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Journal of Surgical Case Reports and Images

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Review Article

Ulcerative Colitis

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Received Date: October 17, 2025; **Accepted Date:** October 25, 2025; **Published Date:** October 31, 2025

Citation: Bon E.I., Maksimovich N.Ye., Hubarevich I.Ye., Kazlouski D., Sitsko A, (2025), Ulcerative Colitis, *J, Surgical Case Reports and Images*, 8(8); **DOI:10.31579/2690-1897/279**

Abstract

Although rectal injury is uncommon, it can lead to a diagnostic conundrum. One must keep a high index of suspicion based on the mechanism of injury. The rectal injury can result from blunt or penetrating trauma. In order to prevent morbidity and mortality an early diagnosis is essential. A high index of suspicion and appropriate diagnostic modality help to make the diagnosis.

Keywords: rectal injury; rectal injury classification; epidemiology; management of rectal injury; complications

Introduction

Ulcerative colitis (UC) is a disease with a less heterogeneous phenotype than Crohn's disease (CD), but it still presents many unique challenges. The incidence of UC in children, which accounts for approximately 15% to 20% of all UC cases, ranges from 1 to 4/100,000/year in most regions of North America and Europe (1). It is extensive in 60% to 80% of all cases, twice as common as in adults (2). Because disease prevalence is consistently associated with disease severity, it is not surprising that children with UC are more likely to require hospitalization for acute severe exacerbations (25%–30% over 3–4 years) (3, 4) and more likely to undergo colectomy for drug-refractory disease (up to 30%–40% at 10-year follow-up (2, 5), although lower colectomy rates have been reported (6–8)). Population-based data from the Health Authority of Canada showed no decrease in colectomy rates from 1994 to 2007, before the widespread use of biologics (9). In addition to more severe colitis, children also have age-specific challenges such as growth, sexual development, nutrition, and bone mineral density, as well as various psychosocial needs. Finally, although mortality from UC in children has become rare, a retrospective collection of cases across Europe over the past 6 years identified 19 deaths in children with UC, mostly due to infections and cancer (1 case of colorectal cancer [CRC]), including 1 case of toxic megacolon (10).

The IBD class system is based on 23 features typical of UC, grouped into 3 classes: those that are completely incompatible with UC and therefore should be diagnosed as UC; those that may be present in UC but rarely (<5%; class 2); and those that may be present in UC infrequently (5%–10%; class 3). The combination of various features, weighted by class, has standardized the diagnosis of IBD. The sensitivity and specificity of the PIBD classes for differentiating UC from CD and IBDU were 80% and 84%, respectively, and for CD from IBDU and UC, 78% and 94%, respectively (11).

For phenotyping childhood ulcerative colitis, the Paris classification is recommended, where E1– E4, A1a–A2, and S0–S1 denote the extent of the disease, age at diagnosis, and severity of the disease, respectively (12). Additional designations may also be added for very early-onset IBD (age ⩽6 years at diagnosis) and infantile-onset IBD (age <2 years) (13).

Current Concept of Ulcerative Colitis Pathogenesis

A widely accepted concept proposes a complex interaction of environmental and host factors that increases susceptibility to the development of ulcerative colitis, with disease onset triggered by events that disrupt the mucosal barrier, alter the healthy balance of intestinal microbiota, and abnormally stimulate the intestinal immune response. In this paper, we discuss common etiologic factors that increase the risk of developing ulcerative colitis and examine the molecular basis of the pathological inflammatory process in this disease. We will briefly review the genetic, environmental, immune, and microbiome factors that currently shape our understanding of the pathogenesis of ulcerative colitis.

Genetics

Genetic studies (including genome-wide association analysis [GWA], whole-genome sequencing [WGS], and fine mapping) have been particularly successful in identifying 260 susceptibility loci (both common and rare genetic variants) associated with IBD 10–14. Several key findings have been obtained. First, most genetic factors are shared between UC and CC. In an initial analysis of 15 GWA datasets, Jostins et al. showed that 110 of 163 (67%) susceptibility loci were associated with

both UC and CC 11. These shared genes encode both innate and adaptive immune pathways, cytokine signaling, and immune sensing (e.g., IL23-R, IL-12, JAK2, CARD9, TNFSF18, and IL-10). Many of these genes (70%) are also shared with other autoimmune diseases, such as ankylosing spondylitis and psoriasis. Second, the strongest genetic signals at UC-specific loci are associated with the human leukocyte antigen (HLA) region on chromosome 6. Sixteen HLA allelic associations (mostly class II) have been described for UC, including HLA DRB1*01*03 for colonic involvement in IBD in deeper genetic mapping. 15 Further analyses indicate that they are associated with colonic involvement in UC and CD. 16 Interestingly, HLA allelic associations with extensive and aggressive UC were noted even before the GWA studies. 17 Recent complete sequencing of nearly 2,000 patients with UC identified a novel but rare missense variant (present in 0.6% of cases) in the adenylate cyclase 7 (ADCY7) gene that doubles the risk of UC. Outside the HLA region, the ADCY7 gene has the strongest genetic association observed with UC. ADCY7 is one of 10 enzyme families that convert ATP to the ubiquitous second messenger cAMP. Furthermore, many UC-specific genes are involved in regulating epithelial barrier function (discussed in more detail below). Third, despite the identification of many susceptibility loci, genetics explains only 19% of the disease heritability in UC. The concordance rate among monozygotic twins for UC is only 6.3% (compared to nearly 60% in CD). Collectively, genetic factors contribute to a small but significant increase in susceptibility to UC. However, many individuals lack a genetic predisposition when assessed using a polygenic risk score that considers all susceptibility loci 19. This suggests a key role for aberrant adaptive immune responses and epithelial barrier dysfunction in the pathogenesis of UC. Non-genetic factors may also play an important role.

