis, roughly double the rate seen in adult-onset disease [60]. An acute exacerbation of UC may manifest with clinical relapse accompanied by local or systemic complications such as massive hemorrhage, toxic megacolon, and multiorgan failure; in some cases, this condition is defined as "fulminant colitis."

The best validated and most widely used index for the diagnosis of adult ASUC is the European Crohn's and Colitis Organization (ECCO) adaptation of the 1955 Truelove and Witts' classification, which defines ASUC as an exacerbation of disease with at least six bloody stools daily and one of the following: tachycardia (>90 beats per minute), temperature >37.8 °C, anemia (hemoglobin <10.5 g/dL), or an elevated ESR (>30 mm/h) [61]. However, the use of these criteria has never been validated in children with severe colitis. Instead, PUCAI scoring is more widely used for children, with severe disease defined as a score of at least 65 points. Unlike the Truelove and Witts' classification, which is only useful in diagnosing the acute presentation of disease, the PUCAI can be used to monitor disease severity over time as well as response to treatment [48].

ASUC carries a mortality rate of around 1% primarily from perforation, TMC, and infectious complications. Emergent colectomy is now performed infrequently, with medical therapies being used as first-line therapy in ASUC [48].

With few exceptions, children with ASUC should be admitted to the hospital for immediate evaluation and intensive medical treatment. Intravenous methylprednisolone 1 mg/kg/day (up to 40 mg/day) once daily is recommended as the initial treatment on admission; a higher dose of 1.5 mg/kg/day (up to 60 mg/day) in 1 or 2 divided doses should be reserved in children with more severe presentations or who have failed oral steroids before admission. According to a

recent prospective study of pediatric patients with ASUC, higher doses of IVCS > 1.5 mg/kg/day were not associated with better outcomes [62]. Approximately 65% of patients will respond to IVCS alone.

Intravenous fluid for rehydration and correction of electrolyte imbalances should be provided. Blood transfusions and albumin infusions may also be required. Although traditionally patients were restricted from taking food orally, there is no data to support NPO status in UC. In general, patients should be allowed an oral diet if tolerated, and enteral or parenteral nutrition should be provided if an oral diet is not tolerated or in patients with malnutrition. However, enteral feeding is contraindicated if there is concern for toxic megacolon [59].

Bacterial causes for ASUC should be excluded by stool PCR, including *C. difficile*. In the case of *C. difficile* colitis, oral Vancomycin should be considered as first-line therapy in a patient with ASUC. Given the risk of toxic megacolon, an abdominal X-ray (AXR) should be performed upon admission with a low threshold in patients with abdominal tenderness, abdominal distension, significant pain, and systemic toxicity.

In patients who are not clinically improving after 2–3 days of IVCS therapy, surgical consultation should be pursued for potential colectomy. Additionally, CMV colitis should be excluded in children not responding to 3 days of IVCS with a flexible sigmoidoscopy and mucosal biopsies. Second-line therapy, also known as "rescue therapy" or "salvage therapy," should be initiated on the fifth day of IVCS treatment in children with a PUCAI > 65, as this indicates a nonresponse to steroid therapy. Infliximab is recommended as the second-line medical therapy of choice for anti-TNF-α naïve children failing IVCS, with infliximab continuing as a maintenance treatment after discharge from the hospital. Calcineurin inhibitors such as Cyclosporine and Tacrolimus are alternative second-line medical therapies, but if commenced should be weaned within several months as a "bridge" to thiopurines or another maintenance medication such as vedolizumab.

In general, prompt referral for urgent colectomy is recommended following failure of one second-line medical therapy. Children should not be discharged from the hospital unless the disease is at most mild (PUCAI < 35 points) but preferably closer to remission (PUCAI < 10 points) [59].

In a systematic review, the pooled steroid-refractory rate in ASUC across all pediatric studies was 34%, slightly higher than the pooled 29% rate found in adult studies. Additionally, a child who has ever developed an episode of ASUC is at a higher risk for more refractory disease and future colectomy. The advent of calcineurin inhibitors and infliximab has reduced the short-term colectomy rate from 40–70% to approximately 10–20% in children and the 1-year colectomy rate from ~60% to 18–22%. Among those who fail IVCS treatment, roughly 50–60% of responders to rescue therapy will require colectomy within 1 to 2 years [52, 59].

Antibiotics are not routinely recommended in children with ASUC; however, they may provide clinical efficacy likely through modulation of the microbiome. According to the recent PRASCO randomized controlled trial based in Israel, hospitalized children with ASUC defined by a PUCAI ≥ 65 were randomized to receive antibiotics in addition to IVCS (amoxicillin, vancomycin, metronidazole, and doxycycline/ciprofloxacin) or IVCS alone for 14 days, with the antibiotic arm achieving lower mean PUCAI scores compared to the IVCS only arm. However, long-term outcomes are unknown [63, 64].

