Chapter

Pediatric Ulcerative Colitis

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Abstract

Inflammatory bowel disease (IBD) is a collective term that includes a group of disorders with unknown etiology characterized by chronic inflammation of the gastrointestinal tract and relapsing and remitting course. Ulcerative colitis (UC) is a type of IBD that affects the large intestine, causing irritation, inflammation, and ulcers in its lining. Approximately 25% of patients with IBD are diagnosed before the age of 18 years. Children and adolescents with UC are more likely to have more severe disease course with more extended intestinal involvement at diagnosis and faster disease progression than adults. Atypical presentation is also common in pediatric age. Treatment recommendations for children and adolescents are different than those for adults and offer many unique challenges for the healthcare professionals.

Keywords: typical ulcerative colitis, atypical ulcerative colitis, severe ulcerative colitis, diagnostic approach, management of pediatric ulcerative colitis

1. Introduction

Inflammatory bowel disease (IBD) represents a group of chronic disorders of the digestive tract with a relapsing and remitting clinical course and a debilitating character. IBD may occur at any age [1]. Approximately 25% of incident cases of inflammatory bowel disease occur during childhood [2–4]. The majority of newly diagnosed pediatric patients are teenagers, but the disease may have an earlier manifestation [5, 6]. According to the Montreal classification of IBD the pediatric IBD (PIBD) is defined as having an age of occurrence younger than 17 years [7]. Later the Paris classification defined A1a group for those children with less than 10 years of age IBD onset and A1b for children with onset of symptoms between 10 and <17 years of age [8]. The latest modification of the IBD classification defines disease onset under the age of 17 as PIBD and this is further classified into early onset IBD (EOIBD) when it occurs under 10 years of age, very early onset IBD (VEOIBD) with less than 6 years of age IBD onset, infantile (and toddler) onset of IBD (less than 2 years of onset) and neonatal IBD (disease onset within first 28 days of age) [9].

Evidence over the last several years have shown that VEOIBD is a separate disease entity with specific clinical features and outcomes that are different from those of adolescent-onset IBD [9, 10]. In most cases VEOIBD is associated with underlying primary immunodeficiencies or has an underlying monogenic etiology. It is characterized by a severe and often treatment-refractory course of disease [11]. Not

surprisingly VEOIBD is accepted currently as a unique disease that requires a specific diagnostic approach and specific treatment. A recent position paper summarized the diagnostic algorithm by suspected VEOIBD and described some of the potential treatments [12].

The classically group of IBDs in childhood includes three nosological entities: Crohn's disease (CD), IBD-unclassified (IBDU) and ulcerative colitis (UC) and [13].

CD is a type of IBD whose predilection site for development is the terminal ileum, but it may affect any part of the gastrointestinal tract, from the mouth to the anus [14]. The changes are usually segmental, the diseased sections alternating with healthy ones—the so-called skip lesions. The inflammation in CD is transmural and may affect the entire bowel wall. Initially, infiltrates are localized around the intestinal crypts, but with the disease progression, deeper layers are involved, and specific histological structures are formed—non-caseating epithelioid granulomas [13–16]. The transmural inflammation predetermines the disease-specific complications: wall thickening and narrowing of the lumen of the intestine, intestinal obstruction, fistulation, and abscess formation [16].

IBDU is the rarest of the IBD subgroups. It is more common in the pediatric population than in adults and is a diagnosis which is made in patients with IBD in whom the inflammation is confined to the colon and the disease has characteristics which do not allow to determine definitively whether it is UC or CD despite all necessary tests [7, 13, 16–18].

In UC, the inflammatory changes are usually localized in the colonic mucosa. The inflammation is ulcerative and purulent. It is continuous, usually starting from the rectum and gradually extending to the more proximal parts of the bowel. Histological findings include chronic inflammation of the mucosa with infiltration of polymorphonuclear neutrophils, accumulation of polymorphonuclear neutrophils in the crypts of the large intestine, formation of crypt abscesses, and disruption of the structure of the mucous glands. In more severe cases, inflammatory pseudopolyps are formed. The wall of the intestine becomes thick and rigid, without haustration [5, 6, 11, 13, 14, 16].

2. Specific features of pediatric ulcerative colitis

Pediatric ulcerative colitis is a different disease entity from adult-onset UC. It has a particular etiopathogenesis, unique clinical characteristics, specific disease course and outcome.