Environmental Factors

The rapid increase in the incidence of ulcerative colitis (UC) in newly industrialized countries demonstrates the importance of environmental factors. This is consistent with trends observed in the Western world in the early 20th century. Specifically, UC first appears in urban areas, its incidence increases rapidly, and then slows; subsequently, the incidence of CD increases, eventually approaching that of UC. Westernization is accompanied by a new urban lifestyle, exposure to pollution, dietary changes, access to antibiotics, better hygiene, and a decrease in infections, which are considered general contributing factors. Despite this, more specific environmental factors associated with UC have long been known. The most striking example is the protective effect of cigarette smoking and the notable observation of new-onset UC in people who quit smoking. Global patterns of smoking and IBD are changing; The growing population of former smokers with UC in China suggests a rapid expansion of the at-risk population. The anti- inflammatory effect of cigarette smoking in UC is intriguing and may be mediated by carbon monoxide. Other examples include the protective effect of appendicitis against future UC development bimodal incidence with a second peak associated with older age in men, and, more recently, an intriguing association with Parkinson's disease (another condition associated with non-smoking and older age). All of these provide more specific etiologic insights into the development of UC. Epidemiological data have shown a potential protective effect of a diet high in n-3 polyunsaturated fatty acids (PUFAs), present in fatty fish and a diet high in red meat on the development of UC.

Gut microbiota

The gut microbiome in IBD is significantly less diverse and stable over time, as recently detailed in the Integrative Human Microbiome Project (iHMP), where 132 individuals with IBD and healthy controls were followed for 1 year 35 and demonstrated in a case-control study of 1800 patients with IBD and irritable bowel syndrome. A depletion of protective bacteria, such as short-chain fatty acid (SCFA)-producing Ruminococcaceae and Lachnospiraceae, was noted, coinciding with an expansion of proinflammatory microbes, such as Enterobacteriaceae, including Escherichia coli, and Fusobacteriaceae. However, these changes are less pronounced in ulcerative colitis compared to Crohn's disease. It is unknown whether Dysbiosis is a consequence or cause of intestinal inflammation in UC. In this regard, the virome and mycobiome are also less diverse in UC. In longitudinal iHMP, microbiome patterns did not predict the likelihood of disease flare-ups. To add complexity, further research in UC has shown that microbial abundance does not necessarily correlate with transcriptional activity. However, from a therapeutic perspective, fecal microbial transplantation (FMT) from healthy donors can treat UC. There are four positive controlled clinical trials of FMT. Restoration of microbial diversity, including bacterial species responsible for short-chain fatty acid production in donor stool, has been suggested as an important factor. Therefore, one of the main effects of dysbiosis in UC is likely to be a decline in epithelial health or a state of epithelial dysfunction, which further enhances the innate susceptibility to UC. In support of this assertion, the fact that stool diversion from the rectum increases inflammation, causing "diversion colitis" in ulcerative colitis is supported; in the case of Crohn's disease, the opposite is true: stool diversion improves inflammation.

Epithelial Dysfunction

Many studies based on histological observations of subepithelial inflammation point to disruption of the epithelial barrier as a pathogenic factor in the development of ulcerative colitis. This occurs either due to altered or impaired secretion (e.g., of antimicrobial peptides, injury-associated molecular patterns, or mucus) or physical defects (e.g., due to disruption of epithelial tight junctions or defective regeneration or detoxification). GWA studies indicate that UC-specific susceptibility genes regulate epithelial morphogenesis (hepatocyte nuclear factor 4 α, Hnf4α), adherens junction stability via E-cadherin (CDH-1), basement membrane anchoring and stability (via laminins, LAMB-1, and extracellular matrix, ECM1), tight junction assembly (guanine nucleotide-binding protein alpha 12, GNA12), ion transport (solute carrier family-26, SLC26A3) and epithelial health via endoplasmic reticulum stress (orsomecoid-like gene 1) 3, ORMDL3).

Interestingly, a genetic truncating variant in RNF186, a single-exon E3 ligase highly expressed in colonic epithelium, protects against ulcerative colitis; however, the underlying mechanism remains unclear. Therefore, there is a potential inherent 'risk' phenotype in which exposure to additional noxious stimuli, such as non-steroidal anti-inflammatory drugs (which reduce the synthesis of protective prostaglandins) and dietary components such as emulsifiers (which reduce the thickness of the mucus layer) , may be a second trigger that induces colitis. As discussed previously, dysbiosis results in loss of short-chain fatty acid production 35, which are necessary for providing the epithelium with energy, mucus production, and proliferation in the colon. Thus, clinical trials using butyrate, propionic acid, prebiotics, and L-carnitine, which facilitate the transport of short-chain fatty acids, have demonstrated some efficacy in the treatment of ulcerative colitis. During active ulcerative colitis, key proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interferon (IFN)-γ, and interleukin (IL)-13 have a direct detrimental effect on epithelial barrier integrity. Remission-maintaining drugs in ulcerative colitis, such as mesalazine, may exert part of their therapeutic effect by maintaining epithelial health. Thus, protecting the “at-risk” group or restoring colonic epithelial health may be a viable strategy for maintaining long-term remission in ulcerative colitis.

Abnormal Immune Response: InnateActive ulcerative colitis involves a complex inflammatory environment consisting of innate and adaptive immune cells infiltrating the lamina propria. Neutrophils, short-lived “first responder” cells, are recruited in abundance with the characteristic “crypt abscess” histology of ulcerative colitis, where neutrophils transmigrate through the colonic epithelium and die within the colonic crypt. The inflammatory environment of ulcerative colitis promotes neutrophil survival (potentially through HIF-1 and hypoxia). This increased survival potentiates their inflammatory effects and tissue injury (in many ways, including the release of serine and matrix metalloproteases, reactive oxygen species, and proinflammatory cytokines). Large numbers of neutrophils undergo uncontrolled proinflammatory cell death (necrosis, necroptosis, and NETosis), which potentiates and amplifies the proinflammatory environment. This is supported by high levels of s100a8/9 (or calprotectin) proteins,

commonly found in neutrophils that are released in the blood and stool and a pronounced serologic response to self-perinuclear anti-p-neutrophil cytoplasmic antibodies (pANCA) in UC, both likely indirect indicators of uncontrolled neutrophil cell death. Neutrophil extracellular traps (NETs) may act as a settling basin for immunogenic molecules that sustain the inflammatory response. Therefore, a rational paradigm exists that, following disease onset, a preceding wave of innate inflammatory neutrophils and monocytes (with their proinflammatory cytokine repertoire, e.g., IL-1 family, IL-6, and TNF-α) creates an inflammatory environment (nutrient, metabolic, and cytokine) that favors the pathological adaptive (probably T cell) immune response. Such an environment may also shape newly arriving inflammatory monocytes, monocyte-macrophage function, their survival and their phenotype, as well as other factors that influence the host's ability to resolve inflammation, restore homeostasis and repair the ulcerative colitis mucosa.