Medications

5-Aminosalicylic Acid Agents (5-ASA)

Aminosalicylates or 5-ASAs are the first-line treatment for induction and maintenance of remission, of mild-to-moderate UC. They have a wide range of anti-inflammatory and immunomodulatory properties, including inhibition of 5-lipoxygenase, scavenging of reactive oxygen metabolites, and inhibition of interleukin-1 synthesis. Free 5-ASA is almost completely absorbed from the stomach and proximal small intestine, so sustained-release preparations have been developed to deliver the medication to more distal sites of inflammation.

Sulfasalazine has traditionally been used in UC and is composed of 5-ASA linked to sulfapyridine via a diazo bond that is cleaved by colonic bacteria. Sulfasalazine can be formulated as a liquid and is useful in young children with UC. However, sulfasalazine has several dose-limiting side effects, including headaches, nausea, anorexia, and reversible oligospermia that limit its use. Newer formulations, including mesalamine, olsalazine, and balsalazide, utilize pH- or time-dependent delivery systems to release higher concentrations of 5-ASA at various sites of the small intestine and colon with fewer side effects, thus allowing treatment to be tailored to the location of disease [11, 65].

5-ASA can also be effectively administered in the form of an enema or a suppository for management of distal colonic inflammation [66, 67]. According to a multicenter nonrandomized study of 49 children with ulcerative proctitis treated with a 5-ASA, 500 mg suppository daily for 6 weeks, there were significant reductions in disease activity index scores at weeks 3 and 6 with treatment [68].

The landmark Predicting Response to Standardized Pediatric Colitis Therapy (PROTECT) study was initiated in 2012 to systematically examine the responses of children and adolescents newly diagnosed with mild-moderate UC, who were placed on treatment regimens of mesalamine and

corticosteroids to determine when escalation to additional therapy was required. Interestingly, only 48% of patients treated with mesalamine achieved steroid-free clinical remission at week 12 without the need for treatment escalation with immunomodulators, anti-TNF-α agents, or colectomy [69]. According to the results from the North American pediatric IBD registry, only about 40% (86/213) of children with UC who were treated with 5-ASA within 1 month of diagnosis were in steroid-free clinical remission at one year [70].

Corticosteroids

The use of corticosteroids for the induction of remission in UC was first described in 1955 and since then has been the mainstay for induction of remission in moderate to severe UC. Methylprednisolone or prednisone is used more frequently than hydrocortisone with a suggested dosage of 1–2 mg/kg up to a maximum of 60 mg/day [54]. Response should be seen within 2 weeks at which point the steroids can be tapered. No defined tapering schedule exists, but a common approach is to taper by 5–10 mg per week until reaching 20 mg, then decreasing by 2.5–5 mg per week until completed [11] (Table 30.3).

Children on long-term steroids may have more steroid-related complications than adults (even when adjusted for weight), including delay of linear growth and puberty, osteopenia, acne, glaucoma, and cataracts. Steroid dependency has also been reported to be higher in children than in adults (45% vs 8%, respectively). Strategies to avoid steroid dependency include optimization of 5-ASA, adjuvant therapy with enemas, and escalation to immunosuppressants or biologic agents. Steroid treatment is not advised for maintenance of remission [65].

Oral steroids with minimal systemic activity (due to high first-pass liver metabolism) such as budesonide-multimatrix (MMX) are effective at inducing remission in mild to moderate UC. Given the lower risk for systemic side effects, these drugs may be considered as alternative first-line induction drugs in those failing 5-ASA [11].

Rectal corticosteroids can be tried as a second-line add-on therapy to induce remission in proctitis or left-sided ulcerative colitis. Rectal corticosteroids can be administered as foam formulations that are often better tolerated than enemas by patients with active distal UC [11].

Table 30.3 Medication dosages in pediatric ulcerative colitis

Agent	Dosage .
Corticosteroids	1.0–2.0 mg/kg/day prednisone equivalent
	IV or PO in divided doses (max 40–60 mg)
Sulfasalazine	25–75 mg/kg/day (max 4 g)
Mesalamine	30–60 mg/kg/day (max 4.8 g/day)
Azathioprine	1–2 mg/kg/day
	Adjust dose based on 6-MP metabolite levels
6-Mercaptopurine	1–1.5 mg/kg/day
	Adjust dose based on 6-MP metabolite levels
Cyclosporine	4–8 mg/kg/day IV or PO
	Trough blood levels 200–250 mcg/ml
Tacrolimus	0.15 mg/kg/day PO
	Trough blood levels 10–15 ng/ml
Infliximab	5 mg/kg intravenous infusion at week 0, 2, and 6 for induction dosing, 5 mg/kg every 8 weeks for maintenance dosing
Vedolizumab	300 mg (adult dosing) at week 0, 2, and 6 for induction dosing, 300 mg every 8 weeks for maintenance dosing
Ustekinumab	Induction IV (adult dosing): ≤55 kg–260 mg as single dose, >55 kg to 85 kg–390 mg as single dose
	Maintenance subcutaneous: 90 mg every 8 weeks
Tofacitinib	10 mg twice daily (adult dosing) for induction and 5 mg twice daily for maintenance