2.1 Etiopathogenesis

The etiopathogenesis of IBD is complex and multifactorial. It is suggested that a dysregulation of mucosal immune system leads to excessive inflammatory response to the contents of the intestinal lumen (microflora, infectious agents, nutrients, etc.). This abnormal immune response results in chronic inflammation and damaging of body's own structures [20]. Different genetic and environmental factors may contribute to the development of the immune dysregulation and the abnormal immune response [21]. Typical for the pathogenesis of pediatric IBD is that the role of the genetic factors is stronger than in adults, while environmental factors are of major importance in later clinical manifestation [22–24].

Childhood-onset UC is often associated with a consanguinity and a positive family history of IBD which provides an additional clue to an underlying genetic predisposition [25].

Currently, over genetic 160 loci have been associated with IBD. Most of the variants lead to aberrations in several mechanisms altering the intestinal immune homeostasis and contribute to both CD and UC risk. However, some polymorphisms are unique to UC- or early-onset UC-specific risk [26–28]. Furthermore, some types of infantile IBD or VEOIBD that manifest phenotypically with UC are thought to be monogenic diseases having a Mendelian inheritance [9, 12].

2.2 Clinical manifestation

The most common symptoms of pediatric UC include abdominal pain, chronic diarrhea with or without blood, weight loss, fatigue, fever, and rectorrhagia [6]. Generally, the clinical manifestation of the disease is associated with its location and the degree of inflammation [29]. Children with UC have more extended disease compared to adults with UC [30]. They are likely to present with pancolitis, whereas in adults the disease is predominantly confined to the rectum or left side of the colon [16]. The differences in disease location result in different clinical presentation in comparison with adult patients with UC. The majority of children with UC report of abdominal pain and bloody diarrhea, whereas adults tend to present most often with rectal bleeding [14, 16]. Furthermore, pediatric patients with UC have more often extraintestinal manifestations, impaired nutritional status or are at impaired general condition compared to adults with UC [30–32].

2.3 Endoscopic findings

The typical endoscopic findings of UC are continuous mucosal inflammation that starts from the rectum, extends proximally, and ends at transition zone anywhere in the colon or involves the whole colon [13]. Sometimes, in case of severe pancolitis the ileocecal valve and the most distal part of the terminal ileum may also be affected. This extension of the inflammatory process is termed "backwash ileitis" [14]. The typical macroscopic features of UC include erythema, granularity, friability, purulent exudates and ulcers which usually appear as superficial small ulcers. The typical histologic findings of UC include chronic inflammation in the mucosa accompanied by cryptitis or crypt abscesses. The inflammation is most severe distally and is getting milder proximally [13].

Pediatric-onset UC may present also with atypical endoscopic findings. Recognized and described are the following 5 phenotypes [13, 19]:

1. **Rectal sparing UC:** 5–30% of pediatric patients with UC have reduced or no inflammation of the rectum compared to proximal colon.

2. **Short duration of disease**: This variant occurs primarily in children younger than 10 years of age and is characterized by patchy disease in biopsies or lack of typical architectural distortion in pathological specimens.

3. **Cecal patch:** This phenotype is observed in 2% of the pediatric patients with UC and is characterized by left sided colitis with an area of cecal inflammation

4. **Involvement of the upper gastrointestinal tract:** 4–8% of the children with UC present with mild ulceration and microscopic involvement of the stomach; 0.8% of them present with inflammatory changes in the esophagus or duodenum—usually erosions, rarely ulcerations.

5. **Acute severe UC:** Children with clinical manifestation of acute severe ulcerative colitis may have several features that are typically characteristic of CD such as transmural inflammation and deep ulcers, which are associated with the severity of the disease.

Based on the specific endoscopic manifestations of pediatric UC in 2013 was introduced the term "atypical UC": a new child-specific IBD category consisting of 5 atypical disease phenotypes. Nowadays the pediatric UC is divided into typical UC and atypical UC [13].

