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A review on Ulcerative Colitis: Epidemiology, Risk Factors, Pathophysiology, Diagnosis, Clinical Management and Treatment Modalities

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ABSTRACT

Ulcerative colitis is a chronic inflammatory disease, which affects in colon. This disease is becoming more common across the world. Genetic susceptibility, epithelial barrier abnormalities, dysregulated immunological responses, and environmental variables all play important role in the pathogenesis of this disease. Patients with ulcerative colitis have mucosal inflammation that starts in the rectum and spreads to the colon's proximal regions. Colonoscopy and histological results are used to diagnose ulcerative colitis, which commonly manifests with bloody diarrhoea. The goal of treatment is to achieve and then maintain remission, which is defined as symptom relief and endoscopic healing. 5-aminosalicylic acid drugs, steroids, and immunosuppressants are all used to treat ulcerative colitis. Colectomy may be required in certain patients with medically resistant illness or colonic neoplasia. The treatment arsenal for ulcerative colitis is growing, and the number of medications with novel targets will increase in the next upcoming years.

INTRODUCTION

Ulcerative colitis is a chronic, idiopathic inflammatory disease of the colon that most typically affects individuals between the ages of 30 and 40 years and causes impairment [1, 2]. It is characterized by recurrent and remitting mucosal inflammation that starts in the rectum and spreads to the colon's proximal regions. The goal of treatment is to achieve and keep clinical and endoscopic remission [3]. In mild to moderate ulcerative colitis, aminosalicylates are the preferred therapy, whereas flares can be treated with local and systemic steroids. In moderate to severe ulcerative colitis, immunosuppressants and biological medicines are employed. Colectomy is required in up to 15% of ulcerative colitis patients [4]. Ulcerative colitis is predicted to cost €12.5–29.1 billion in Europe and US$8.1–14.9 billion in the United States per year in direct and indirect expenditures [5].

Epidemiology

In ulcerative colitis, there is no sex preponderance [6-8]. This disease is mostly seen between the age group of 30 - 40 years [7, 9]. Ulcerative colitis has been rising in frequency and prevalence across the world [10]. Northern Europe (24.3 per 100 000), Canada (19.2 per 100 000), and Australia have the highest rates of ulcerative colitis (17.4 per 100 000) [6, 10, 11]. Europe (505 per 100 000), Canada (248 per 100 000), and the United States have the greatest prevalence rates (214 per 100 000) [7, 10, 12, 13]. In Europe there appears to be regional disparities in ulcerative colitis occurrence, but western and northern nations having greater rates than eastern countries [14]. Children who are migrants from low-incidence to high-incidence nations had the same chance of getting ulcerative colitis as non-immigrants [15–17]. Although there is a scarcity of data from developing nations, ulcerative colitis is increasing in Asia, the Middle East, and South America [18–21].

Risk factors

8–14% of ulcerative colitis patients have a family history of inflammatory bowel disease, and first-degree relatives are four times more likely to acquire the condition [22, 23]. Ulcerative colitis is more common among Jewish people than in other ethnic groups [24, 25]. To present, 200 risk loci for inflammatory bowel disease have been found by genome-wide association studies, with the majority of genes contributing to both ulcerative colitis and Crohn's disease phenotypes [26, 27]. Human leukocyte antigen and genes related with barrier function, such as HNF4A and CDH1, are examples of loci linked to increased ulcerative colitis susceptibility [27 28]. On the other hand, genetics barely explains 7.5 percent of illness variation, has low phenotypic predictive potential, and is now of poor therapeutic utility [27, 28]. The increasing prevalence of ulcerative colitis across the world implies that environmental factors play a role in its development. Former cigarette smoking is one of the strongest risk factors for ulcerative colitis (odds ratio [OR] 1.79, 95 percent confidence interval [CI] 1.37–2.34), while active smokers are less likely to develop ulcerative colitis (OR 0.58, 95 percent confidence interval 0.45–0.75) and have a milder disease course [24, 29–32]. Appendectomy appears to protect against the development of ulcerative colitis, especially in young individuals with acute appendicitis [33]. Patients with ulcerative colitis who are newly diagnosed are more likely than matched controls to have a history of gastroenteritis [34, 35]. Oral contraceptives, hormone replacement treatment, and non-steroidal anti-inflammatory drugs (NSAIDS) have all been linked to a higher incidence of ulcerative colitis, while antibiotic exposure has not [36–42]. Breast feeding tends to lower the incidence of ulcerative colitis, but urban life appears to raise it [43, 44]. Certain ulcerative colitis risk factors that are prominent in industrialized nations may not have the same impact on people in developing Asia or the Middle East. When comparing affluent countries to underdeveloped Asian or Middle Eastern countries, for example, smoking may not have as significant an effect, appendectomy does not appear to reduce risk, and antibiotics have been proven to be protective [40, 41]. A meta-analysis of 11 European prospective studies found no link between stress and new-onset ulcerative colitis [45].

Pathophysiology

Although the pathophysiology of ulcerative colitis is frequently compared to that of Crohn's disease in the literature, there are significant distinctions. Colonic epithelial cells (colonocytes), as well as mucous barrier and epithelial barrier abnormalities, are all implicated in ulcerative colitis etiology. In the colonocytes of individuals with ulcerative colitis, the expression of peroxisome proliferator activated receptor gamma (PPAR-γ), a negative regulator of NF-κB-dependent inflammation, is decreased, implying a causal relationship [46, 47]. The cardiac and metabolic toxicity of existing PPAR-γ agonists limits their use. Novel 5-aminosalicylic acid (5-ASA) analogues with higher PPAR-γ agonistic activity are being developed [48]. In ulcerative colitis, autoantibodies against colonocyte-associated tropomyosins have been identified, however sufficient evidence categorising ulcerative colitis as an autoantibody-mediated illness is lacking. In ulcerative colitis, XBP1 abnormalities in colonocytes, a crucial component of the endoplasmic reticulum stress response system, have been described [50]. In individuals with ulcerative colitis, changes in trefoil factors, a family of goblet cell-derived proteins that are generated in response to mucosal damage and contribute to the integrity of the mucosal barrier, have been observed [51, 52]. The fact that individuals with active ulcerative colitis have reduced colonic goblet cells and a permeable mucus barrier supports the theory that barrier function abnormalities are the major drivers of illness [53]. Dysbiosis is observed in ulcerative colitis patients, however to a lower extent than in Crohn's disease patients [54].

In individuals with ulterative colitis, there was a decrease in biodiversity, with a reduced proportion of Firmicutes and a rise in Gamma-proteobacteria and Enterobacteriaceae [55]. Patients with the condition also have more sulphite-reducing Deltaproteobacteria in their intestines [56]. It is unclear if dysbiosis is the cause or the result of mucosal inflammation. In active ulcerative colitis, the expression levels of Toll-like receptors 2 (TLR2) and TLR4 are raised in colonocytes and the lamina propria, albeit it is unclear whether this is a cause or a result of mucosal inflammation [57]. TLR4 polymorphisms have also been found in individuals with ulcerative colitis and Crohn's disease, although their significance in disease etiology is unknown [58]. Patients with active ulcerative colitis have more activated neutrophils in their blood and colonic tissue than healthy people [59]. Dendritic cells from ulcerative colitis patients have higher levels of costimulatory molecules and are more likely to be the initial responders in the event of a barrier breach [60]. Innate lymphoid cells (ILCs) may have a role in inflammatory bowel disease etiology. ILC3 are important mediators of chronic inflammatory bowel disease [61]. ILCs isolated from individuals with active ulcerative colitis also had higher gene expression of major ILC3 cytokines (IL17A and IL22), transcription factors (RORC and AHR), and cytokine receptors (including IL23R) [62]. The hypothesis that ILCs are involved in disease etiology, that has led to the development of a variety of new therapeutic targets. Although higher IgM, IgA, and IgG concentrations have been found in inflammatory bowel disease, individuals with ulcerative colitis have a significant rise in IgG1 antibodies. It is unclear if B cells play a role in illness etiology or are simply reacting to barrier disturbance. Innate and adaptive cellular immunity are both implicated in disease development, according to a study.