Immunosuppressive Therapy

Thiopurines

6-Mercaptopurine (6-MP) and its prodrug azathioprine are purine analogs commonly used in the treatment of steroid-dependent UC or in children with frequent relapses (>2 a year) who have failed aminosalicylates [71]. The therapeutic effect of thiopurines may take up to 10–14 weeks after the start of treatment. The recommended dose is 2.5 mg/kg of azathioprine and 1–1.5 mg/kg of 6-MP in a single daily dose [72]. Previous meta-analyses of adult data concluded that azathioprine is not more effective than placebo for induction of remission in UC but is superior to placebo in preventing relapse [71, 73]. Prospective pediatric studies reported steroid-free remission rates of 49% at 1 year and 72% at 2 years in thiopurine-treated children [74, 75].

Thiopurines are associated with a less favorable safety profile than 5-ASA. TPMT assay (either phenotype or genotype) should be used before starting thiopurines to identify patients who are at risk for dose-dependent myelosuppression, and in whom this drug should either not be used (if homozygous for variant alleles or having very low TPMT activity) or administered at lower doses (if heterozygous for variant alleles or having low TPMT activity). TPMT testing does not, however, replace the need for mandatory monitoring of complete blood counts (CBCs) especially when starting treatment.

Dose-independent adverse reactions include fever, pancreatitis, rashes, arthralgias, nausea, vomiting, and diarrhea, while dose-dependent toxicities included leukopenia (up to 5%), thrombocytopenia, infections, and hepatitis [65]. Hepatosplenic T-cell lymphoma (HSTCL) is a rare but fatal

complication of thiopurine therapy. Of over 40 reported cases of IBD-related HSTCL, the majority of patients received thiopurines, with or without anti-TNF-a, and almost all were males; there are only extremely rare and anecdotal case reports of children with HSTCL who were treated solely with an anti-TNF-α medication [65].

Therapeutic drug monitoring, which involves measuring thiopurine metabolites 6-TGN and 6-MMP, is a way of optimizing drug efficacy and avoiding myelosuppression. Dose adjustments following measurement of metabolites have been shown to increase disease remission rates and prevent relapse [65].

Thiopurines may also be used in "combination therapy" with the biologic infliximab. In a prospective trial of combination therapy with azathioprine and infliximab for UC, combination therapy was found to be more effective than either azathioprine or infliximab therapy alone for induction of steroid-free clinical remission and clinical response. Combination therapy results in lower rates of antibodies to infliximab and results higher infliximab concentrations, which are associated with greater efficacy. However, there was no statistically significant difference in mucosal healing at 16 weeks between combination therapy and infliximab therapy alone [76].

Methotrexate

Methotrexate (MTX) is a potent folic acid antagonist that decreases purine production at the cellular level. At high doses, MTX has antiproliferative and cytotoxic effects by inhibiting the enzyme Dihydrofolate reductase leading to defective DNA synthesis and cell death. At low doses that are commonly used in the treatment for IBD, it functions as an immunomodulator.

The immunomodulatory effect of MTX is poorly understood, but involves increased concentrations of adenosine, inhibition of cellular proliferation and induction of apoptosis, and decreased production of inflammatory mediators such as interleukins and eicosanoids [77].

A previous Cochrane meta-analysis of methotrexate for induction and maintenance therapy in adult UC concluded that there is no evidence supporting its use; however, this conclusion relied on low-quality evidence. In the METEOR double-blind placebo-controlled trial of 111 steroid-dependent adults with UC, although clinical remission was significantly higher in the methotrexate-treated group vs. placebo (42% vs. 24%, respectively), there was no statistically significant difference in steroid-free remission at week 16 between methotrexate and placebo [65, 78], which calls into question its potential efficacy in UC.

Tacrolimus

Tacrolimus, a calcineurin inhibitor, is a macrolide antibiotic isolated from the soil bacterium *Streptomyces tsukubaensis* that blocks IL-2 synthesis and thus inhibits the proliferation of T-cells, clonal expansion, and the production of cytokines involved in the immunological response [79]. It possesses potent immunosuppressive properties and has been used to prevent organ rejection after allogeneic organ transplantation or graft-versus-host disease after hematopoietic stem cell transplantation [80]. Tacrolimus is commonly used in inducing remission in patients with steroid-resistant UC due to its fast onset of action, in order to prevent or delay colectomy. Tacrolimus is also useful as a temporary treatment "bridge" for steroid-dependent patients until a new maintenance therapy takes effect. Long-term use is not recommended due to adverse effects such as nephrotoxicity [79, 81].