2.4 Evolution and outcome

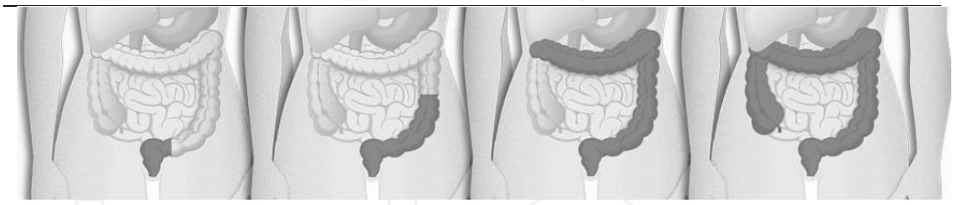
In contrast to adult-onset presentations, children with UC have extended disease and are likely to present with pancolitis [26, 33]. This more extended disease is consistently associated with a more severe and aggressive disease course. According to the literature, within 5 years from diagnosis a significantly higher percentage of patients with childhood-onset UC are admitted to emergency units for acute severe colitis, compared to adult-onset disease [33]. Furthermore, children with UC are more likely to receive corticosteroids, be initiated on immunomodulators, and require surgery in the first year after diagnosis than adults with UC [26, 33].

The colectomy rate is significantly higher in children compared to adult UC populations [33]. Based on the literature the colectomy rate within 10 years from diagnosis is over 40% in pediatric-onset UC compared to less than 20% in adult-onset UC [34]. However, other studies show lower colectomy rates of 25% in 6 years and 15% in 10 years [35, 36].

Another specific feature of childhood-onset UC is the possible change in the diagnosis from onset to long-term follow-up [6]. A recent study of the natural history of pediatric-onset IBD showed an increased disease reclassification over time from UC diagnosis to CD diagnosis [37]. Patients initially diagnosed as UC (a correct initial diagnosis) developed findings that led to a diagnostic change to CD [38].

3. Classification of pediatric ulcerative colitis

In May 2009 an international group of experts in pediatric IBD met in Paris and created a classification which reflects the specific phenotypic characteristics of pediatric IBD—the so-called Paris classification (**Table 1**). It represents a pediatric modification of the adult Montreal Classification of IBD. The classification of pediatric UC disease according to the Paris classification. With respect to disease extent it is divided into four categories: ulcerative proctitis (E1), left-sided UC (E2), extensive UC (E3) and pancolitis (E4). Disease severity is categorized as never severe (S0) and ever severe (S1) [8].

Extent of disease			
E1	**E2**	**E3**	**E4**
			
Ulcerative proctitis	Left-sided UC (distal to splenic flexure)	Extensive (hepatic flexure distally)	Pancolitis (proximal to hepatic flexure)
Severity of disease			
S0		**S1**	
Never severe (never PUCAI≥65)		Ever severe (ever PUCAI≥65)	

PUCAI: Pediatric Ulcerative Colitis Activity Index

Table 1.
Paris classifications for pediatric ulcerative colitis (adapted from Levine et al. [8]).

For measuring disease activity and evaluation of disease severity is used a validated, multi-item, scoring system—the so-called Pediatric Ulcerative Colitis Activity Index (PUCAI) (**Table 2**). The PUCAI is a score comprised of six parameters, including the assessment of abdominal pain, rectal bleeding, stool consistency, number of stools per 24 h, nocturnal stools, and activity level. Each item is assigned a value contributing to a combined total PUCAI score ranging from 0 to 85. Categories of UC disease activity are defined by the following total PUCAI scores: 0–9 (no activity), 10–34 (mild activity), 35–64 (moderate activity), and 65–85 (severe activity) [39]. The items that are included in the PUCAI score and their corresponding points are presented.

Item	Characteristics	Points
Abdominal pain	No pain	0
	Pain can be ignored	5
	Pain cannot be ignored	10
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
Stool consistency of most stools	Formed	0
	Partially formed	5
	Completely unformed	10
Number of stools per 24 h	0–2	0
	3–5	5
	6–8	10
	>8	15
Nocturnal stools (any episode causing wakening)	No	0
	Yes	10
Activity level	No limitation of activity	0
	Occasional limitation of activity	5
	Severe restricted activity	10
Total score:		

Table 2.
Pediatric ulcerative colitis activity index (adapted from Turner et al. [39]).

4. Diagnosis of pediatric ulcerative colitis

The diagnosis of pediatric UC is based on standard consensus-based criteria for diagnosing IBD in pediatric patients, the so-called Porto criteria. They were prepared and issued in 2005 by the IBD Working Group of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition [16]. In 2013 the initial criteria were revised and updated [13]. According to the Porto criteria the diagnosis of pediatric UC involves history taking, physical and laboratory examination, esophagogastroduodenoscopy and ileocolonoscopy with histology, and imaging of the small bowel [11, 13, 16]:

1. **History:** Abdominal pain and bloody diarrhea are the most common presenting symptoms in pediatric UC. Other symptoms may be rectal bleeding, fever, weight loss, growth retardation, malnutrition, psychiatric symptoms, arthropathy, erythema nodosum, retardation of pubertal development, secondary amenorrhea, etc. Suspicious are symptoms which persist for ≥4 weeks or recurrent symptoms (≥2 episodes within 6 months).