According to previous research, ulcerative colitis is a modified T-helper-2 (Th2) illness, whereas Crohn's disease is a Th1 disease. Colonic lamina propria cells from ulcerative colitis patients were discovered to possess Th2-polarized T cells that generate interleukin-5 (IL-5) [63]. In addition, IL-4 and IL-13 mRNA levels in rectal samples from ulcerative colitis patients were considerably higher than those in the control group [64]. IL-13 has since been linked to the pathophysiology of ulcerative colitis, according to new research. IL-13, a critical modulator of epithelial cytotoxicity and barrier failure in ulcerative colitis, is generated by non-classical natural killer T cells (perhaps a member of the ILC family) [65, 66]. Extending the T-helper Th1/Th2 paradigm for Crohn's disease vs ulcerative colitis, results from 2014 demonstrate that the transcription factor PU.1 recognizes a unique pool of CD4-positive Th cells that release IL-9 and contributes to the development of ulcerative colitis [67]. Undifferentiated Th (Th0) cells meet MHC class II-antigen complexes in the presence of the cytokines transforming growth factor-β and IL-4, and evolve into Th9 cells. Th9 cells release IL-9, which suppresses cellular growth and repair while also impairing intestinal barrier function. Tumour necrosis factor-α (TNF-α) concentrations in tissue are also increased by IL-9, albeit in a small but substantial way. During activation, naive lymphocytes are imprinted with unique trafficking programmes. Dendritic cells are vital to this process because they integrate environmental inputs and induce the production of certain integrins and chemokine receptors. Dendritic cells in Peyer's patches or small bowel draining lymph nodes, for example, metabolise vitamin A to create retinoic acid, which causes T and B lymphocytes to express integrin α4β7 and CCR9. As a result, imprinted cells enter circulation and bind their respective ligands—MAdCAM-1(for α4β7) and CCL25 (for CCR9) when they re-enter the gut vasculature. While errors in mucosal homing have yet to be identified in ulcerative colitis patients, treatment techniques focusing on the α4β7 interaction with MAdCAM have become important tools in the therapy of ulcerative colitis [68].

Clinical presentation and differential diagnosis

Ulcerative colitis is a chronic illness that affects the mucosa of the colon and is characterized by blood in the stool and diarrhoea. Up to 15% of individuals may show with severe illness in acute stage [69]. Urgency, incontinence, exhaustion, increased frequency of bowel movements; mucus discharge, nocturnal defecation, and abdominal discomfort (cramps) are all possible symptoms. However abdominal pain is less common in Crohn's disease [70]. Severe illness might also cause fever and weight loss. The level of colonic involvement is used to classify ulcerative colitis [71]. Depending on the severity of the condition, the clinical presentation may differ. Patients with proctitis may experience urgency and tenesmus (a sense of incomplete evacuation), but patients with pancolitis may have bloody diarrhoea and stomach discomfort. Patients with proctitis or left-sided colitis may experience paradoxical constipation in up to 10% of cases. On rectal examination, symptoms of anaemia, abdominal pain, and blood may be discovered. Colonic dilatation may be indicated by abdominal distention and tympany on percussion, necessitating immediate radiographic evaluation. Anal fissures or skin tags may develop in patients with ulcerative colitis as a result of diarrhoea irritation; however the development of anal or perianal fistulas should arouse concern for Crohn's disease. *Clostridium difficile* is a common cause of flare-ups and is linked to a higher risk of surgery and death. It should be screened out at the time of diagnosis and flare-ups [72, 73]. Extra-intestinal signs can occur in roughly a third of ulcerative colitis patients, and up to a quarter of people may have extra-intestinal manifestations before being diagnosed with inflammatory bowel disease [75, 76]. The most prevalent extra-intestinal symptom appears to be peripheral arthritis; primary sclerosing cholangitis and pyoderma gangrenosum are more common in ulcerative colitis than in Crohn's disease [75, 76]. In patients with inflammatory bowel disease, the risk of venous thromboembolism is three to four times higher, and the risk is even higher if the patient is in with a flare or is on corticosteroids [77-80]. Clinicians should have a high index of suspicion for venous thromboembolism, and venous thromboembolism prophylaxis should be administered to hospitalised ulcerative colitis patients [81].

Diagnostic investigations

Ulcerative colitis is diagnosed using a combination of symptoms, endoscopic findings, histology, and the lack of other diseases [69, 82]. To exclude out enteric superimposed infections, all patients with ulcerative colitis should have stool tests (stool culture and *Clostridium difficile* assay). Anemia, iron deficiency, leucocytosis, and thrombocytosis are all possible diagnoses. Hypoalbuminaemia is a predictor of colectomy and poor response to biological therapies in patients with severe illness [83, 84]. Inflammatory markers like ESR and C-reactive protein might be high (severe ulcerative colitis) or normal (mild to moderate disease). Anti-neutrophil cytoplasmic antibodies can be raised in ulcerative colitis, however they are non-specific and have a poor sensitivity (0.55 %, 95 % CI 0.53-0.58), hence they aren't suggested as a diagnostic test [69, 71, 82, 85]. Intestinal inflammation can be detected more precisely with non-invasive stool indicators [86]. Because individuals with low faecal calprotectin have a less than 1% risk of developing inflammatory bowel disease. Faecal calprotectin, a protein detected in faeces that corresponds with higher neutrophils in the colon, can be helpful in ruling out inflammatory bowel disease [86–88]. But fecal calprotectin can not discriminate between different types of intestinal inflammation and it is utilised as a definitive diagnostic tool in ulcerative colitis [69].

The only approach to diagnose ulcerative colitis is to do an endoscopy with biopsies. Patients with suspected inflammatory bowel illness should have a colonoscopy with intubation of the terminal ileum. Erythema, lack of normal vascular pattern, granularity, erosions, friability, bleeding, and ulcerations are all common endoscopic findings in ulcerative colitis [82, 89]. The illness usually starts in the rectum and spreads proximally in a circular pattern. Rectal sparing or patchy illness can be caused by topical or systemic drugs, and they are not always indicative of Crohn's disease [90]. Although histological inflammation can be seen in normal looking mucosa, mucosal inflammation frequently displays an obvious boundary between inflamed and normal mucosa [82, 89]. In contrast to Crohn's disease, when the surrounding mucosa might seem uninflamed, ulcerative colitis ulcers are invariably accompanied with mucosal inflammation [69]. Up to 75% of people with ulcerative colitis who have distal disease also have a cecal patch, which is an isolated region of inflammation surrounding the appendiceal opening [91, 92]. Backwash ileitis, which affects up to 20% of pancolitis patients, is a minor inflammatory alteration in the terminal ileum [89, 93]. Severe ileitis or ileitis without pancolitis should raise suspicions of Crohn's disease. In individuals with upper-gastrointestinal symptoms, an esophagogastroduodenoscopy should be performed to rule out Crohn's disease [93]. Since inflammatory alterations may become visible on microscopy, at least two biopsies should be collected from six distinct locations (terminal ileum, ascending, transverse, descending, sigmoid colon, and rectum), including normal appearing areas [89]. Distortion of crypt architecture, crypt shortening, increased lymphocytes and plasma cells in the lamina propria (basal plasmacytosis), mucin depletion, and paneth cell metaplasia are all possible histological findings [82, 94]. In most cases, imaging investigations are ineffective in establishing a diagnosis. A simple upright abdomen film should be used to check for toxic megacolon (defined as mid-transverse colon dilatation > 5.5 cm) in individuals with acute severe ulcerative colitis [95].