Rectal tacrolimus has been reported in children and adults as a successful third-line treatment of ulcerative proctitis. In a recent double-blind placebo-controlled trial, 8/11 adult patients receiving rectal tacrolimus ointment (1.5 mg twice daily) achieved mucosal healing by week 8, compared with 1/10 receiving placebo. Although usually well tolerated, rare toxicity episodes have been reported [65].

Biologics

Infliximab

Since the advent of biologics for the treatment of pediatric UC, there has been a significant reduction in overall 2-year colectomy rates [82]. Tumor necrosis factor alpha (TNF-α) is a potent proinflammatory cytokine found in the serum and inflamed intestinal tissue in IBD and is involved in the pathogenesis of disease. TNF-α is a cofactor in the production of inflammatory cytokines such as IFN-y and IL-2. Infliximab (IFX) is a chimeric monoclonal antibody (75% human, 25% murine) against TNF-α. IFX has been shown to induce clinical, endoscopic, and histologic remission, to reduce hospitalizations and surgery rates, and is a leading therapy for moderate-to-severe pediatric IBD. The efficacy of anti-TNF-α therapies has been widely demonstrated in adult and pediatric patients with UC. The Active Ulcerative Colitis Trial I (ACT I) and ACT II trials clearly showed the efficacy of IFX in achieving clinical remission, clinical response, and mucosal healing. IFX is effective for the induction and maintenance of clinical remission for pediatric UC. The standard regimen for this therapy is 5 mg/kg at weeks 0, 2, and 6, followed by maintenance doses every 8 weeks [83, 84].

Studies in children have shown a pooled long-term success rate of infliximab in UC of 64% and a steroid-free

remission rate of 38% and 21% at 12 and 24 months, respectively, with a likelihood of avoiding colectomy at 2 years of 61% [85].

There has been an increasing interest in more intensified dosing regimens of IFX with greater emphasis on maintaining therapeutic drug levels to improve remission rates. Patients with severe disease often have lower serum albumin and IFX loss in the stool, which are factors known to affect IFX pharmacokinetics [86]. Therapeutic drug monitoring (TDM) is based on measurement of IFX trough serum levels and antibodies to IFX for assistance in clinical decision-making. Reactive TDM has been shown to improve outcomes, with trough levels between 3 and 7 μg/mL being correlated with clinical and endoscopic remission. Conversely, given the chimeric nature of this medication, the development of antibodies to IFX is possible. Positive antibodies to IFX have been associated with immunogenic loss-of-response to therapy, which may require a switch to a different agent or combination therapy with a thiopurine [87].

Adalimumab

Adalimumab (ADA), a fully human monoclonal antibody against TNF-α, is less immunogenic than the chimeric antibody IFX and has been initially proven to be as effective as IFX in CD. The pivotal Ulcerative colitis Long-Term Remission and maintenance with ADA (ULTRA) 1 and 2 clinical trials showed the effectiveness and safety of ADA compared to placebo in inducing and maintaining remission at week 8 and 52 weeks in patients with moderate to severe UC who had failed conventional treatment [88]. The open-label extension study, ULTRA 3, confirmed a favorable long-term safety profile of ADA [89]. ADA is commonly used in clinical practice as an off-label treatment for children with UC. According to a retrospective study by Aloi et al., of 32 children who received ADA after prior IFX treatment (either due to nonresponse or the presence of anti-IFX antibodies), 41% were in steroid-free remission and 28% achieved mucosal healing after 52 weeks [90].

Vedolizumab

Vedolizumab is a humanized α4-β7 integrin antagonist, characterized by a gut-selective mechanism of action and less risk of systemic immunosuppression. By binding to surface-expressed α4-β7 integrin, it inhibits T-cell migration into inflamed intestinal tissue. Its efficacy and safety have been evaluated in numerous studies, mostly in adult patients with moderate to severe UC and CD [91]. In two integrated randomized double-blind placebo-controlled trials of vedolizumab in patients with active UC (GEMINI I), vedolizumab was found to be more effective than placebo for both induction and maintenance of remission. Response rates at week 6 (induction) were 47.1% in the vedolizumab group and 25.5% in the placebo group. At week 52 (maintenance), 41.8% of patients who received vedolizumab every 8 weeks and 44.8% of patients who received vedolizumab every 4 weeks maintained clinical remission, compared to 15.9% in the placebo group [92].