2. **Physical examination:** Physical examination might reveal signs of anemia, abdominal tenderness, and blood on rectal exam. Looking for presence of malnutrition or extraintestinal manifestations (skin abnormalities, arthritis, etc.) is an important part of the full examination.

3. **Blood tests:** Screening blood tests should include full blood count, erythrocyte sedimentation rate, C-reactive protein, serum levels of urea and creatinine, serum albumin, immunoelectrophoresis, liver function tests and (in certain cases) celiac screen.

4. **Microbiological investigations:** The search for bacterial infections should include a stool culture to exclude Samonella, Shigella, Yersinia, Campylobacter as well as *Clostridum difficile* toxins in all children.

5. **Screening for tuberculosis**

6. **Serological investigations:** No serology pattern can preclude the diagnosis of UC, due to imperfect test performance of all existing antibodies. However, the presence of pANCA+/ASCA- serology increases the likelihood of UC.

7. **Fecal markers of inflammation:** Pediatric data exist primarily for fecal calprotectin and lactoferrin. Both markers are excellent tools for identifying the presence of intestinal inflammation but are unspecific.

8. **Ileocolonoscopy and esophagogastroduodenoscopy with biopsies:** Colonoscopy including intubation of the terminal ileum and multiple biopsies for histology obtained from all segments of the lower intestinal tract (ileum, cecum, ascending colon, transverse colon, descending colon, sigmoid and rectum) is essential for the diagnosis of pediatric UC. In addition, an esophagogastroduodenoscopy is advocated is recommended in all patients to exclude a CD or to confirm an atypical UC.

9. **Imaging of the small bowel:** It is recommended for all patients unless the diagnosis favors typical UC. **Magnetic resonance enterography** is the imaging modality

of choice in children IBD at diagnosis with high diagnostic accuracy. Alternatively, **wireless capsule endoscopy** can be used to identify small bowel mucosal lesions in children in whom magnetic resonance enterography cannot be performed. **Abdominal ultrasound** is also a useful imaging modality that accurately detects and characterizes inflammation of the bowel wall, but it is more valuable in CD diagnosis and usually should be complemented by more sensitive imaging method.

10. **Genetic tests and immunological investigations:** They are recommended for all patients with suspected VEOIBD, presenting with UC phenotype.