Abnormal Immune Response: Adaptive

Strong genetic associations of ulcerative colitis with HLA (primarily class II) suggest that abnormal antigen(s) eliciting abnormal T-cell responses, which then shape a pathological cytokine milieu, are likely the key causative factors. How HLA influences the presentation (and identity) of commensal and/or self-antigens to T cells and, consequently, the pathogenic T-cell response, remains unclear and complex. Approaches to studying, screening, and defining T cell epitopes have improved significantly, and progress is likely. Traditionally, ulcerative colitis has been associated with a Th2 response with high levels of IL-4, IL-5, and IL-13, whereas Crohn's disease has a predominantly Th1/Th17 response. Earlier studies showing lower levels of IL-4 in ulcerative colitis, with CD1d-restricted IL-13-producing natural killer T cells, suggest a non-classical Th2 response. Several recent developments have overtaken the field. These include the identification of IL-23 as a key driver of the Th17 response, genetic associations with IL-23 and related genes 11, and the presence of Th17 (and Th9) cells in ulcerative colitis. The Th2 angle becomes less clear when anrukinzumab (a drug that blocks IL-13 by binding to IL-4Ra, a common subunit of the IL-13 and IL-4 receptors) and tralokinumab (a drug that blocks binding to both IL-13Ra andIL-13Ra2) are ineffective in ulcerative colitis. However, blocking IL-23 is effective in ulcerative colitis, such as mirikizumab (anti-p19 subunit of IL-23) and ustekinumab (anti-p40 subunit of IL-23). The example of anti-TNF treatment first used in CD and then showing the same efficacy in ulcerative colitis demonstrates that basing a translational approach on a pure Th cytokine profile may be overly simplistic. Furthermore, although CD4 T cells are considered more important in the pathogenesis of IBD, it has been found that transcriptomic signatures of CD8 T cells influence whether ulcerative colitis and Crohn's disease will acquire a more aggressive disease course (in this study, CD4 T cell signatures were not useful). New data characterizing adaptive immune populations at the transcriptomic (and single-cell) level will open up many more new possibilities. The recent discovery of innate lymphoid cells (ILCs) as another mediator of the IL-23-induced inflammatory response in the colon99 represents another new direction in the study of ulcerative colitis.

Mitochondria and Ulcerative Colitis

Recent progress has been driven by a focus on direct studies of inflamed mucosa, particularly in newly diagnosed or drug-naive patients. Interestingly, using bulk RNA sequencing in 206 newly diagnosed children with ulcerative colitis (the PROTECT study), Haberman et al. showed a significant decrease in the expression of mitochondrial genes that encode the oxidative phosphorylation chain (responsible for energy production) and nuclear genes such as PPARGC1A (responsible for mitochondrial biogenesis), implicating mitochondriopathy as a pathogenic process in ulcerative colitis. Mitochondria are double-membrane-spanning intracellular organelles that perform many important physiological functions such as energy production, regulation of cell death and immune responses . Over the past 10 years, many seminal studies have highlighted mitochondria as a major previously unknown "puzzle piece" in inflammation. Mitochondrial dysfunction has long been implicated in ulcerative colitis, dating back to the 1980s (reviewed by Nowak et al. 106), but new data in the past 3 years have refocused this concept. Similar dysregulation of genes controlling mitochondrial function has been shown in previous colon microarray studies in ulcerative colitis (UC). Functional studies indicate that mitochondria are in a uniquely damaging environment (in the colon, to a greater extent than in other tissues) . Loss of mitochondrial homeostasis (including mitophagy and autophagic removal of damaged mitochondria—the IBD susceptibility genes PARK7 and LRRK2) can lead to impaired energy production, increased oxidative stress in the mitochondria, and even the release of mitochondrial products (mitochondrial DNA) as proinflammatory DAMPs. These findings contribute to key aspects of UC, such as epithelial dysfunction, a proinflammatory mucosal environment, and direct triggers of the inflammatory response. This combination of data has led to the development of new approaches to targeting proinflammatory mitochondria, such as mitochondrial antioxidant therapy for active ulcerative colitis.

Diagnostic Evaluation

The diagnosis of ulcerative colitis cannot be definitively established by any single diagnostic test. It is based on a comprehensive interpretation of clinical manifestations, laboratory tests, and endoscopic, histological, and radiographic data (1). Infectious causes must be excluded at diagnosis and subsequently, if an acute episode occurs. Classic microbial pathogens, particularly Clostridioides difficile, should be considered (antigen and toxin titers should be determined, and, if possible, the pathogen should be identified by culture or PCR). In cases resistant to therapy, reactivated cytomegalovirus (CMV) infection should be confirmed or excluded, as recommended in current guidelines (1). Laboratory tests should include measurements of inflammatory markers in the blood (white blood cell (WBC) differential and count, platelet count, CRP) and stool (calprotectin or lactoferrin concentration). The primary differential diagnosis is Crohn's disease, followed by rarer types of colitis, such as nonsteroidal anti-inflammatory drug (NSAID)-induced colitis and ischemic, lymphogenous, collagenous, or eosinophilic colitis. In rare cases of treatment-resistant proctitis, sexually transmitted diseases, radiation proctitis, or malignant colon infiltration should be excluded. Proctologic diseases should be excluded in the presence of exclusively proctitis symptoms or isolated bloody stools (1).

History and Physical Examination

The most prominent manifestation is bloody diarrhea (>90%), often associated with cramping pain (tenesmus, >70%) in the left lower quadrant or along the entire colon in patients with pancolitis. Urgent stool (>70%) is also common. Depending on the severity and extent of the disease, physical examination may be unremarkable. In patients with severe colitis, abdominal tenderness, along with fever and peritoneal signs, is a warning sign indicating a poor prognosis, with the potential for fulminant colitis, including toxic megacolon.

Laboratory Tests

In acute steroid-dependent or steroid-refractory ulcerative colitis, Clostridioides difficile superinfection or cytomegalovirus reactivation should be considered in the differential diagnosis and excluded with appropriate testing. Classic inflammatory parameters (leukocytes and CRP) are usually not elevated, except in cases where the inflammatory activity of ulcerative colitis is very intense. Therefore, elevated inflammatory parameters indicate a severe course of the disease. In mild colitis or isolated proctitis, stool inflammatory parameters, such as calprotectin, are much more sensitive. Therefore, they are suitable for the subsequent evaluation of all disease variants. A fecal calprotectin value below 150–200 µg per gram of stool is considered a reliable marker of remission (1). Iron deficiency anemia is the most common extraintestinal manifestation of chronic inflammatory bowel disease; Therefore, screening for iron deficiency (complete blood count, ferritin, transferrin saturation) should be performed approximately once a year, even in patients in clinical remission (1, 4). Because concomitant primary sclerosing cholangitis (PSC), if present, can have serious

implications for the treatment and prognosis of ulcerative colitis, bilirubin concentrations and cholestasis parameters should also be checked approximately once a year (5).