Disease severity assessment

The severity and degree of ulcerative colitis must be determined before the best therapy may be chosen. Remission, mild, moderate, and severe disease are the most common classifications. The Mayo score, Lichtiger score, and Simple Clinical Colitis Activity Index are three of the most regularly used ulcerative colitis severity indexes [69, 96-98]. Endoscopy is critical for determining illness severity since endoscopic healing is linked to higher remission rates and a lower risk of colectomy [99]. The endoscopy subscore of the Mayo score and the Ulcerative Colitis Endoscopic Index of Severity are two commonly used endoscopic ulcerative colitis scores [96, 100]. Histological disease activity may also be characterised using histological scores like the Robarts Histopathology index or the Nancy index [101, 102]. Ulcerative colitis severity scores are based on disease activity at a particular timepoint and may not account for all of ulcerative colitis' effects. As a result, there is a push to redefine disease severity based on composite criteria that include -

(1) Disease effect on patient symptoms, quality of life, and disability;
(2) Measureable inflammatory burden using objective markers of disease activity and extent; and
(3) Disease course, which includes structural damage, number of flares, and extra-intestinal manifestations [103].

Natural History

In population-based research, 30 - 60 percent of patients with ulcerative colitis had proctitis at presentation, 16 - 45 percent have left-sided colitis, and 14 - 35 percent have severe pancolitis [4]. After 5 years, 10 – 19 % of individuals with ulcerative colitis proceed proximally, and up to 28 % of patients after 10 years [4]. Ulcerative colitis is a recurrent and remitting illness with periodic flares in the majority of patients [7]. Patients are more likely to require immunosuppressants, biological drugs, or surgery when ulcerative colitis flares are associated with proximal disease extension [104, 105]. Patients with illness beginning beyond the age of 60 years have milder disease than younger patients, suggesting that the age of commencement influences the disease course [106]. When compared to individuals with ulcerative colitis without primary sclerosing cholangitis, primary sclerosing cholangitis-associated ulcerative colitis is more likely to be widespread, milder, and linked with rectal sparing and so-called backwash ileitis [107]. In younger age at beginning (40 years), pancolitis, lack of endoscopic healing at the time of clinical remission, deep ulcerations, and high amounts of perinuclear anti-neutrophil cytoplasmic antibodies are all risk factors for severe or complex illness [104]. A small percentage of people (5 - 10%) who were first diagnosed with ulcerative colitis may subsequently be diagnosed with Crohn's disease [7]. The colon can be damaged structurally and functionally in patients with ulcerative colitis, resulting in benign strictures, colonic dysmotility, and anorectal dysfunction [2]. Colorectal cancer is more common in patients with the disease, but the risk has decreased over time and may be approaching that of the general population; however, the risk remains elevated in certain populations, such as those with long-term disease, primary sclerosing cholangitis, and uncontrolled inflammation [108, 109]. The risk of surgery in ulcerative colitis has declined in recent decades, but is still substantial with 11.6 percent probability of needing surgery after five years and 15.6 percent likelihood after ten years [110]. Age less than 40 years at diagnosis, significant illness, the necessity for systemic steroids, and high inflammatory markers have all been included to a prediction model for

colectomy [111]. Patients with ulcerative colitis do not appear to have a higher overall death rate than the general population, but they are more likely to be disabled and so unable to work [1, 112, 113].

Management

Primary goal of this disease is to induce and sustain remission, with the long-term goal of avoiding disability, colectomy, and colon cancer. Endoscopic healing, which is commonly defined as an endoscopic Mayo score of zero or one, and resolution of clinical symptoms, which is defined as cessation of rectal bleeding and improvement in bowel habits, are both targets for remission [3, 114]. The endoscopic activity of ulcerative colitis may not match with patient symptoms or physician evaluation [115 - 117]. Endoscopic healing has been found to considerably enhance long-term clinical remission, reduce the risk of colectomy, and minimise corticosteroid use, therefore it is crucial to monitor mucosal and histological inflammation directly using colonoscopy [99]. The selection of drugs is guided by disease severity. It is advisable to take a quick step-up strategy based on the severity of ulcerative colitis and treatment response while continuously monitoring intestinal inflammation. In patients brought to the hospital with acute severe ulcerative colitis, as well as steroid-refractory ulcerative colitis, biological medicines should be evaluated early. To sustain remission, drugs can be maintained or added once remission has been achieved. Those with proctitis may just require topical medication (such as suppositories), but patients with more widespread illness may benefit from systemic therapy [82, 114, 118].

A) Mild to moderate disease

The 5-ASA drugs, which can be given as suppositories, enemas, or oral formulations are the first-line therapy for mild to severe illness. There appears to be no difference in efficacy or safety across the various 5-ASA formulations [119]. Sulfasalazine, which is metabolised to 5-ASA, looks to be equally effective as 5-ASA medications but has a worse tolerability [114]. Patients with proctitis should be first treated with 5-ASA suppositories, which are more efficient than oral 5-ASA because they target the site of inflammation directly [114, 118, 120]. To reach the splenic flexure in patients with left-sided colitis, 5-ASA should be given as an enema rather than a suppository. Oral 5-ASA should be administered in conjunction with topical 5-ASA to achieve remission in individuals with left-sided or severe illness [114, 118]. Inducing and sustaining remission with oral 5-ASA dosages of 2 g or more per day is more successful than with smaller doses [121 - 123]. Start with 2.0 - 2.4 g of 5-ASA per day and gradually increase to 4.8 g if necessary [114, 123]. 5-ASA given once a day is equally effective as split dosages and may improve adherence [114, 123]. Patients usually observe results after 14 days, although clinical remission might take up to 8 weeks [114]. Patients who establish remission with 5-ASA medications should stay on the same treatment [114].

Corticosteroids can be used to treat patients who do not react to 5-ASA medications or do not reach remission. Rectal corticosteroids can be used as a second-line add-on treatment for proctitis or ulcerative colitis on the left side. Topical 5-ASA induces remission better than topical corticosteroids (OR 2.01, 95 percent CI 1.41–2.88) [114]. When rectal 5-ASA and corticosteroids are combined clinical and endoscopic improvement may be greater [124]. Rectal corticosteroids can also be given as foam formulations, which are frequently more tolerated by individuals with active distal ulcerative colitis than enemas [114]. In individuals with mild to severe illness who do not respond to 5-ASA therapy, oral corticosteroids are required to achieve remission. Oral steroids like budesonide-multimatrix and delayed release beclomethasone dipropionate, which have low systemic action (owing to high first-pass liver metabolism), are helpful at producing remission in ulcerative colitis [125 - 127]. These medications should be evaluated as an alternate first-line induction therapy for mild to moderate ulcerative colitis patients who have failed 5-ASA due to the decreased risk of systemic adverse effects. With a number needed to treat of three, systemic glucocorticoids are successful in achieving remission for ulcerative colitis [128]. Prednisone at a dosage of 40 - 60 mg per day is a common beginning dose [82]. Within two weeks, a response should be seen, and the steroids can then be decreased. Although there is no set tapering strategy, a usual technique is to taper by 5 - 10 mg per week until reaching 20 mg, then reduce by 2.5 - 5 mg per week until done [82, 118]. Because of their lack of long-term effectiveness and danger of adverse effects, corticosteroids should not be used to maintain remission [114]. In individuals with a minor flare who were just diagnosed or are naive to 5-ASA, 5-ASA might be considered for maintenance if remission is achieved with corticosteroids. Patients with poor prognostic factors (young age of disease onset, extensive colitis, deep ulcerations), who require two or more courses of steroids in a year or who are unable to taper off steroids effectively, should step up therapy and begin treatment with thiopurines or biological drugs (anti-TNF-α or anti-integrin therapy) [114].

B) Moderate to severe disease

Thiopurines, biological medicines, or both should be used to treat patients with mild to severe colitis. Thiopurines (azathioprine or 6-mercaptopurine) can be administered to sustain remission in individuals with steroid-dependent moderate to severe illness. Methotrexate has a minor effectiveness in ulcerative colitis, according to many studies

[129,130], but the findings of a clinical study [131] were mixed, thus its function in ulcerative colitis treatment is currently being researched.