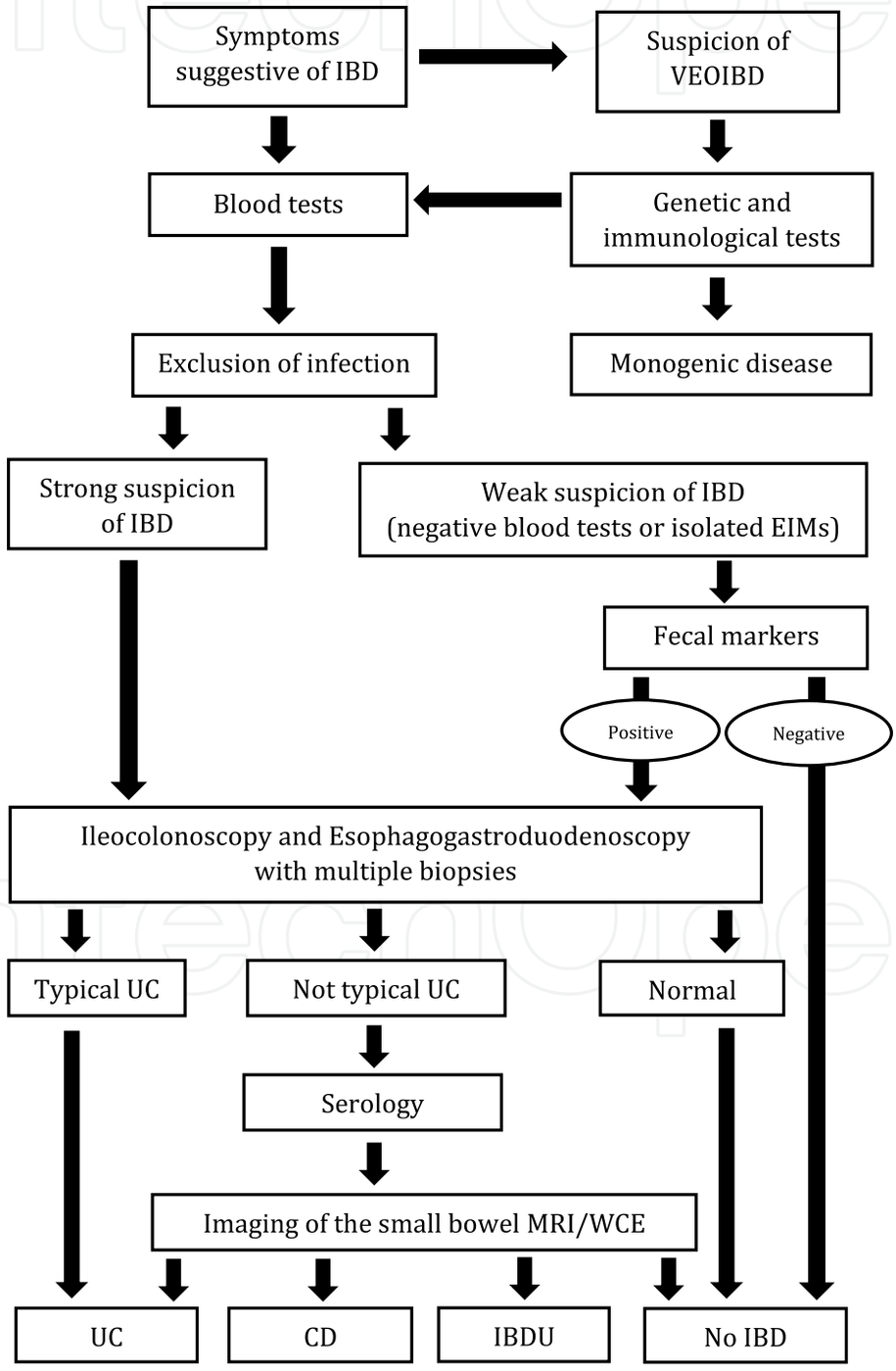


Figure 1.
Diagnostic algorithm for pediatric ulcerative colitis. IBD: inflammatory bowel disease; VEOIBD: very early onset inflammatory bowel disease; EIM: extraintestinal manifestation; UC: ulcerative colitis; MRI: magnetic resonance imaging; WCE: wireless capsule endoscopy; CD: Crohn's disease; IBDU: Inflammatory bowel disease unclassified.

A summary of the diagnostic algorithm for suspected pediatric UC is presented at **Figure 1**.

5. Therapy of pediatric ulcerative colitis

The management of pediatric UC is based on therapeutic guidelines produced by the European Crohn's and Colitis Organization (ECCO) and European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) [40, 41]. Generally, the treatment strategy should be guided by the endoscopic extent of inflammation and disease severity. However, in children with UC the therapy depends mainly on disease severity, assessed by the corresponding disease activity index: Pediatric Ulcerative Colitis Activity Index (PUCAI) [39, 40]. The treatment goal is induction and maintenance of steroid-free complete remission [40].

5.1 Medical therapy

5.1.1 5-Aminosalicylates (5-ASA)

5-ASA are the preferred first-line therapy for induction and maintenance of remission for patients with mild (PUCAI 10–34) and some patients with moderate disease (PUCAI 35–64) [40]. The preparations are available as forms for local administration (suppositories and enemas) and forms for systemic administration (tablets and granules). Topical 5-ASA are effective in mild-to-moderate distal UC, but usually they are combined with oral 5-ASA, as the combination therapy is more effective than either treatment alone [40, 42]. Rectal 5-ASA are superior to rectal steroids for induction and maintenance of remission in distal UC [43]. Oral 5-ASA preparations are generally preferred to sulfasalazine due to a superior side effect profile combined with similar efficacy. However, sulfasalazine is cheaper and available in liquid formulation [40, 42]. The recommended dosing for oral mesalamine is 60–80 mg/kg/day (maximum 4.8 g daily) and for oral sulfasalazine 40–70 mg/kg/day (maximum 4 g daily). Both are usually given in divided doses, but according to the studies once daily dosing of 5-ASA may be as effective as twice daily dosing [44]. The recommended dosing for rectal mesalamine is 25 mg/kg up to 1 g daily (1 g daily is as effective as higher doses) [40]. Lack of meaningful response to 5-ASA within 2–3 weeks of therapy is an indication for treatment modification and initiation of steroids [40, 42].