Endoscopy

Ulcerative colitis is visualized endoscopically as an inflammatory process continuously extending from the rectum in an oral direction. Depending on the nature of the lesion, it can be classified as follows: proctitis, i.e., inflammation limited to the rectum,left-sided colitis, and colitis extending beyond the splenic flexure. The spectrum of endoscopic findings ranges from low-grade ulceration with a rough, granular mucosa, sparse vascular pattern, and no more than mild erythema to severe ulceration with ulcers (sometimes confluent) and spontaneous, predominantly petechial hemorrhages (6). The degree of inflammatory activity can be classified based on its endoscopic appearance, for example, using the Mayo score or the Ulcerative Colitis Severity Index (UCEIS) (1, 6). The transition from normal to inflamed mucosa is usually sharp, and the inflammation typically intensifies distally. The rectum may be spared in patients with sclerosing cholangitis and ulcerative colitis, as well as in children and adolescents with ulcerative colitis. Less severe inflammation may also be observed distally as a result of local treatment with suppositories, enemas, or foam. In left-sided colitis, an isolated focus of inflammatory activity in the cecum, known as a cecal flap, may be observed.

When initiating any treatment or switching to another therapy, especially when initiating treatment with any biologic agent, the response to treatment should be monitored endoscopically after three to six months (5). The goal of treatment is endoscopically confirmed mucosal healing, even if this may not be achieved in all patients. In the absence of endoscopy, the response to treatment should be assessed using objective indirect measures, such as a decrease or normalization of fecal calprotectin or normalization of bowel wall thickness measured by ultrasound (5, 7). Patients with disease extension beyond the rectum should undergo regular endoscopy, starting six to eight years after diagnosis, at intervals depending on risk stratification (insert). Colon carcinoma may arise as a complication of long-standing ulcerative colitis: according to recent studies, approximately 7% of patients with ulcerative colitis develop colon cancer within 30 years of disease onset (8). The risk of colon cancer has decreased in recent years due to close surveillance programs and better inflammatory control (e4). Surveillance colonoscopy should be performed either as chromoendoscopy or as high-resolution white-light endoscopy with targeted biopsy in both cases (1). If possible, it should be performed during remission or a phase of lower inflammatory activity, since more severe inflammation may also reflect the inflammatory process accompanying low-grade intraepithelial neoplasia (5). Patients with concurrent primary sclerosing cholangitis have a significantly higher risk of hepatobiliary carcinoma, and their risk of early colon cancer increases fivefold. Therefore, they should undergo intensive surveillance, with annual colonoscopy, beginning at the time of diagnosis of primary sclerosing cholangitis (1).

Treatment

Conventional Treatment for Uncomplicated Ulcerative Colitis Surveillance Colonoscopy.

Surveillance colonoscopy should be performed regularly, beginning six to eight years after the diagnosis of ulcerative colitis, at intervals depending on risk stratification.

Standard Treatment for Mild to Moderate Uncomplicated Colitis.

Mesalamine is the standard treatment for mild to moderate uncomplicated colitis.

The choice of treatment for ulcerative colitis is generally based on the nature of the lesion and its degree of clinical activity. Mesalamine, also known as 5-aminosalicylic acid (5-ASA), is the mainstay of pharmacotherapy for ulcerative colitis. It can be administered orally or rectally as suppositories, foam, or enemas. Meta-analyses of randomized controlled trials have demonstrated its superiority over placebo and rectal steroids in the treatment of ulcerative colitis not only for remission induction but also as maintenance therapy (9, 10). Rectal administration of mesalamine provides up to 100-fold higher concentrations of the active substance at the site of inflammation, so its use is preferable to oral administration for remission induction. For all types of lesions, combined rectal and oral administration is more effective than monooral administration, both for remission induction and for maintenance therapy. In the treatment of proctitis, topical mesalamine is more effective than topical steroids and is therefore the drug of choice (e6). If mesalamine alone does not result in proctitis remission, it should be combined with topical or systemic steroids. First-line therapy for mild to moderate left-sided ulcerative colitis should include combined oral and rectal mesalamine (11). Left-sided ulcerative colitis with mild to moderate inflammatory activity that is refractory to mesalazine can be treated with oral budesonide-MMX. Patients with mild to moderate ulcerative colitis and extensive disease should be initially treated with oral mesalamine-releasing agents at a dose of at least 3 g/day in combination with mesalazine enemas or foam (12).

Systemic glucocorticoids.

Systemic glucocorticoids are used if remission cannot be achieved by other means, as well as for the initial treatment of patients with acute severe ulcerative colitis.

Remission maintenance therapy.

Remission maintenance therapy should be continued for at least two years. E. coli Nissle treatment is an alternative for patients intolerant to mesalazine. Systemic glucocorticoids are used if remission cannot be induced by the above-mentioned methods; they are also used for the initial treatment of patients with acute severe ulcerative colitis. In the latter case, glucocorticoids are more effective when administered intravenously than orally. Due to their well-known numerousmside effects, steroids should only be prescribed for a short period (maximum several weeks) and not as maintenance therapy.

Mesalamine is the standard maintenance therapy option for remission maintenance in uncomplicated ulcerative colitis (1, 3). In addition to the remission maintenance effect, it also has a preventive effect against carcinoma with an odds ratio (OR) of 0.51 (95% CI [0.37; 0.69]). For remission maintenance, mesalamine can be administered topically for distal colitis or orally for extensive colitis (9). Treatment for remission maintenance should be continued for at least two years (1). Treatment with E. coli Nissle is an alternative for patients intolerant to mesalazine. Non- inferiority of E. coli Nissle to mesalazine was demonstrated in a meta-analysis of three controlled trials (13). However, because there is significantly more data on mesalazine than on E. coli Nissle, mesalazine should be preferred. More than half of patients experience relapse after discontinuing mesalazine (14, 15).mIn most patients with ulcerative colitis, remission can be achieved with standard therapy with mesalazine and/or glucocorticoids, and then maintained with mesalazine maintenance therapy.