Infliximab, adalimumab, and golimumab are anti-TNF-α medicines that are effective at eliciting and sustaining remission in moderate to severe illness [132 - 135]. Infliximab, the most extensively used biological treatment ulcerative colitis, can also be utilised in hospitalised patients with severe ulcerative colitis [132, 133]. Azathioprine alone is less effective than infliximab in achieving clinical remission and endoscopic healing, with the difference between azathioprine alone and infliximab monotherapy statistically significant only for endoscopic healing [136].
Anti-adhesion molecule inhibitors, new class of biological medicines are currently accessible [68]. Vedolizumab is a drug that inhibits the gut-homing α4β7 integrin and is authorised for moderate to severe ulcerative colitis that has been resistant to other treatments. Vedolizumab might be regarded a first-line biological for ulcerative colitis based on effectiveness and safety findings [137].

C) Acute severe ulcerative colitis

Patients with acute severe ulcerative colitis should be hospitalized if they have six or more bloody bowel movements per day and at least one of the following: pulse rate > 90 beats per minute, fever > 37.8°C, haemoglobin count < 10.5 g/dL, or ESR > 30 mm/h [69]. Acute severe ulcerative colitis is associated with 1 % death rate and considerable morbidity [138]. In the beginning, patients are given intravenous corticosteroids, to which around 65 percent of them react [139]. Rescue medicinal treatment with ciclosporin or infliximab can be tried if individuals do not respond to intravenous corticosteroids after 3 to 5 days. In acute severe ulcerative colitis, both medications work equally well [140, 141]. Delays in surgery can lead to more postoperative problems, and fatality rates rise dramatically beyond seven days [142,143]. Colectomy should be performed if none of these medications work.

Surgery

Uncontrolled bleeding, perforation, and colorectal cancer or dysplastic lesions that are not amenable to endoscopic excision are all absolute reasons for surgery [82, 144]. In cases of resistant acute severe ulcerative colitis or medically refractory illness, surgery may be necessary [82]. Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the most frequent operation for ulcerative colitis. When surgery is needed quickly, it is usually done in two or three stages, beginning with a subtotal colectomy and temporary ileostomy (first stage) to reduce the risk of early postoperative complications including anastomotic leak or pelvic infection [145]. With a diverting ileostomy (second stage), the ileal pouch is constructed and anastomosed to the anal canal, which is later removed to restore intestinal continuity (third stage). IPAA surgery should be performed in high-volume referral centres with a reduced risk of pouch failure [146].

In up to 33% of patients, early postoperative problems after IPAA might develop [147]. With the exception of pouchitis, late complications such as intestinal blockages and strictures can affect up to 30% of patients, with pouch failure rates as high as 5% [145, 146]. Reduced fertility and increased sexual dysfunction are two frequent concerns associated with IPAA [148]. When compared to controls that had an appendectomy, laparoscopic restorative proctocolectomy with IPAA is linked with a considerably greater incidence of pregnancy than open surgery and a similar rate of infertility [149, 150]. Because of the deleterious effects of active ulcerative colitis on libido, up to 25% of men may develop erectile dysfunction or retrograde ejaculation after IPAA, although satisfaction with sexual life may not be affected or may even increase [151].

Pouchitis is a nonspecific inflammatory disease of the ileal pouch that is the most prevalent postoperative complication after IPAA [152]. Up to 46% of IPAA patients will experience at least one episode of pouchitis, demonstrating that colectomy is not a cure for ulcerative colitis [153]. Patients may have four to seven bowel motions per day at first, but pouchitis is characterised by increasing frequency, urgency, incontinence, or stomach discomfort [153]. Most bouts can be treated satisfactorily with ciprofloxacin (1000 mg daily) or metronidazole (20 mg/kg daily) for 2–4 weeks; one study [154] showed that ciprofloxacin was more effective than metronidazole. [152,154] Chronic pouchitis can occur in 10 - 15 percent of patients, with repeated relapses or symptoms that last longer than four weeks after therapy [152]. At the anastomosis between the ileum and the anal canal, patients may have remnant rectal tissue, referred to as a rectal cuff. In contrast to pouchitis, this region can become inflamed, resulting in cuffitis, which commonly manifests with bleeding and can usually be effectively treated with 5-ASA suppositories [152].

Disease monitoring and long-term management

In ulcerative colitis, the treatment method has developed into a treat to target approach, in which patients are monitored on a frequent basis to ensure that they are reaching rigorous disease management goals. Endoscopic remission and resolution of patient-reported outcomes (rectal bleeding and diarrhoea) are the goals for ulcerative colitis [3]. Because

endoscopic healing is so important, the colon should be evaluated 3–6 months after starting a new therapy [3]. Endoscopic healing can be assessed with a flexible sigmoidoscopy [155]. Patients should be seen at least once every three months until their symptoms have resolved, and then at least once every six to twelve months to maintain tight control [3]. Non-invasive indicators, such as faecal calprotectin, can be used to monitor disease activity while patients are in remission. A faecal calprotectin threshold of 150 mg/kg was optimal for endoscopic remission in a post-hoc analysis of a clinical study (sensitivity of 0.79 and specificity of 0.75) [156].

When patients show sign and symptoms of an ulcerative colitis flare, infection should be ruled out, and objective tests like sigmoidoscopy, faecal calprotectin, or stool lactoferrin should be performed. For active inflammation, faecal calprotectin appears to have the best sensitivity and specificity [157, 158]. If there is objective evidence of inflammation, medication dose, administration, and adherence should all be reviewed. Adequate dosage can be ensured via therapeutic drug monitoring. Patients on azathioprine or 6-mercaptopurine can have their blood concentrations of the active metabolite 6-thioguanine tested to ensure they are getting enough of it [159]. Anti-TNF-α medication concentrations can also be measured for therapeutic purposes. Higher infliximab and adalimumab serum concentrations during induction and at trough are linked to endoscopic healing and clinical remission [160, 161]. Infliximab dose based on a target trough of 3 - 7 μL/mL did not increase remission at one year, but it did lead to more efficient drug usage and a lower chance of recurrence, according to the results of a randomised study [162]. Biological concentration tests also offer information on the development of antidrug antibodies, which have been linked to lower drug concentrations and a lack of responsiveness [163]. Colon cancer monitoring and health maintenance are the most important aspects of chronic treatment for ulcerative colitis patients. Patients with ulcerative colitis should get a colonoscopy on a regular basis to check for dysplasia and early cancer. Starting 8 years following diagnosis, patients with severe colitis and left-sided illness should have a colonoscopy every 1 - 2 years [82]. Because proctitis is not associated with an elevated risk of colorectal cancer, these individuals should adhere to conventional colorectal cancer screening protocols [89]. Because the risk of colorectal cancer is up to five times higher in individuals with ulcerative colitis and primary sclerosing cholangitis than in other patients with the condition, monitoring should begin at the time of diagnosis and continue yearly [164, 165].

Because non-polypoid, flat, ill-defined, or multifocal dysplasia and neoplastic lesions in ulcerative colitis are common, a common technique has been to take four random samples every 10 cm in the colon to enhance neoplasia identification [89]. The SCENIC (Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus Recommendations) statement recommends using chromo-endoscopy to improve visualisation by spraying the colon with methylene blue or indigo carmine and taking targeted biopsies [144]. If colorectal cancer or high-grade dysplasia that is not endoscopically resectable is found, a colectomy is advised. Patients who have multifocal low-grade dysplasia, thick pseudo-polyposis, or strictures that prevent adequate monitoring may need surgery [109].