5.1.2 Steroids

Treatment with steroids is recommended for induction of remission in children with moderate and severe UC. It is not recommended for maintenance of remission [40]. Available are forms for oral, intravenous, and local administration. Steroid dependency is defined as response or remission with corticosteroid treatment, but recurrence of symptoms when the dose is lowered or within 3 months following complete taper [40]. Steroid refractory UC is defined as lack of clinical response to oral prednisolone at doses 0.75–1 mg/kg/day (max. 40 mg/day) within 4 weeks or lack of clinical response to intravenous prednisolone at doses 0.75–1 mg/kg/day (max. 60 mg/day) within 1 week [40, 41].

Oral steroids should be used as second-line therapy for mild or moderate UC not responding to 5-ASA (oral ± rectal) and may be considered as first line in more

severe moderate disease. The recommended daily dose for oral prednisolone/prednisone is 1 mg/kg/day up to 40 mg/day administered once daily (in the morning) for 2–3 weeks followed by a tapering period of up to 8–10 weeks [40]. Second-generation oral steroids with lower systemic effect such as beclomethasone dipropionate and budesonide-MMX may be considered in patients with mild disease refractory to 5-ASA before oral prednisolone. The recommended dosing schedule for beclomethasone dipropionate is 5 mg once daily for 4 weeks and for budesonide-MMX 9 mg for 8 weeks. The recommendations are for patients with weight > 30 kg. Dosing for children <30 kg has not been established [40].

Intravenous steroids should be used as first-line therapy in patients with severe UC (PUCAI ≥ 65) (See section Acute severe ulcerative colitis) [40, 41].

Rectal steroid preparations are useful for patients who are 5-ASA intolerant and in selected patients refractory to 5-ASA before starting oral prednisolone [40].

5.1.3 Immunomodulators

Thiopurines are recommended for maintaining remission in children with UC. They should be used as second-line therapy for maintaining remission in children with mild or moderate UC after 5-ASA failed and as first-line therapy for maintaining remission in children with severe UC and in 5-ASA intolerant patients. Although thiopurines have been shown to be more effective than 5-ASA they should generally be reserved as second-line therapy, considering their safety profile [40]. Before starting therapy with thiopurines it is recommended the determination of thiopurines methyltransferase (TPMT) genotype or phenotype to identify patients at greater risk of early profound myelosuppression or other thiopurine associated toxicity. Dose should be reduced in heterozygous patients or in those with low activity. Thiopurines should not be used in children homozygous mutants for TPMT or those with very low TPMT activity. Concomitant use of allopurinol 50 mg once daily in patients <30 kg and 100 mg once daily in patients ≥30 kg (maximum 5 mg/kg) with reduced dose of azathioprine (to approximately 25–30% of initial dose) is a valid therapeutic option in cases of hyperactive TPMT resulting in high 6-MMP and low 6-TGN. The recommended dosing in patients with normal TPMT is 2–2.5 mg/kg/day for azathioprine and 1–1.5 mg/kg/day for mercaptopurine, in a single daily dose [40]. The therapeutic effect of thiopurines may take up to 10–14 weeks after the start of treatment. Measurement of thiopurine metabolites, 6-methyl mercaptopurine and 6-thioguanine is helpful to assess compliance, adjust therapy and avoid adverse events [40, 42].

Methotrexate may be considered as alternative therapeutic option for maintaining remission in selected children with UC. Generally, there is no evidence supporting its routine use for maintenance of remission in UC, therefore it should be used only when other alternatives are not possible or available [40, 45].

Tacrolimus is a potent immunomodulator which administration is reserved for special occasions. Oral tacrolimus may be considered in selected outpatient UC children as another option to steroids for bridging to thiopurines or vedolizumab. The target trough level should be 10–15 ng/mL when initiating the treatment, and 5–10 ng/mL during the follow up period. Rectal tacrolimus may be considered as third-line therapy in patients with ulcerative proctitis who are either refractory or intolerant to mesalamine and steroids topical therapies. The recommended dose is 0.07 mg/kg/day, maximum 3 mg/day [40].