In a phase 3b double-blind randomized trial conducted at 245 centers in 34 countries, vedolizumab was found to be superior to adalimumab in achieving clinical remission and endoscopic improvement, but not in achieving steroid-free remission at week 52 [93]. In a retrospective study of pediatric IBD patients receiving vedolizumab (of which 42% had UC), week 14 remission rates were 76% in patients with UC versus 42% in patients with CD. Additionally, anti-TNF-a naïve patients experienced higher remission rates compared to those with previous anti-TNF-α exposure [94]. The clinical response with vedolizumab is slow compared to anti-TNF-α therapies. While the clinical response compared to placebo may be seen at week 6, peak effect of vedolizumab may not be expected until weeks 10–14 [95], which sometimes necessitates the addition of a treatment "bridge" such as Tacrolimus.

Ustekinumab

Ustekinumab is a monoclonal antibody to the p40 subunit of interleukin-12 (IL-12) and interleukin-23 (IL-23) and has been approved for the treatment of psoriasis, psoriatic arthritis, moderate to severe CD in adults, and more recently in moderate to severe UC in adults. In a phase 3 clinical trial of Ustekinumab in adult patients with moderate-to-severe UC, Ustekinumab was more effective than placebo in achieving induction of clinical remission at 8 weeks and maintenance of remission at 44 weeks. This effect was observed in both biologic-naïve patients and patients who had failed a previous biologic [96]. In a recent single-center retrospective study on the use of Ustekinumab in pediatric IBD in which 8% of the study patients had UC, 90% of patients who were biologic-naïve and 50% of patients who failed a previous biologic achieved steroid-free clinical remission at 52 weeks, indicating the efficacy of this medication in the treatment of IBD [97].

Tofacitinib

Tofacitinib is a newer oral small-molecule Janus Kinase (JAK) inhibitor that is approved in multiple countries for the treatment of moderate to severe biologic-refractory UC. The JAK family comprises four intracellular tyrosine kinases—

JAK1, JAK2, JAK3, and nonreceptor tyrosine-protein kinase 2—that regulate signaling for multiple immune mediators implicated in IBD, including IFN-y and interleukins 2, 4, 6, 7, 9, 12, 15, 21, 23, and 27. Tofacitinib inhibits all JAKs but preferentially inhibits JAK1 and JAK3 [98]. In 2018, tofacitinib was approved for the treatment of adults with moderate to severe UC. It has not yet been approved in pediatric populations [99].

Three phase 3 trials known as OCTAVE investigated the use of tofacitinib in induction and maintenance of remission for UC. In two identical phase 3 trials of induction therapy with tofacitinib in patients with moderate to severe UC (OCTAVE induction 1 and 2), the rates of clinical response, clinical remission, and mucosal healing at 8 weeks were significantly higher in patients who received oral tofacitinib 10 mg twice daily than in patients who received placebo. Tofacitinib was shown to have a rapid onset of action, with significant improvement in partial Mayo score observed as early as 2 weeks into treatment. In a third phase 3 trial (OCTAVE Sustain) which evaluated maintenance therapy with tofacitinib, clinical response, clinical remission, and mucosal healing were maintained at 52 weeks with tofacitinib at a dose of either 5 mg or 10 mg twice daily [98].

Tofacitinib has a similar safety profile compared to biologic agents; however, it is associated with an increased risk of herpes zoster infection. This infection risk is dose-dependent, with 10 mg twice daily being more associated with herpes zoster than 5 mg twice daily [100].

Probiotics and Dietary Therapy

Nutritional therapies for IBD have garnered significant interest due to their limited side effect profile, bowel-sparing nature, and naturalistic approach. An individual's diet is thought to play a key role in IBD development as certain foods have been found to increase proinflammatory cytokines, change intestinal permeability, and affect the composition of the intestinal microbiome. Examples of "pro-inflammatory foods" include animal fats and nondigestible dietary carbohydrates as is typical in "Western diets." Conversely, diets high in fruits, vegetables, and fiber have been shown to be associated with a decreased risk of developing IBD [101]. However, the benefit of nutrition as primary therapy for the treatment of UC has not been proven, and enteral or parenteral nutritional supplementation does not appear to increase remission rates or reduce the need for colectomy in UC [102].

Limited studies have explored the relationship between specialized diets and UC. Gearry et al. retrospectively evaluated low fermentable, oligo-, di-, monosaccharides and polyols (FODMAP) diets in 72 patients with IBD (52 CD and 20 UC) for 3 months. Based on self-report, 70% of patients remained adherent to the diet after 3 months, and symptoms of pain, bloating, and diarrhea improved among those who were adherent to the diet. However, there was no significant reduction in disease activity [103, 104].