Patients' immunisation status should be checked on a regular basis. Immunosuppression makes live vaccinations contraindicated [82]. Annual influenza vaccinations, tetanus and diphtheria boosters, and pneumococcal vaccinations every five years are also advised [166]. Before starting anti-TNF-α medication, the patient's hepatitis B status should be verified, and those who are not immune should be vaccinated. If a patient has been exposed to corticosteroids for at least 3 months, or has usual risk factors (postmenopausal women, family history, and smoking), they should be evaluated for osteoporosis. Thiopurines raise the risk of non-melanoma skin cancer (hazard ratio 5.9, 95 percent confidence interval 2.1 - 16.4), whereas biological medicines raise the risk of melanoma (OR 1.88, 95 percent confidence interval 1.08 - 3.29) [167 - 169]. Patients using these drugs should avoid exposure to the sun and get yearly dermatological examinations.

Future directions and controversies

In the near future, the number of medications that modulate various disease pathways is projected to increase. At least 27 novel medicines for ulcerative colitis are in clinical studies or have just finished testing [170]. Tofacitinib, an oral pan-janus kinase inhibitor, has proven in phase 2 trials to have a greater incidence of clinical remission than placebo [171]. In a phase 2 study, etrolizumab, a subcutaneous monoclonal antibody that inhibits the β7 subunit of the heterodimeric integrins α4β7 and αEβ7, had a greater clinical remission rate than placebo [172]. In a phase 2 study, an oral anti-4 integrin treatment (AJM300) dramatically enhanced clinical remission and endoscopic healing [173]. An oral medication that prevents lymphocyte egress from lymph nodes by blocking sphingosine-1-phosphate receptors has also been found to be effective [174]. Curcumin enhanced endoscopic remission in mild to moderate ulcerative colitis as an add-on treatment in a limited study of 5-ASA non-responders [175]. The use of biosimilar biological pharmaceuticals should lower the cost of treatment. CT-P13, an infliximab biosimilar, has shown effectiveness in initiating endoscopic

healing in ulcerative colitis in preliminary investigations [176]. Immunogenicity and effectiveness remain a concern, especially in patients moving from the original to the biosimilar [177].

The findings of studies on the effectiveness of faecal microbiota transplantation (FMT) in ulcerative colitis have been mixed. While one trial found no increase in clinical or endoscopic remission after two infusions of FMT product from healthy donors via a nasogastric tube over a 12-weeks period, a second study found that patients treated with weekly FMT enemas had greater endoscopic remission at 7 weeks [178, 179].

FOCUS [180], the biggest randomized FMT research to date, found a greater rate of clinical and endoscopic remission or response at 8 weeks after FMT delivered by colonoscopy and enemas five times a week. Although these findings are fascinating, there isn't enough data to recommend FMT for ulcerative colitis. FMT appears to be safe but ineffective in treating recurrent *Clostridium difficile* in people with inflammatory bowel disease (including those on immunosuppression) [181]. Another area where more study is needed is establishing the best therapeutic targets. The ideal amount of symptom management and mucosal repair required to avoid long-term consequences has yet to be determined. In ulcerative colitis, histological remission may one day become a therapeutic target [182, 183].

In ulcerative colitis, the need for precision medicine will be stronger than ever, as doctors must pick which therapy to employ and which biological route to target. To personalise therapy to individual patients, a better knowledge of pharmacogenomics, biomarkers, and clinical traits that indicate subpopulations of patients who will react well to certain drugs would be required. Combining biological treatments with head-to-head trials to discover the most appropriate medicines and how to best present new pharmaceuticals are two other prospective research approaches.

REFERENCES

[1]. Høivik ML, Moum B, Solberg IC, et al. Work disability in inflammatory bowel disease patients 10 years after disease onset: results from the IBSEN Study. *Gut.* 2013;62:368–75.
[2]. Torres J, Billioud V, Sachar DB, Peyrin-Biroulet L, Colombel J-F. Ulcerative colitis as a progressive disease: the forgotten evidence. *Inflamm Bowel Dis.* 2012;18:1356–63.
[3]. Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): determining therapeutic goals for treat-to-target. *Am J Gastroenterol.* 2015;110:1324–38.
[4]. Magro F, Rodrigues A, Vieira AI, et al. Review of the disease course among adult ulcerative colitis population-based longitudinal cohorts. *Inflamm Bowel Dis.* 2012;18:573–83.
[5]. Cohen RD, Yu AP, Wu EQ, Xie J, Mulani PM, Chao J. Systematic review: the costs of ulcerative colitis in Western countries. *Aliment Pharmacol Ther.* 2010;31:693–707.
[6]. Bernstein CN, Wajda A, Svenson LW, et al. The epidemiology of inflammatory bowel disease in Canada: a population-based study. *Am J Gastroenterol.* 2006;101:1559–68.
[7]. Cosnes J, Gower-Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology.* 2011;140:1785–94.
[8]. Loftus EV. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. *Gastroenterology.* 2004;126:1504–17.
[9]. Shapiro JM, Zoega H, Shah SA, et al. Incidence of Crohn's disease and ulcerative colitis in Rhode Island: report from the Ocean State Crohn's and Colitis Area Registry. *Inflamm Bowel Dis.* 2016;22:1456–61.
[10]. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology.* 2012;142:46–54.e42.
[11]. Shivananda S, Lennard-Jones J, Logan R, et al. Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD) *Gut.* 1996;39:690–97.
[12]. Bengtson M-B, Solberg C, Aamodt G, et al. Familial aggregation in Crohn's disease and ulcerative colitis in a Norwegian population-based cohort followed for ten years. *J Crohns Colitis.* 2009;3:92–99.
[13]. Loftus CG, Loftus EV, Harmsen WS, et al. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940–2000. *Inflamm Bowel Dis.* 2007;13:254–61.
[14]. Burisch J, Pedersen N, Čuković-Čavka S, et al. East-West gradient in the incidence of inflammatory bowel disease in Europe: the ECCO-EpiCom inception cohort. *Gut.* 2014;63:588–97.
[15]. Benchimol EI, Mack DR, Guttmann A, et al. Inflammatory bowel disease in immigrants to Canada and their children: a population-based cohort study. *Am J Gastroenterol.* 2015;110:553–63.
[16]. Benchimol EI, Manuel DG, To T, et al. Asthma, type 1 and type 2 diabetes mellitus, and inflammatory bowel disease amongst South Asian immigrants to Canada and their children: a population-based cohort study. *PLoS One.* 2015;10:e0123599.