5.1.4 Biologics

Treatment with biologics is recommended as second- or third-line therapy for children with moderate or severe UC. Currently approved for pediatric use are three tumor necrosis factor (TNF)-alpha inhibitors: *infliximab*, *adalimumab*, *golimumab*; and one anti-integrin drug: *vedolizumab*. However, the mainstay of pediatric UC management is the therapy with *infliximab*. It is used for induction and maintenance of remission in children and adolescents who have had an inadequate response to conventional therapy including corticosteroids and thiopurines or who are intolerant to or have medical contraindications for such therapies. The recommended dose is 5 mg/kg per dose at weeks 0, 2, and 6, then 5 mg/kg every 8 weeks thereafter. Higher dosing should be considered in children with low body weight (<30 kg) or high BMI, and in the presence of higher inflammatory burden and hypoalbuminemia. A combination therapy with immunomodulator is preferred to reduce the likelihood of developing drug-antibodies and to enhance the effectiveness [40]. Target trough levels during induction are ≥15 μg/mL and post induction at the start of maintenance (week 14) ≥5 μg/mL [46–48].

Adalimumab or *golimumab* may be considered as therapeutic option in children with moderate to severe UC who are intolerant to *infliximab* or initially respond but then lose response to *infliximab* (secondary loss of response). The recommended dosing for *adalimumab* is 160 mg at week 0, followed by 80 mg after 2 weeks and then 40 mg every other week in adolescents with weight ≥ 40 kg. In children with weight < 40 kg the recommended dosing is 92 mg/m^2 at week 0, followed by 46 mg/m^2 after 2 weeks and then 23 mg/m^2 every other week. *Adalimumab* target levels should be ≥13 μg/mL during the induction phase and ≥7.5 μg/mL during the maintenance phase [47, 49]. The recommended dosing for *golimumab* is 200 mg at week 0 followed by 100 mg at week 2 and every 4 weeks thereafter in adolescents with weight ≥ 45 kg. In children with weight < 45 kg the recommended dosing is 115 mg/m^2 at week 0, followed by 60 mg/m^2 at week 2 and every 4 weeks thereafter. Recommended target trough levels during maintenance are >2 mg/mL [40].

5.1.5 Antibiotics

Antibiotics should not be routinely used for induction or maintenance of remission of pediatric [40]. However, recent studies demonstrated that a combination of specific antibiotics—the so called wide-spectrum antibiotic cocktail could be used as therapeutic option for pediatric patients with severe UC resistant to other treatments [50, 51].

5.1.6 Probiotics

The use of specific probiotic agents (e.g., VSL#3 or *Escherichia coli* Nissle 917) may be considered as an adjuvant therapy in pediatric patients with mild UC or as first-line therapy in selected patients with mild UC intolerant to 5-ASA [40].

5.2 Surgical therapy

Despite advances in conventional therapy surgery remains an integral part of the management strategy in children with UC. It should be considered in patients with active, or steroid-dependent, UC despite optimized medical therapy, and in those with colon dysplasia [40]. The most common surgery that is carried out is a

subtotal/total colectomy with a temporary stoma [42]. A minimally invasive laparoscopic approach is recommended for superior outcomes. Generally, the restorative proctocolectomy with ileal pouch-anal anastomosis and a covering loop ileostomy, performed as one- or two- or three-stage procedures is the recommended elective surgery for pediatric patients with UC [40].

5.3 Acute severe ulcerative colitis

Acute severe ulcerative colitis (ASC) is defined by a PUCAI score of at least 65 points [39]. According to the literature 11–23% of children with UC experience at least one severe exacerbation during the course of their disease [52–54]. ASC is an emergency which requires immediate management. Children with ASC should be treated in a hospital by a multidisciplinary team. They need close monitoring and frequent reevaluation [41].

Intravenous methylprednisolone is used as first-line treatment for ASC in children. It is preferred over hydrocortisone due to its minimal mineralocorticoid activity. The recommended dosage is 1–1.5 mg/kg/day (up to 60 mg/day) given in one or two divided daily doses. The majority of patients will respond to this treatment. However, sequential measurement of PUCAI scores is essential for identifying those patients requiring a step up in treatment with second-line (rescue) therapy [41, 42]. A PUCAI score of >45 on day 3 indicated a likelihood of steroid failure and should dictate planning for second-line therapy. In children with a PUCAI of 35–65 on day 5 intravenous steroids should be continued for an additional 2–5 days before a decision on second-line therapy is made. A PUCAI score of >65 on day 5 indicated the need for starting a rescue therapy [41].