One of the more commonly used dietary therapies for IBD is the specific carbohydrate diet (SCD), developed by Dr. Sydney Haas, a pediatrician, in the 1930s to treat patients with celiac disease. The SCD was popularized in the late twentieth century by Elaine Gottschall, after her daughter with UC was successfully treated with SCD by Dr Haas. The SCD diet excludes all grains, sugars (except for honey), processed foods, and dairy, except for specific fermented yogurt and some hard cheeses. It is hypothesized that this diet decreases intestinal inflammation by changing the intestinal microbiome from a proinflammatory state to an anti-inflammatory state [105]. There are currently limited studies formally evaluating SCD and its effectiveness for the treatment of IBD. Patient perception seems to support the use of SCD, with 33% reporting remission 2 months after initiation of SCD and 42% achieving clinical remission at 6 and 12 months. A small retrospective study of pediatric patients demonstrated persistent mucosal disease in patients on a modified SCD (rice, oats, quinoa, and potatoes added to diet), who were otherwise asymptomatic with normal or mildly abnormal labs (including fecal calprotectin). Therefore, despite the positive clinical response seen on a strict SCD, the diet is difficult for many patients to maintain long term, and its efficacy in both serological and histological improvement of disease is unclear [101].

Probiotics have been suggested to be beneficial for induction and maintenance of remission in pediatric UC. Specifically, the probiotic preparation VSL #3 has been shown in a small randomized placebo-controlled trial of 29 patients to be efficacious in active pediatric UC, with 92.8% of patients achieving remission with VSL #3 as well as standard IBD therapy compared to only 36.4% of patients achieving remission with standard IBD therapy alone [106]. In a meta-analysis of 12 randomized controlled trials on UC evaluating the effect of different bacterial strains (VSL #3, Bifidobacteria, and *E. Coli* Nissle) on induction of remission, only VSL #3 showed a significantly increased response rate. However, probiotics had no beneficial effect compared to placebo on maintenance of remission [107].

The ECCO/ESPGHAN consensus guidelines on the management of pediatric UC assert that there is insufficient evidence to recommend routine probiotic use for induction or maintenance of remission. As for pediatric pouchitis, there was a 100% consensus for the usefulness of probiotics in the maintenance of an antibiotic-induced remission in subjects with recurrent or chronic pouchitis [108].

Fecal Microbiota Transplantation

"Dysbiosis," which is characterized by alterations in the composition of the commensal microbiome in a host compared to healthy individuals, is thought to play a major role in the pathogenesis of both UC and CD. There is increasing evidence that the composition of gut microbes in a patient with IBD is different and possibly abnormal and that correction of this abnormality might help control the inflammation seen in patients with IBD. While there have been several controlled studies investigating the efficacy of FMT for adults with UC, relatively few trials have taken place testing FMT in children with UC. These small, uncontrolled studies and case reports have had mixed results [16]. The first published study involved five enemas administered daily to nine UC patients aged 7–21, with 6 of the 9 patients maintaining clinical response at one-month follow-up [109]. In a 2015 case series, a single FMT infusion was administered via nasogastric tube (NGT) to four UC patients, with no clinical response seen [110].

The pediatric literature for FMT remains limited, and conclusions are difficult to draw from such small sample sizes. Yet these studies illustrate several key observations. The failure of FMT delivered via NGT suggests that tailoring modes of FMT delivery to individual patients' disease location and targeting specific "hot spots" may influence patient response rates. Also, microbial material may be degraded from gastric acid exposure during proximal delivery techniques. These studies also demonstrated that UC is best treated by targeting the colon directly with *per rectal* therapy [111]. The translation of this practice to the clinical setting is challenging in most pediatric centers where general anesthesia is required for colonoscopy. This is particularly challenging if multiple FMT administrations are required to maximize efficacy. Lastly, these studies suggest that serial treatment may be required to achieve an appreciable response in IBD patients, in contrast to single or short-course FMT administrations in the treatment of recurrent *C. difficile* infections [16, 111, 112].

Psychosocial Barriers

The chronic nature of UC along with the waxing and waning nature of clinical symptoms can be especially disruptive to children's physical, social, and academic development. Young people with IBD are at an increased risk for behavioral and emotional difficulties compared to healthy children, with depression rates as high as 25% [113, 114]. In pediatric IBD, poorer psychosocial functioning including depression is associated with nonadherence to medical management, risk of relapse, worsened disease activity, and higher healthcare costs. Depressive and anxiety symptoms correlate with disease activity, possibly due in part to the effect of proinflammatory cytokines on the brain, sleep disturbance, and side effects from corticosteroid use [113]. According to a recent study, pediatric patients with UC had significantly more sleep disturbance compared to patients with CD, even without significant differences in nocturnal bowel movements or nocturnal pain [115].

Annual depression screening should be a routine part of IBD care, and clinicians should refer patients for treatment when indicated [113].