[17]. Carr I, Mayberry JF. The effects of migration on ulcerative colitis: a three-year prospective study among Europeans and first- and second- generation South Asians in Leicester (1991–1994) *Am J Gastroenterol.* 1999;94:2918–22.
[18]. Ng SC, Tang W, Ching JY, et al. Incidence and phenotype of inflammatory bowel disease based on results from the Asia-pacific Crohn's and colitis epidemiology study. *Gastroenterology.* 2013;145:158–65.
[19]. Sood A, Midha V, Sood N, Bhatia AS, Avasthi G. Incidence and prevalence of ulcerative colitis in Punjab, North India. *Gut.* 2003;52:1587–90.
[20]. Tozun N, Atug O, Imeryuz N, et al. Clinical characteristics of inflammatory bowel disease in Turkey: a multicenter epidemiologic survey. *J Clin Gastroenterol.* 2009;43:51–57.
[21]. Victoria CR, Sassak LY, de C Nunes HR. Incidence and prevalence rates of inflammatory bowel diseases, in midwestern of São Paulo State, Brazil. *Arq Gastroenterol.* 2009;46:20–25.
[22]. Halme L, Paavola-Sakki P, Turunen U, Lappalainen M, Farkkila M, Kontula K. Family and twin studies in inflammatory bowel disease. *World J Gastroenterol.* 2006;12:3668–72.
[23]. Moller FT, Andersen V, Wohlfahrt J, Jess T. Familial risk of inflammatory bowel disease: a population-based cohort study 1977–2011. *Am J Gastroenterol.* 2015;110:564–71.
[24]. Ananthakrishnan AN. Epidemiology and risk factors for IBD. *Nat Rev Gastroenterol Hepatol.* 2015;12:205–17.
[25]. Bernstein CN, Rawsthorne P, Cheang M, Blanchard JF. A population-based case control study of potential risk factors for IBD. *Am J Gastroenterol.* 2006;101:993–1002.
[26]. Liu JZ, van Sommeren S, Huang H, et al. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. *Nat Genet.* 2015;47:979–86.
[27]. Jostins L, Ripke S, Weersma RK, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature.* 2012;491:119–24.
[28]. UK IBD Genetics Consortium. Barrett JC, Lee JC, et al. Genome-wide association study of ulcerative colitis identifies three new susceptibility loci, including the HNF4A region. *Nat Genet.* 2009;41:1330–34.
[29]. Mahid SS, Minor KS, Soto RE, Hornung CA, Galandiuk S. Smoking and inflammatory bowel disease: a meta-analysis. *Mayo Clin Proc.* 2006;81:1462–71.
[30]. Odes HS, Fich A, Reif S, et al. Effects of current cigarette smoking on clinical course of Crohn's disease and ulcerative colitis. *Dig Dis Sci.* 2001;46:1717–21.
[31]. Beaugerie L, Massot N, Carbonnel F, Cattan S, Gendre JP, Cosnes J. Impact of cessation of smoking on the course of ulcerative colitis. *Am J Gastroenterol.* 2001;96:2113–16.
[32]. Birrenbach T, Böcker U. Inflammatory bowel disease and smoking: a review of epidemiology, pathophysiology, and therapeutic implications. *Inflamm Bowel Dis.* 2004;10:848–59.
[33]. Sahami S, Kooij IA, Meijer SL, Van den Brink GR, Buskens CJ, Te Velde AA. The link between the appendix and ulcerative colitis: clinical relevance and potential immunological mechanisms. *Am J Gastroenterol.* 2016;111:163–69.
[34]. García Rodríguez LA, Ruigómez A, Panés J. Acute gastroenteritis is followed by an increased risk of inflammatory bowel disease. *Gastroenterology.* 2006;130:1588–94.
[35]. Gradel KO, Nielsen HL, Schønheyder HC, Ejlertsen T, Kristensen B, Nielsen H. Increased short- and long-term risk of inflammatory bowel disease after salmonella or campylobacter gastroenteritis. *Gastroenterology.* 2009;137:495–501.
[36]. Cornish JA, Tan E, Simillis C, Clark SK, Teare J, Tekkis PP. The risk of oral contraceptives in the etiology of inflammatory bowel disease: a meta-analysis. *Am J Gastroenterol.* 2008;103:2394–400.
[37]. Ananthakrishnan AN, Higuchi LM, Huang ES, et al. Aspirin, nonsteroidal anti-inflammatory drug use, and risk for Crohn disease and ulcerative colitis: a cohort study. *Ann Intern Med.* 2012;156:350–59.
[38]. Khalili H, Higuchi LM, Ananthakrishnan AN, et al. Hormone therapy increases risk of ulcerative colitis but not Crohn's disease. *Gastroenterology.* 2012;143:1199–206.
[39]. Ungaro R, Bernstein CN, Gearry R, et al. Antibiotics associated with increased risk of new-onset Crohn's disease but not ulcerative colitis: a meta-analysis. *Am J Gastroenterol.* 2014;109:1728–38.
[40]. Ng SC, Tang W, Leong RW, et al. Environmental risk factors in inflammatory bowel disease: a population-based case-control study in Asia-Pacific. *Gut.* 2015;64:1063–71.
[41]. Ko Y, Kariyawasam V, Karnib M, et al. Inflammatory bowel disease environmental risk factors: a population-based case-control study of Middle Eastern migration to Australia. *Clin Gastroenterol Hepatol.* 2015;13:1453–63.e1.
[42]. Hviid A, Svanström H, Frisch M. Antibiotic use and inflammatory bowel diseases in childhood. *Gut.* 2011;60:49–54.

[43]. Soon IS, Molodecky NA, Rabi DM, Ghali WA, Barkema HW, Kaplan GG. The relationship between urban environment and the inflammatory bowel diseases: a systematic review and meta-analysis. *BMC Gastroenterol.* 2012;12:51.
[44]. Klement E, Cohen RV, Boxman J, Joseph A, Reif S. Breastfeeding and risk of inflammatory bowel disease: a systematic review with meta-analysis. *Am J Clin Nutr.* 2004;80:1342–52.
[45]. Heikkilä K, Madsen IEH, Nyberg ST, et al. Job strain and the risk of inflammatory bowel diseases: individual-participant meta-analysis of 95,000 men and women. *PLoS One.* 2014;9:e88711.
[46]. Jiang C, Ting AT, Seed B. PPAR-gamma agonists inhibit production of monocyte inflammatory cytokines. *Nature.* 1998;391:82–86.
[47]. Dubuquoy L, Jansson EA, Deeb S, et al. Impaired expression of peroxisome proliferator-activated receptor gamma in ulcerative colitis. *Gastroenterology.* 2003;124:1265–76.
[48]. Rousseaux C, Lefebvre B, Dubuquoy L, et al. Intestinal antiinflammatory effect of 5-aminosalicylic acid is dependent on peroxisome proliferator-activated receptor-gamma. *J Exp Med.* 2005;201:1205–15.
[49]. Geng X, Biancone L, Dai HH, et al. Tropomyosin isoforms in intestinal mucosa: production of autoantibodies to tropomyosin isoforms in ulcerative colitis. *Gastroenterology.* 1998;114:912–22.
[50]. Kaser A, Lee AH, Franke A, et al. XBP1 links ER stress to intestinal inflammation and confers genetic risk for human inflammatory bowel disease. *Cell.* 2008;134:743–56.
[51]. Mashimo H, Wu DC, Podolsky DK, Fishman MC. Impaired defense of intestinal mucosa in mice lacking intestinal trefoil factor. *Science.* 1996;274:262–65.
[52]. Podolsky DK, Isselbacher KJ. Glycoprotein composition of colonic mucosa. Specific alterations in ulcerative colitis. *Gastroenterology.* 1984;87:991–98.
[53]. Johansson MEV, Gustafsson JK, Holmén-Larsson J, et al. Bacteria penetrate the normally impenetrable inner colon mucus layer in both murine colitis models and patients with ulcerative colitis. *Gut.* 2014;63:281–91.
[54]. Andoh A, Imaeda H, Aomatsu T, et al. Comparison of the fecal microbiota profiles between ulcerative colitis and Crohn's disease using terminal restriction fragment length polymorphism analysis. *J Gastroenterol.* 2011;46:479–86.
[55]. Frank DN, St Amand AL, Feldman RA, Boedeker EC, Harpaz N, Pace NR. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. *Proc Natl Acad Sci USA.* 2007;104:13780–85.
[56]. Roediger WE, Moore J, Babidge W. Colonic sulfide in pathogenesis and treatment of ulcerative colitis. *Dig Dis Sci.* 1997;42:1571–79.
[57]. Hausmann M, Kiessling S, Mestermann S, et al. Toll-like receptors 2 and 4 are up-regulated during intestinal inflammation. *Gastroenterology.* 2002;122:1987–2000.
[58]. Senhaji N, Diakité B, Serbati N, Zaid Y, Badre W, Nadifi S. Toll-like receptor 4 Asp299Gly and Thr399Ile polymorphisms: New data and a meta-analysis. *BMC Gastroenterol.* 2014;14:206.
[59]. Hanai H, Takeuchi K, Iida T, et al. Relationship between fecal calprotectin, intestinal inflammation, and peripheral blood neutrophils in patients with active ulcerative colitis. *Dig Dis Sci.* 2004;49:1438–43.
[60]. Hart AL, Al-Hassi HO, Rigby RJ, et al. Characteristics of intestinal dendritic cells in inflammatory bowel diseases. *Gastroenterology.* 2005;129:50–65.
[61]. Buonocore S, Ahern PP, Uhlig HH, et al. Innate lymphoid cells drive interleukin-23-dependent innate intestinal pathology. *Nature.* 2010;464:1371–75.
[62]. Geremia A, Arancibia-Cárcamo CV, Fleming MPP, et al. IL-23-responsive innate lymphoid cells are increased in inflammatory bowel disease. *J Exp Med.* 2011;208:1127–33.
[63]. Fuss IJ, Neurath M, Boirivant M, et al. Disparate CD4+ lamina propria (LP) lymphokine secretion profiles in inflammatory bowel disease. Crohn's disease LP cells manifest increased secretion of IFN-gamma, whereas ulcerative colitis LP cells manifest increased secretion of IL-5. *J Immunol.* 1996;157:1261–70.
[64]. Inoue S, Matsumoto T, Iida M, et al. Characterization of cytokine expression in the rectal mucosa of ulcerative colitis: correlation with disease activity. *Am J Gastroenterol.* 1999;94:2441–46.
[65]. Fuss IJ, Heller F, Boirivant M, et al. Nonclassical CD1d-restricted NK T cells that produce IL-13 characterize an atypical Th2 response in ulcerative colitis. *J Clin Invest.* 2004;113:1490–97.
[66]. Heller F, Florian P, Bojarski C, et al. Interleukin-13 is the key effector Th2 cytokine in ulcerative colitis that affects epithelial tight junctions, apoptosis, and cell restitution. *Gastroenterology.* 2005;129:550–64.
[67]. Gerlach K, Hwang Y, Nikolaev A, et al. TH9 cells that express the transcription factor PU.1 drive T cell-mediated colitis via IL-9 receptor signaling in intestinal epithelial cells. *Nat Immunol.* 2014;15:676–86.
[68]. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med.* 2013;369:699–710.
[69]. Dignass A, Eliakim R, Magro F, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. *J Crohns Colitis.* 2012;6:965–90.