Immunomodulators

Recommendations

Thiopurines are recommended for remission maintenance in children with corticosteroid dependence or frequent relapses (≥2 relapses/year) despite optimal 5-ASA therapy, as well as in patients intolerant of 5-ASA [LE3, LE1 for adults]; thiopurines should be considered after discharge from the acute severe colitis unit [LE4, LE3 for adults]. (98% agreement) Thiopurines should not be used for remission induction in children with ulcerative colitis [LE5, LE2 for adults]. (100% agreement) Measurement of thiopurine metabolites is recommended in patients with an incomplete response to a stable thiopurine dose, in patients with leukopenia or elevated transaminases, and if noncompliance is suspected [LE2, LE2 for adults]. (95% agreement)

Practical recommendations

Thiopurines may be somewhat more effective than 5-ASA in maintaining remission in ulcerative colitis, but given their safety profile, they should generally be reserved as second-line therapy after 5-ASA failure. (93%

agreement) Determination of the TPMT genotype or phenotype (i.e., TPMT activity) is recommended to identify patients at increased risk of profound myelosuppression. The dose should be reduced in heterozygous patients or patients with low TPMT activity. Thiopurines should not be used in children with homozygous TPMT mutations or with very low TPMT activity, as determined by any laboratory. (93% agreement) Routine monitoring of blood counts and liver enzymes is recommended in all cases: every 1-2 weeks for the first month, then monthly up to 3 months, and then every 3 months. (100% agreement) Families should be advised to use sunscreen when taking thiopurines and other immunosuppressants. (100% agreement) Given the excellent safety profile of 5-ASA, it is reasonable to continue the use of thiopurines with 5-ASA, at least initially, despite the lack of evidence. 5-ASA inhibits the TPMT enzyme, thereby increasing the levels of the active metabolite 6-thioguanine (6-TGN). (88% agreement) The maximum therapeutic effect of thiopurines may not be seen until 10–12 weeks of treatment. (98% agreement) The dose of thiopurines should be approximately 2–2.5 mg/kg azathioprine and 1–1.5 mg/kg mercaptopurine once daily in patients with normal TPMT. Measurement of thiopurine metabolites can assist in further dose adjustments and reduce the incidence of adverse events, with 6-TGN levels of 235 to 450 pmol/8 x 108 red blood cells and 6-methylmercaptopurine ribonucleotides (6- MMP) < 6700 pmol/8 x 108 red blood cells considered optimal (note that cutoff values may vary depending on the method (128). (95% agreement) Patients with gastrointestinal intolerance or a flu-like reaction to one thiopurine compound may tolerate lower doses or a switch to another thiopurine (from azathioprine to 6-mercaptopurine and vice versa). Limited data suggest that dividing the daily dose into 2 doses may reduce gastrointestinal and hepatotoxicity in patients with hyperactivity. TPMT. (95% agreement) Thiopurines should be discontinued in the presence of clinically significant myelosuppression or pancreatitis. Resumption of thiopurines after leukopenia (but usually not pancreatitis) may be considered at a lower dose after careful risk-benefit assessment and after measuring thiopurine metabolite levels and/or TPMT. (95% agreement) Therapy modification should be considered in patients with active disease despite adequate 6- TGN levels after at least 12 weeks of thiopurine treatment. (98% agreement) Concomitant use of allopurinol (50 mg once daily in patients weighing <30 kg) and 100 mg once daily in patients weighing ≥30 kg (maximum 5 mg/kg) with a reduced dose of azathioprine (to approximately 25–30% of the starting dose) may be effective. A therapeutic option in cases of hyperreactive TPMT leading to elevated 6-MMP levels (often associated with elevated transaminases) and decreased 6-TGN levels, in units with appropriate expertise. Children should be closely monitored due to the increased risk of toxicity. (95% agreement)

The benefit of discontinuing thiopurine should be carefully weighed against the increased risk of relapse. Discontinuation of thiopurine may be considered in patients in sustained clinical remission after long-term treatment (at least 1 year) after achieving complete mucosal healing and, preferably, histological remission. In the case of thiopurine discontinuation, treatment with 5- ASA may help maintain remission (especially in patients not previously treated with 5-ASA). (91% agreementMethotrexate may be considered in rare cases in patients with ulcerative colitis who do not respond to or cannot tolerate thiopurine therapy when other alternatives are not possible. Oral tacrolimus (FK-506) may be considered in selected ambulatory children with ulcerative colitis as an alternative to steroids for bridging to thiopurines or vedolizumab (given its longer time to onset of action). Initially, high target serum levels (10–15 ng/mL) should be achieved, with gradual titration to lower levels (5–10 and ultimately 2–5 ng/mL) to avoid serious adverse effects. Selected patients may benefit from long-term, low-dose treatment (i.e., target drug levels of 2 ng/mL), but potential toxicity should be carefully considered, as should the limited supporting evidence. (93% agreement) The efficacy of thiopurines (azathioprine and 6-mercaptopurine) has been systematically evaluated for both induction and maintenance of remission in adult patients with ulcerative colitis. A meta-analysis of adult data showed that azathioprine is no more effective than placebo for inducing remission but is superior to placebo in preventing relapses. In a recent prospective cohort study, sustained clinical response was achieved in 60% of 255 adult patients with ulcerative colitis treated with azathioprine after 5-ASA failure, with a median follow-up of 30 months. Prospective pediatric studies have reported steroid-free remission rates of 49% at 1 year and 72% at 2 years in children treated with thiopurines, with no differences in clinical or endoscopic endpoints between early or late treatment initiation. Several retrospective studies in children have confirmed the effectiveness of thiopurines in maintaining remission and tapering steroid doses, with a median time to achieve thiopurine steady-state levels of 55 days (139). Cox proportional hazards modeling based on retrospective data from 1175 children and young adults with the disease found no benefit of early thiopurine use in reducing the risk of colectomy. Despite one negative study in small adult patients, combining 5-ASA with thiopurines appears reasonable given the former's excellent safety profile and its possible additive effects, including chemoprotective activity. 5-ASA may partially inhibit TMPT activity and therefore increase 6-TGN levels. Most studies in adults have used doses of 2.5 mg/kg for azathioprine and 1.5 mg/kg for 6- MP. However, no clear dose-response relationship was observed for azathioprine, suggesting that low-dose azathioprine (1.5 mg/kg) may be as effective as standard doses (144). Children under 6 years of age may require higher doses of azathioprine per unit body weight, up to 3 mg kg^{-} day^{-1}. The relative risk of serious adverse events with thiopurines in a Cochrane meta-analysis of adult data was 2.82 (130). The discontinuation rate of thiopurines due to adverse events in large pediatric cohorts was 18% (147) and 30% (148). Dose-independent adverse reactions included fever, pancreatitis, rash, arthralgia, nausea, vomiting, and diarrhea, while dose-dependent toxicities included leukopenia (up to 5%), thrombocytopenia, infections, and hepatitis. A meta- analysis of 6-MP studies found it to be well tolerated by 68% of 455 adult patients intolerant to azathioprine, supporting the rationale for switching between these agents in cases of specific dose-independent adverse events. Switching between drugs in pancreatitis has traditionally not been recommended, but some recent case series have questioned this idea.