Psychotherapy has been shown to be effective in young patients with IBD, including cognitive behavioral therapy (CBT) and supportive nondirective therapy (SNDT). Pharmacotherapy may be helpful as an adjunct to therapy [113, 114].

Nutrition, Growth, and Vitamin D

Malnutrition and growth failure are less common in children with UC compared with patients with CD, but nutritional deficiencies can develop quickly during periods of active disease. In newly diagnosed IBD, short stature has been noted only in CD, and for the most part, children with UC are able to reach their expected adult height. It has been documented that bowel rest with total parenteral nutrition (TPN) or exclusive enteral nutrition (EEN) does not have any therapeutic role in acute UC, although bowel rest can alleviate abdominal pain when severe [34, 116].

Children with IBD are particularly prone to disturbed bone health because of increased circulating inflammatory cytokines, malnutrition, delayed puberty, decreased physical activity, treatment with corticosteroids, and in girls, primary or secondary amenorrhea. Severe osteopenia was present in 3% to 6% of patients with UC compared to 12% to 18% of those with CD. DEXA is the preferred screening tool for bone density measurement in children and adolescents, provided that age- and sex-matched z scores are used. It has been suggested that DEXA be performed in all children newly diagnosed with IBD and repeated in cases of severe disease course, including suboptimal growth velocity, prolonged malnutrition, amenorrhea, delayed puberty, and long or repeated treatments with steroids [34, 117].

Children with IBD are particularly at risk for vitamin D deficiency, and emerging data over the past decade have suggested that vitamin D plays a significant role in both epithelial and immune system dysregulation contributing to IBD pathogenesis. According to the multicenter PROTECT study, vitamin D insufficiency was highly prevalent in children with newly diagnosed UC. Also, free and bioavailable vitamin D, but not total 25(OH) vitamin D, was associated with mean PUCAI scores, indicating that bioavailable vitamin D

may contribute to UC clinical activity. It is widely accepted that vitamin D levels be routinely measured and deficiency treated with vitamin D supplementation, especially in children with decreased BMD. Nutrition support, weight-bearing exercise, and disease control using steroid-sparing strategies are also advocated to improve bone formation [118].

Surgical Therapy

In the majority of cases, medical therapy remains the first-line treatment for UC. However, colectomy may be required for patients with severe or medically refractory disease or in those with colonic dysplasia to prevent the development of colorectal cancer (CRC). Timely surgical intervention in the appropriate setting is imperative to avoid complications of UC. Indications for emergent colectomy in a patient with UC include fulminant colitis or a complication of colitis such as massive hemorrhage, perforation, or toxic megacolon. It is also important to consider colectomy in patients with ASUC who have PUCAI scores > 65 at 11 to 14 days after the start of rescue therapy, as surgery is often unavoidable in these situations. In emergency conditions, the primary surgical strategy is to address the complications of disease by removing the diseased colon and constructing an ileostomy. Elective colectomy should be considered in children with active or steroid-dependent UC despite optimized medical therapy and in those with colonic dysplasia [119].

Except in the setting of emergent colectomy, a complete evaluation should be performed to ensure that there is no evidence of CD prior to colectomy, with small bowel imaging or video capsule endoscopy (VCE), upper endoscopy, and colonoscopy unless there is a contraindication.

Total restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the procedure of choice in patients with adequate anal sphincter function, as it avoids a permanent ileostomy and allows for a preserved body image with a near-normal life for the patient. An IPAA involves a total proctocolectomy with construction of an ileal reservoir anastomosed to the anus. Surgery restores intestinal continuity, preserves sphincter function, and maintains continence. Several types of ileal pouches can be constructed including the J-shaped, S-shaped, W-shaped, and the lateral-lateral pouch. The J-pouch design is the most commonly used for IPAA [120].

The IPAA may be performed in two or three stages, with the use of a one-stage procedure being extremely rare. However, the choice of a two-stage vs. three-stage procedure is more variable [121]. In general, a three-stage procedure (1st stage: subtotal colectomy with ileostomy creation, 2nd stage: proctectomy and IPAA creation, and 3rd stage: stoma closure) [122] is recommended for patients with ASUC, in those treated with high-dose steroids or recent anti-TNF-α therapy, severe malnutrition, or IBD-U. The most common complication of IPAA is pouchitis, which may clinically manifest as diarrhea, tenesmus, and/or constitutional symptoms [121].

Pediatric patients tend to have a higher rate of pouch-related complications than adult patients after IPAA, including pouch stricture and an eventual diagnosis of CD of the pouch. Postoperative pouch-associated hospitalizations and a requirement of postoperative anti-TNF-a biologics were also more frequent among pediatric patients [123]. According to a previous systematic review, there was no association found between number of surgical stages and the following outcomes: pouch failure rates, complication rates, and quality of life [121].