[70]. Baumgart DC, Sandborn WJ. Inflammatory bowel disease: clinical aspects and established and evolving therapies. *Lancet.* 2007;369:1641–57.
[71]. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol.* 2005;19(suppl A):5A–36.
[72]. Ananthakrishnan AN, McGinley EL, Binion DG. Excess hospitalisation burden associated with Clostridium difficile in patients with inflammatory bowel disease. *Gut.* 2008;57:205–10.
[73]. Nguyen GC, Kaplan GG, Harris ML, Brant SR. A national survey of the prevalence and impact of Clostridium difficile infection among hospitalized inflammatory bowel disease patients. *Am J Gastroenterol.* 2008;103:1443–50.
[74]. Abreu MT, Harpaz N. Diagnosis of colitis: making the initial diagnosis. *Clin Gastroenterol Hepatol.* 2007;5:295–301.
[75]. Vavricka SR, Brun L, Ballabeni P, et al. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. *Am J Gastroenterol.* 2011;106:110–19.
[76]. Vavricka SR, Rogler G, Gantenbein C, et al. Chronological order of appearance of extraintestinal manifestations relative to the time of IBD diagnosis in the Swiss inflammatory bowel disease cohort. *Inflamm Bowel Dis.* 2015;21:1794–800.
[77]. Harbord M, Annese V, Vavricka SR, et al. The first European evidence-based consensus on extra-intestinal manifestations in inflammatory bowel disease. *J Crohns Colitis.* 2016;10:239–54.
[78]. Higgins PDR, Skup M, Mulani PM, Lin J, Chao J. Increased risk of venous thromboembolic events with corticosteroid vs biologic therapy for inflammatory bowel disease. *Clin Gastroenterol Hepatol.* 2015;13:316–21.
[79]. Nguyen GC, Bernstein CN, Bitton A, et al. Consensus statements on the risk, prevention, and treatment of venous thromboembolism in inflammatory bowel disease: Canadian Association of Gastroenterology. *Gastroenterology.* 2014;146:835–48.e6.
[80]. Grainge MJ, West J, Card TR. Venous thromboembolism during active disease and remission in inflammatory bowel disease: a cohort study. *Lancet.* 2010;375:657–63.
[81]. Ananthakrishnan AN, Cagan A, Gainer VS, et al. Thromboprophylaxis is associated with reduced post-hospitalization venous thromboembolic events in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol.* 2014;12:1905–10.
[82]. Kornbluth A, Sachar DB, Practice Parameters Committee of the American College of Gastroenterology Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol.* 2010;105:501–23.
[83]. Lennard-Jones JE, Ritchie JK, Hilder W, Spicer CC. Assessment of severity in colitis: a preliminary study. *Gut.* 1975;16:579–84.
[84]. Ho GT, Mowat C, Goddard CJ, et al. Predicting the outcome of severe ulcerative colitis: development of a novel risk score to aid early selection of patients for second-line medical therapy or surgery. *Aliment Pharmacol Ther.* 2004;19:1079–87.
[85]. Reese GE, Constantinides VA, Simillis C, et al. Diagnostic precision of anti-Saccharomyces cerevisiae antibodies and perinuclear antineutrophil cytoplasmic antibodies in inflammatory bowel disease. *Am J Gastroenterol.* 2006;101:2410–22.
[86]. Sands BE. Biomarkers of inflammation in inflammatory bowel disease. *Gastroenterology.* 2015;149:1275–85.e2.
[87]. Røseth AG, Schmidt PN, Fagerhol MK. Correlation between faecal excretion of indium-111-labelled granulocytes and calprotectin, a granulocyte marker protein, in patients with inflammatory bowel disease. *Scand J Gastroenterol.* 1999;34:50–54.
[88]. Menees SB, Powell C, Kurlander J, Goel A, Chey WD. A meta-analysis of the utility of C-reactive protein, erythrocyte sedimentation rate, fecal calprotectin, and fecal lactoferrin to exclude inflammatory bowel disease in adults with IBS. *Am J Gastroenterol.* 2015;110:444–54.
[89]. Annese V, Daperno M, Rutter MD, et al. European evidence based consensus for endoscopy in inflammatory bowel disease. *J Crohns Colitis.* 2013;7:982–1018.
[90]. Bernstein CN, Shanahan F, Anton PA, Weinstein WM. Patchiness of mucosal inflammation in treated ulcerative colitis: a prospective study. *Gastrointest Endosc.* 1995;42:232–37.
[91]. D'Haens G, Geboes K, Peeters M, Baert F, Ectors N, Rutgeerts P. Patchy cecal inflammation associated with distal ulcerative colitis: a prospective endoscopic study. *Am J Gastroenterol.* 1997;92:1275–79.
[92]. Park SH, Loftus EV, Yang S-K. Appendiceal skip inflammation and ulcerative colitis. *Dig Dis Sci.* 2014;59:2050–57.