A meta-analysis (25,728 patient-years with IBD) showed that patients younger than 30 years have a high relative risk of developing non-Hodgkin's lymphoma (SIR = 6.99), with the highest risk in young men. However, the absolute risk is significantly higher in older patients. In patients younger than 30 years, the absolute risk is estimated to be only 1 in 4000–5000 . Hepatosplenic T-cell lymphoma (HT-SCLL) is a very rare but fatal complication of thiopurine therapy. Of more than 40 reported cases of IBD-associated HT-SCLL, almost all received thiopurines, with or without anti- TNF, and almost all were men; there are only extremely rare and isolated reports of children with HHT-SCLL receiving anti-TNF alone. TPMT analysis (phenotype or genotype) can be used before initiating thiopurine therapy to identify certain patients at risk for dose-dependent myelosuppression, in whom the drug should either not be used (if the patient is homozygous for variant alleles or has very low TPMT activity) or should be started at a lower dose (if the patient is heterozygous for variant alleles or has low TPMT activity). However, TPMT testing does not replace the need for mandatory complete blood count monitoring, particularly at the beginning of treatment. In a study in adults, a significantly lower proportion of dose-adjusted TPMT variant carriers developed hematologic adverse events (RR = 0.11). In a pediatric study, 7 of 46 (15%) carriers of at least 1 variant allele or low/intermediate TPMT activity developed myelosuppression, compared with 0/62 in the wild-type/high-activity group (156). In contrast, a study of 72 children found no association between TPMT gene polymorphisms and the occurrence of thiopurine- related adverse events. In cases of TPMT hyperactivity leading to elevated 6-MMP and decreased 6-TGN levels, concomitant administration of allopurinol with a reduced dose of azathioprine may be an effective treatment, but should be used with caution. Adequate dose reduction and regular monitoring of complete blood count and 6-TGN/6-MMP levels are necessary to prevent myelosuppression-related adverse events. In studies involving adults, allopurinol was administered at a dose of 100 mg once daily, while several case series in younger children used lower doses (50 or 75 mg once daily).

Therapeutic drug monitoring, specifically measuring thiopurine metabolite levels, particularly 6- TGN and 6-MMP, has been introduced as a means of optimizing efficacy and preventing myelosuppression. In a

meta-analysis including 1026 children with IBD, higher 6-TGN concentrations were not consistently associated with leukopenia, while they were marginally associated with a higher likelihood of clinical remission. High 6-MMP levels were correlated with hepatotoxicity, and low thiopurine metabolite levels were associated with noncompliance. In a retrospective study including 86 children with IBD, 6-TGN levels >250 pmol/8 × 108 red blood cells were associated with a higher response rate (OR = 4.14). An association between bone marrow toxicity and clinical response to treatment with 6-TGN levels has been demonstrated in prospective studies in adults and in several retrospective cohort studies in children.Dose adjustment after metabolite measurement has been reported to increase disease remission rates. Children with IBD have been shown to have fewer flares when thiopurine metabolites are measured. In a study of 78 children with IBD, 6-TGN levels above 405 pmol/8 × 108 RBCs were the only predictor of azathioprine resistance (OR 10.8), suggesting the need for alternative therapy in patients with active disease and adequate 6-TGN levels.

Discontinuation of thiopurines after achieving sustained remission is controversial. In a retrospective study of 127 patients with ulcerative colitis in remission, approximately one-third of patients relapsed within 12 months of drug discontinuation, and two-thirds relapsed within 5 years. In 108 patients with ulcerative colitis who discontinued treatment after long-term thiopurine therapy, the moderate/severe relapse rate was 26% within 2 years. A Cochrane meta-analysis of the use of methotrexate (MTX) for induction (2 RCTs, 101 patients) or maintenance (3 RCTs, 165 patients) (174) of remission in ulcerative colitis in adults concluded that there is no evidence to support the use of MTX for induction or maintenance of remission in ulcerative colitis. However, this conclusion is based on low-quality evidence. In the double-blind, placebo-controlled METEOR trial in 111 adult patients with ulcerative colitis receiving steroids, steroid-free remission at week 16 was not statistically different from that with placebo (32% vs. 20%, respectively; P > 0.05), although clinical remission was different (42% vs. 24%, respectively; P = 0.04) (175). In a retrospective study of 32 children with ulcerative colitis unresponsive to or intolerant of thiopurines, response/remission was achieved in 72%, 63%, and 50% of patients receiving parenteral methotrexate at 3, 6, and 12 months, respectively.

Tacrolimus has been studied in outpatients with ulcerative colitis. A randomized controlled trial comparing high target tacrolimus levels (10–15 ng/mL) with low levels (5–10 ng/mL) and placebo in adult patients with moderate-to-severe ulcerative colitis hospitalized for study participation reported a significantly higher response rate in the high-level group (68% versus 38% versus 10%, respectively). A retrospective cohort study of 25 ambulatory adult patients with moderate- to-severe ulcerative colitis reported a 52% clinical improvement and 44% clinical remission at 6 months. Three small retrospective pediatric studies including 18 patients with steroid-refractory/ dependent ulcerative colitis 10 and 8 steroid-resistant patients receiving tacrolimus reported response rates ranging from 50% to 95%; however, most patients ultimately underwent colectomy during follow-up. In subgroup analyses, patients receiving steroids had a significantly higher rate of freedom from long-term colectomy compared with steroid-refractory patients (78% vs. 0%).