The second-line therapy involves either *infliximab* or calcineurin inhibitors (*cyclosporin* or *tacrolimus*) [41]. Both are equally effective in inducing clinical remission in children with ASC [55]. Due to increased clearance of *infliximab* in ASC the recommended dosing for induction of remission is higher up to 10 mg/kg per dose and may be given more frequently than usual (e.g., weeks 0, 1, and 4–5). After achievement of remission target drug levels should be 5–10 μg/mL. The recommended dosage for *tacrolimus* is 0.1 mg/kg per dose orally twice daily with target drug levels during induction 10–15 ng/mL and 5–7 ng/mL once remission achieved. The recommended induction dosage for *cyclosporine* is 2 mg/kg/day administered as continuous intravenous infusion. Target drug levels should be 150–300 ng/mL during the induction phase and 100–200 ng/mL during the maintenance phase. Response to rescue therapy should be judged daily by PUCAI. If the rescue therapy fails, there is an option for a second-line rescue therapy in selected patients or it should be proceeded to a surgical management [41].

Many gastrointestinal infections have been associated with pediatric ASC. Exclusion of several specific pathogens, such as *Clostridium difficile* or Cytomegalovirus is crucial for the adequate management. In addition, for all patients on triple immunosuppressive therapy which includes *anti-TNF* or a calcineurin inhibitor plus *thiopurines* or *methotrexate* plus steroids should be considered a *Pneumocystis jiroveci* pneumonia prophylaxis with *trimethoprim-sulfamethoxazole*. The recommended trimethoprim-sulfamethoxazole dosing is 450 mg/m^2 twice daily (maximum 1.92 g daily) for 3 days each week, either consecutive or alternate day dosing [41].

ASC is associated with increased risk for venous thromboembolic events (VTE) [56–58]. However, thromboprophylaxis with subcutaneous low molecular weight heparin is recommended only for children or adolescents with an underlying

predisposition such as smoking, use of oral contraceptives, complete immobilization, obesity, concurrent significant infection, known prothrombotic disorder, previous VTE, family history of VTE, etc. [41].

Adequate nutrient intake and early treatment of the accompanying conditions such as anemia, infections, etc., are also an integral part of the successful management of ASC and should not be overlooked.

5.4 Very early onset inflammatory bowel disease with colitis phenotype

The colitis phenotype is the most common in the VEOIBD group [40]. The clinical manifestation could be very heterogeneous and requires a different treatment approach altogether [12]. A large percentage of children with VEOIBD presenting as colitis have a mild disease which can be easily managed with 5-ASA [59]. Others demonstrate an extended disease with severe and treatment refractory course. They require escalated dosing strategies and more intensive treatments: early introduction of biologics, combination therapies, higher dosage of immunomodulators or biologics, etc. [12]. Additionally, many of the patients with VEOIBD with colitis phenotype have an underlying monogenic disorder and benefit from specific targeted therapies [12, 40]. If the molecular defect is caused by a mutation affecting predominantly immunological cells (e.g., IL10 signaling defects, XIAP and chronic granulomatous disease), hematopoietic stem cell transplantation may be curative [40]. Therapies that inhibit the hyperactive T-cell signaling could be used successfully in patients with *CTLA4* or *LRBA* defects [60]. *Abatacept* and *rapamycin* could also be used in those patients and in patients with other defects that involve loss of Tregs or unchecked T-cell activation, such as *FOXP3* and *PIK3CD* mutations. Generally, targeted medical therapies can be used in a variety of monogenic diseases as a maintenance therapy, and in some cases, as a bridge to hematopoietic stem cell transplantation [12].

6. Conclusions

Pediatric UC is a disease with a heterogeneous phenotype which poses many unique challenges. The majority of children with UC present with pancolitis. Since disease extent is consistently associated with disease severity, it is not surprising that they have more aggressive disease course requiring more intensive therapies. Furthermore, children with UC have some unique age-related issues, such as delay of growth and pubertal development, nutrition disorders, psychological or emotional problems. Pediatric UC may present also atypically making the diagnosis difficult and demanding specific diagnostic tests and procedures. In addition, there is a group of patients with early-onset UC who needs a completely different diagnostic and treatment approach.

Pediatric UC is a disease with unique features and characteristics. Its correct diagnosis and successful management always require a hard teamwork and multidisciplinary approach.

Conflict of interest

The authors declare no conflict of interest.

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