Pouchitis

Nonspecific inflammation of the ileal pouch reservoir, called pouchitis, is the most common complication following IPAA. The symptoms and severity of pouchitis vary from patient to patient, but typically include increased stool frequency and urgency, loose watery stools, abdominal pain, and hematochezia. Duration of pouchitis can be categorized as acute (<4 weeks), chronic (>4 weeks), or recurrent (≥3 episodes of acute pouchitis a year). The reported prevalence of pouchitis in children with UC after IPAA is variable, and data on predictive factors for the development of pouchitis in children are scarce.

A recent multicenter retrospective cohort study from the Pediatric IBD Porto Group of ESPGHAN that included 129 children who underwent IPAA showed that 67% of children developed pouchitis during a median follow-up of 10.5 months from creation of the pouch, including 26% who developed chronic pouchitis. In an older cohort of 399 UC children with a mean age of 18 ± 3 years at colectomy, 36% had at least one episode of acute pouchitis and 9% had pouch failure [124].

Several reports have identified the risk factors of pouchitis as younger age at the time of UC onset, extensive colonic disease or pancolitis, presence of EIMs, preoperative pANCA positivity, and preoperative steroid use. Endoscopic features of pouchitis may include hyperemia, diminished vascular pattern, friability, hemorrhage, and ulcers. Abnormalities may be focal or diffuse and are often more severe in the distal compared to the proximal pouch. Mucosal biopsies typically demonstrate partial to complete villous blunting with crypt hyperplasia and increased mononuclear inflammatory cells and eosinophils in the lamina propria, crypt abscesses, and ulcerations. Mucosal biopsies should be obtained from the pouch and from the afferent ileal loop, but not from the staple line, as erosions and/or ulcers along the staple line do not necessarily indicate pouchitis.

Antibiotic treatment is considered first-line therapy for pouchitis. Only small placebo-controlled trials have been conducted in adult patients to support this practice, and none in children. A 14-day course of ciprofloxacin and/or metronidazole is recommended, with ciprofloxacin possibly being slightly more effective than metronidazole and with fewer adverse events. Chronic and recurrent pouchitis are less responsive to antibiotic therapy. Oral or topical budesonide can be used in refractory cases. Infliximab and adalimumab have also shown efficacy in refractory pouchitis. The probiotic VSL#3 was additionally effective in maintaining remission in adult patients with chronic pouchitis as shown in two double-blind placebo-controlled trials from Italy [124–126].

Cuffitis may cause symptoms similar to those of pouchitis, especially bleeding. The cuff is the remaining rectal mucosa, referred to as a rectal cuff, at the anastomosis between the ileum and anal canal. This area can become inflamed leading to cuffitis, which, in contrast with pouchitis, typically presents with bleeding and can usually be successfully treated with 5-ASA suppositories [11].

Long-Term Prognosis, Colorectal Cancer, and UC

The association between UC and colorectal cancer (CRC) has been a focus of study for many years. IBD-associated CRC (IBD CRC) affects patients at a younger age than sporadic cancer, but the prognosis is similar, with a 5-year survival of approximately 50%.

Chronic inflammation is believed to promote carcinogenesis. The genetic features that lead to sporadic CRC chromosome instability and DNA hypermethylation also occur in colitis-associated CRC. Unlike normal colonic mucosa, cells of the inflamed colonic mucosa have genetic alterations before there is any histological evidence of dysplasia or cancer. Oxidative stress is likely to be involved in carcinogenesis through reactive oxygen and nitrogen species.

In a meta-analysis, UC increased the risk of CRC by 2.4-fold, accounting for an overall occurrence of 1.6% (including sporadic cases) during the first 14 years of follow-up. Male sex, diagnosis at a young age, extensive colitis, presence of PSC, and family history of CRC are all risk factors for the development of CRC [127].

Evidence-based guidelines advise that patients with colitis receive a surveillance colonoscopy 8–10 years after diagnosis, with the interval for further surveillance guided by risk factors. For a subset of patients, annual CRC screening from the onset of disease has been recommended. This includes patients with coexisting PSC and with a first-degree relative diagnosed with CRC before the age of 50. Because CRC lesions in IBD may be harder to detect as they are often flat and multifocal, it has long been advised to take random biopsies every 10 cm throughout the length of the colon, but this approach represents less than 1% of the colonic mucosa and has been shown to miss many dysplasia-associated lesions. Chromoendoscopy is a method in which the colonic mucosa is colored with a dye to enhance mucosal patterns, therefore making it easier to detect dysplastic lesions. Narrow-band imaging, which is now available on most endoscopes, is thought to help visualize dysplastic/neoplastic lesions through enhancing vessels, pit patterns, and soft tissue structures, but it has not been shown to increase identification of dysplastic lesions compared to standard colonoscopy [127, 128].

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