Surgery

Colectomy is the most common surgical treatment for ulcerative colitis. According to various studies, the colectomy rate ranges from 8% to 24% over a ten-year period; this procedure is typically performed on patients with pancolitis . The main indications for colectomy are ulcerative colitis refractory to medical therapy and colitis-associated neoplasms. The decision to perform surgery should be made by gastroenterologists and visceral surgeons in close interdisciplinary collaboration. Before surgery, the patient should be informed of the risk of developing pouchitis, which is acute or chronic inflammation of the small intestinal reservoir used as a substitute for the rectum, as well as the increased risk of infertility (16) and sexual dysfunction in both men and women (17). The reported cumulative prevalence of pouchitis at 1, 5, and 10 years is 15.5%, 36%, and 45.5%, respectively (18). Adenocarcinoma is an absolute indication for colectomy, as is epithelial dysplasia in a lesion that cannot be resected endoscopically (1). A recent meta-analysis concluded that even with low-grade epithelial dysplasia, the risk of developing carcinoma is 14 per 1000 patient-years, corresponding to a ninefold increased risk. Thus, proctocolectomy should also be considered in this situation, and surveillance colonoscopies should be scheduled frequently as a non-surgical alternative. Colonic stenosis in a patient with ulcerative colitis is also a relative indication for surgery, since there is no safe diagnostic method to exclude malignancy; High-grade carcinoma or dysplasia is already present in approximately 7% of such stenoses (19). Limited (partial) colectomy should be performed only in rare, special cases, which should be carefully discussed in advance by an experienced team of visceral physicians and surgeons. In patients with increased surgical risk or who have been receiving immunosuppressant or biologic therapy up until the time of surgery, proctocolectomy should be performed in a staged manner, in three sequentially planned surgeries (20).

Nutrition, Growth, and Bone Health

Practice Guidelines

High intakes of red or processed meat, protein, alcoholic beverages, sulfur, and sulfates are associated with disease flares. However, due to the lack of compelling evidence, elimination diets should not be used to induce or maintain remission in children with ulcerative colitis, as they may lead to nutritional deficiencies. (100% agreement) DXA (adjusted for height for age to obtain age- and sex-matched z-scores (21)) should be considered in high-risk patients, such as those with severe disease, long-term malnutrition, amenorrhea, delayed puberty, and/or steroid dependence. (98% agreement) To maintain bone health, stimulation of mucosal healing, adequate nutrition, weight-bearing exercise, smoking cessation, and steroid-sparing strategies should be used. Rare use of bisphosphonates should be limited to patients with pathological fractures and should be discussed with a pediatric osteopathic specialist. (100% agreement) Growth impairment is rare in children with steroid-independent UC. Therefore, in the presence of significant growth impairment, Crohn's colitis or primary growth hormone deficiency should be considered. (100% agreement) Vitamin D should be supplemented if 25-OH vitamin D levels are <50 nmol/L, regardless of steroid use. (93% agreement) Various strategies exist for treating vitamin D deficiency in addition to daily treatment (>2000 IU/ day). A commonly used strategy is to administer a "loading dose" (50,000 IU vitamin D3 orally once a week for 2-3 months or 3 times a week for 1 month). A single high-dose oral vitamin D3 supplement of 300,000 to 500,000 IU (i.e., the Stoss dosing method) has been reported (22) to be effective and safe (98% agreement). Although nutritional deficiencies can develop rapidly during periods of active ulcerative colitis (23), normal growth is maintained in more than 95% of children with ulcerative colitis who are not steroid-dependent (23–25). A more detailed review of all nutritional issues in children with IBD can found in the recently published guidelines of the ESPGHAN IBD Study Group in Porto (26). Patients with active ulcerative colitis often reduce fiber intake without supporting evidence. Corn and corn products, nuts, milk, and bran were avoided by more than 20% of patients with ulcerative colitis (27). However, soluble fiber is the best way to obtain short-chain fatty acids, such as butyrate, which has anti-inflammatory effects (418). Furthermore, many patients with ulcerative colitis have been advised to avoid tomatoes, dairy products, chocolate, wheat, tomato sauce, and fruit juices (27). However, there are no clearly established dietary interventions for ulcerative colitis, and the reader is referred to an excellent recent review on this topic (28).

Peak bone mass, achieved in adolescence, is a major determinant of skeletal health throughout life. Some osteopenia occurs in 22% of children with ulcerative colitis (29), but severe osteopenia occurs in only 3–6% of patients with ulcerative colitis, compared with 12–18% in Crohn's disease (30–32). Nutritional status appears to have a greater impact on bone health than corticosteroid therapy (30). Children with IBD are at particular risk of vitamin D deficiency, but no direct association with osteopenia has been found (424). Nevertheless, vitamin D deficiency should be treated, especially in children with reduced bone mineral density. A recent meta-analysis showed that low vitamin D levels are associated with more active disease (425). Age-appropriate nutrition,

weight-bearing exercise, and adequate disease control using steroid-sparing strategies have been proposed as means to improve bone formation (21, 28, 33), but supporting data are lacking. Indeed, a prospective study that followed 58 children with celiac disease for 2 years found no significant improvement in bone mineral density, despite an increase in growth z-score and a decrease in disease activity (28).

The most important factor in the treatment of osteopenia, in addition to steroid avoidance, is effective treatment aimed at mucosal healing, as osteopenia can typically be a consequence of proinflammatory cytokines (34). Indeed, interventions that promote mucosal healing, such as anti-TNF therapy and exclusive enteral nutrition, have shown rapid improvement in serum bone markers in children with celiac disease (35–39). Bisphosphonates are effective in improving bone mineral density in IBD, but their use in pediatrics should be limited to exceptional circumstances, typically in the presence of pathological fractures, which is rare in UC.

Psychosocial Support, Adherence to Treatment, and Transitional Care

Recommendations

Adolescents should be included in transitional care programs for adults, which can be adapted to the local organization of pediatric and adult care settings [EL4]. (100% agreement)

Practice Recommendations

Pediatric IBD treatment centers should provide psychosocial support in accordance with local resources. (100% agreement)

Adherence to treatment should be regularly assessed through patient interviews, monitoring medication levels (e.g., serum concentrations), and refill rates. (100% agreement) Adherence to treatment can be improved by providing complete information about prescribed medications, minimizing the number of pills taken, using once-daily dosing whenever possible, using electronic reminders, and providing pillboxes. (100% agreement) Several systematic reviews have concluded that adolescents with IBD, particularly boys, experience reduced health-related quality of life, including anxiety, depression, social problems, and low self-esteem (39–42). Changes in quality of life in children with IBD can impact the entire family, which often lacks adequate strategies to cope with this challenging situation (43).

Depression rates can reach up to 25% and are often underestimated by both parents and healthcare providers. Anxiety and depression appear to be risk factors for early disease relapse and adversely affect its course, but can also often be a reactive response to active disease. Cognitive behavioral therapy has been shown to be particularly effective in reducing depressive symptoms and improving functioning in children with IBD (44). Lack of adherence to treatment in IBD is observed in 50–66% of children (39, 46), especially during adolescence. Barriers specific to children include fear of medication side effects, a sense of disease inactivity, a belief that medication is not working, taking more than one pill per day, forgetfulness, interference with other activities, difficulty swallowing pills (47), lack of motivation, and parent-child conflict (48).

Transition is defined as the planned transition of adolescents and young adults with chronic somatic diseases from a child-centered to an adult-centered health care system. The optimal timing of the transition from pediatric to adult UC management should be determined individually by a joint team of pediatric and adult gastroenterologists (49). Several proposals for transition programs have been published, but none have been formally evaluated (50). The transition period typically begins between 14 and 18 years of age, depending on the patient's development and the availability of qualified pediatric and adult gastroenterologists. The timing of the transition should be individually tailored to the patient's psychosocial readiness. If possible, it is recommended to arrange at least one joint consultation between a pediatric and adult gastroenterologist during the transition period. Adolescents should be encouraged to take increasing responsibility for their care and to attend the clinic at least once unaccompanied by their parents. The ECCO topical review on transition to adult care details all aspects related to the steps to be followed during the transition period (51).

Treatment Features in Children and Adolescents

Surgical Treatment.

Colectomy is the most common surgical treatment for ulcerative colitis. Colectomy rates, reported in various studies, range from 8% to 24% per decade; the surgery is typically performed in patients with pancolitis.

Multidisciplinary Pediatric Teams.

In children and adolescents, ulcerative colitis often has a rapidly progressive, complicated course and should be managed by a multidisciplinary pediatric team specializing in chronic inflammatory bowel disease.

In Germany, between 2,000 and 2,600 children and adolescents develop chronic inflammatory bowel disease for the first time each year, and more than a third of these patients have ulcerative colitis. Children of any age can be affected. The younger the child at diagnosis, the higher the likelihood that the inflammatory process is limited to the colon. Often, the disease cannot be clearly classified as Crohn's disease or ulcerative colitis even after a complete diagnostic workup, and is then classified as unclassified chronic inflammatory bowel disease. Other diseases subject to differential diagnosis, such as allergic enterocolitis or monogenetic immunodeficiency, must be excluded. The initial diagnostic workup always includes ileocolonoscopy and upper endoscopy; in doubtful cases, small bowel imaging is also performed. In infants and young children with chronic inflammatory bowel disease, the initial workup should be supplemented by immunological testing and, if a monogenic disease is suspected based on family history or clinical presentation, also by genetic testing, possibly including whole exome sequencing (WES). Ulcerative colitis that begins in childhood or adolescence is characterized by a protracted course, high disease activity, and progression. Two-thirds of affected children have extensive colitis at diagnosis, compared to only 20–30% of adults. Another characteristic of ulcerative colitis in children, in addition to the aforementioned mild rectal involvement, is concomitant upper gastrointestinal involvement with active, sometimes erosive or granulomatous gastritis. In routine clinical practice, disease activity should be characterized using the PUCAI index. A higher percentage of children than adults require hospitalization for treatment of acute, severe colitis. The rate of colectomy 10 years after diagnosis is higher in patients with childhood onset than in those with adult onset. The aggressive course of ulcerative colitis in children and adolescents' contrasts with the relative limitations of therapeutic options and variable side effect profiles in this age group. Biologic agents were approved for the treatment of chronic inflammatory bowel disease in children with an average delay of seven years after their approval in adults. To date, only infliximab is approved for the treatment of patients under 18 years of age with ulcerative colitis. Other biologic agents can be used off-label, but only after obtaining a preliminary guarantee of reimbursement from the patient's insurance company. Due to differences in pharmacokinetics in childhood, these patients typically require higher drug doses (per kilogram of body weight) and shorter follow-up intervals.

Mortality in individuals with ulcerative colitis that begins in childhood or adolescence is four times higher than mortality in the reference population. The earlier the disease is diagnosed, the higher the risk of malignancies. Causes of death include complications of the disease itself (postoperative complications, embolism, infections, colon cancer occurring 10 years after diagnosis) and certain medications used to treat it (e.g., cancer or hemolytic lymphoblastic leukemia with thiopurines, infections with anti-TNF and corticosteroids). The risk of developing a tumor is already increased in childhood. When making treatment decisions, it should be considered that children continue to grow and gain bone mass during the first two decades of life. Ulcerative colitis negatively impacts muscle mass in these patients, as well as bone growth, geometry, and quality, through both direct mechanisms (inflammation, loss of protein and micronutrients in the intestine) and indirect ones (reduced anabolic effect of sex hormones due to delayed puberty, malnutrition due to loss of appetite or abdominal pain, and decreased physical activity due to active inflammation). Systemic corticosteroids, which must be prescribed repeatedly to patients with ulcerative colitis,

have an adverse effect, especially when prescribed during the pubertal growth spurt Chronic inflammatory bowel disease in young patients threatens not only their physical health but also their psychosocial and professional development. In a German study using questionnaires and diagnostic interviews with patients and their parents, half of the children and adolescents with ulcerative colitis met DSM-IV criteria for one or more mental illnesses—most commonly adjustment disorder, depression, and anxiety disorders. Their quality of life (assessed using the HRQoL IMPACT III and QoL EQ-5D scales) was significantly reduced, and this correlated with disease activity. Only a small proportion of patients were receiving or were receiving treatment from a psychotherapist or child and adolescent psychiatrist. Psychosocial sequelae and comorbidities have a significant negative impact on medication adherence in adolescent patients and on their transition to treatment in adulthood. In summary, ulcerative colitis in children and adolescents is particularly challenging due to the severity of the disease and its adverse impact on physical and psychosocial development. Therefore, such patients should be treated in a center for chronic inflammatory bowel diseases in conjunction with a pediatric clinic. They must be accompanied by an interdisciplinary team of specialists (pediatric gastroenterologist, endocrinologist, nutritionist, psychologist, social worker, etc.), and it is also necessary to ensure their transfer to adult practice.

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DOI:10.31579/2690-1897/279