[93]. Simpson P, Papadakis KA. Endoscopic evaluation of patients with inflammatory bowel disease. *Inflamm Bowel Dis.* 2008;14:1287–97.
[94]. Magro F, Langner C, Driessen A, et al. European consensus on the histopathology of inflammatory bowel disease. *J Crohns Colitis.* 2013;7:827–51.
[95]. Panes J, Bouhnik Y, Reinisch W, et al. Imaging techniques for assessment of inflammatory bowel disease: joint ECCO and ESGAR evidence-based consensus guidelines. *J Crohns Colitis.* 2013;7:556–85.
[96]. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med.* 1987;317:1625–29.
[97]. Lichtiger S, Present DH, Kornbluth A, et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med.* 1994;330:1841–45.
[98]. Walmsley RS, Ayres RC, Pounder RE, Allan RN. A simple clinical colitis activity index. *Gut.* 1998;43:29–32.
[99]. Shah SC, Colombel JF, Sands BE, Narula N. Mucosal healing is associated with improved long-term outcomes of patients with ulcerative colitis: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol.* 2016;14:1245–55.
[100]. Travis SPL, Schnell D, Krzeski P, et al. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) *Gut.* 2012;61:535–42.
[101]. Mosli MH, Feagan BG, Zou G, et al. Development and validation of a histological index for UC. *Gut.* 2015 doi: 10.1136/gutjnl-2015-310393. published online Oct 16.
[102]. Marchal-Bressenot A, Salleron J, Boulagnon-Rombi C, et al. Development and validation of the Nancy histological index for UC. *Gut.* 2015 doi: 10.1136/gutjnl-2015-310187. published online Oct 13.
[103]. Siegel CA, Whitman CB, Spiegel BM, et al. Development of an index to define overall disease severity in IBD. *Gut.* 2016 doi: 10.1136/gutjnl-2016-312648. published online Oct 25.
[104]. Reinisch W, Reinink AR, Higgins PDR. Factors associated with poor outcomes in adults with newly diagnosed ulcerative colitis. *Clin Gastroenterol Hepatol.* 2015;13:635–42.
[105]. Etchevers MJ, Aceituno M, García-Bosch O, et al. Risk factors and characteristics of extent progression in ulcerative colitis. *Inflamm Bowel Dis.* 2009;15:1320–25.
[106]. Charpentier C, Salleron J, Savoye G, et al. Natural history of elderly-onset inflammatory bowel disease: a population-based cohort study. *Gut.* 2014;63:423–32.
[107]. Loftus EV, Harewood GC, Loftus CG, et al. PSC-IBD: a unique form of inflammatory bowel disease associated with primary sclerosing cholangitis. *Gut.* 2005;54:91–96.
[108]. Choi CHR, Rutter MD, Askari A, et al. Forty-year analysis of colonoscopic surveillance program for neoplasia in ulcerative colitis: an updated overview. *Am J Gastroenterol.* 2015;110:1022–34.
[109]. Beaugerie L, Itzkowitz SH. Cancers complicating inflammatory bowel disease. *N Engl J Med.* 2015;372:1441–52.
[110]. Frolkis AD, Dykeman J, Negrón ME, et al. Risk of surgery for inflammatory bowel diseases has decreased over time: a systematic review and meta-analysis of population-based studies. *Gastroenterology.* 2013;145:996–1006.
[111]. Solberg IC, Høivik ML, Cvancarova M, Moum B, IBSEN Study Group Risk matrix model for prediction of colectomy in a population-based study of ulcerative colitis patients (the IBSEN study) *Scand J Gastroenterol.* 2015;50:1456–62.
[112]. Siebert U, Wurm J, Gothe RM, et al. Predictors of temporary and permanent work disability in patients with inflammatory bowel disease: results of the swiss inflammatory bowel disease cohort study. *Inflamm Bowel Dis.* 2013;19:847–55.
[113]. Gower-Rousseau C, Sarter H, Savoye G, et al. the International Programme to Develop New Indexes for Crohn's Disease (IPNIC) group, International Programme to Develop New Indexes for Crohn's Disease IPNIC group Validation of the Inflammatory Bowel Disease Disability Index in a population-based cohort. published online Dec 8. *Gut.* 2015 doi: 10.1136/gutjnl-2015-310151.
[114]. Bressler B, Marshall JK, Bernstein CN, et al. Clinical practice guidelines for the medical management of nonhospitalized ulcerative colitis: the Toronto consensus. *Gastroenterology.* 2015;148:1035–58.e3.
[115]. Jharap B, Sandborn WJ, Reinisch W, et al. Randomised clinical study: discrepancies between patient-reported outcomes and endoscopic appearance in moderate to severe ulcerative colitis. *Aliment Pharmacol Ther.* 2015;42:1082–92.
[116]. Falvey JD, Hoskin T, Meijer B, et al. Disease activity assessment in IBD: clinical indices and biomarkers fail to predict endoscopic remission. *Inflamm Bowel Dis.* 2015;21:824–31.
[117]. Regueiro M, Rodemann J, Kip KE, et al. Physician assessment of ulcerative colitis activity correlates poorly with endoscopic disease activity. *Inflamm Bowel Dis.* 2011;17:1008–14.
[118]. Dignass A, Lindsay JO, Sturm A, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. *J Crohns Colitis.* 2012;6:991–1030.

[119]. Feagan BG, Chande N, MacDonald JK. Are there any differences in the efficacy and safety of different formulations of oral 5-ASA used for induction and maintenance of remission in ulcerative colitis? Evidence from cochrane reviews. *Inflamm Bowel Dis.* 2013;19:2031–40.
[120]. Gionchetti P, Rizzello F, Venturi A, et al. Comparison of oral with rectal mesalazine in the treatment of ulcerative proctitis. *Dis Colon Rectum.* 1998;41:93–97.
[121]. Lie MRKL, Kanis SL, Hansen BE, van der Woude CJ. Drug therapies for ulcerative proctitis: systematic review and meta-analysis. *Inflamm Bowel Dis.* 2014;20:2157–78.
[122]. Ford AC, Achkar JP, Khan KJ, et al. Efficacy of 5-aminosalicylates in ulcerative colitis: systematic review and meta-analysis. *Am J Gastroenterol.* 2011;106:601–16.
[123]. Feagan BG, Macdonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev.* 2012;10:CD000544.
[124]. Mulder CJ, Fockens P, Meijer JW, van der Heide H, Wiltink EH, Tytgat GN. Beclomethasone dipropionate (3 mg) versus 5-aminosalicylic acid (2 g) versus the combination of both (3 mg/2 g) as retention enemas in active ulcerative proctitis. *Eur J Gastroenterol Hepatol.* 1996;8:549–53.
[125]. Van Assche G, Manguso F, Zibellini M, et al. Oral prolonged release beclomethasone dipropionate and prednisone in the treatment of active ulcerative colitis: results from a double-blind, randomized, parallel group study. *Am J Gastroenterol.* 2015;110:708–15.
[126]. Sandborn WJ, Danese S, D'Haens G, et al. Induction of clinical and colonoscopic remission of mild-to-moderate ulcerative colitis with budesonide MMX 9 mg: pooled analysis of two phase 3 studies. *Aliment Pharmacol Ther.* 2015;41:409–18.
[127]. Danese S, Siegel CA, Peyrin-Biroulet L. Review article: integrating budesonide-MMX into treatment algorithms for mild-to-moderate ulcerative colitis. *Aliment Pharmacol Ther.* 2014;39:1095–103.
[128]. Ford AC, Bernstein CN, Khan KJ, et al. Glucocorticosteroid therapy in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol.* 2011;106:590–99.
[129]. Kozarek RA, Patterson DJ, Gelfand MD, Botoman VA, Ball TJ, Wilske KR. Methotrexate induces clinical and histologic remission in patients with refractory inflammatory bowel disease. *Ann Intern Med.* 1989;110:353–56.
[130]. Wang Y, MacDonald JK, Vandermeer B, Griffiths AM, El-Matary W. Methotrexate for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev.* 2015(8):CD007560.
[131]. Carbonnel F, Colombel JF, Filippi J, et al. Methotrexate is not superior to placebo for inducing steroid-free remission, but induces steroid-free clinical remission in a larger proportion of patients with ulcerative colitis. *Gastroenterology.* 2016;150:380–88.e4.
[132]. Järnerot G, Hertervig E, Friis-Liby I, et al. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. *Gastroenterology.* 2005;128:1805–11.
[133]. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med.* 2005;353:2462–76.
[134]. Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. *Gut.* 2011;60:780–87.
[135]. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology.* 2014;146:85–95.
[136]. Panaccione R, Ghosh S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. *Gastroenterology.* 2014;146:392–400.e3.
[137]. Colombel JF, Sands BE, Rutgeerts P, et al. The safety of vedolizumab for ulcerative colitis and Crohn's disease. *Gut.* 2016 doi: 10.1136/gutjnl-2015-311079. published online Feb 18.
[138]. Lynch RW, Lowe D, Protheroe A, Driscoll R, Rhodes JM, Arnott IDR. Outcomes of rescue therapy in acute severe ulcerative colitis: data from the United Kingdom inflammatory bowel disease audit. *Aliment Pharmacol Ther.* 2013;38:935–45.
[139]. Turner D, Walsh CM, Steinhart AH, Griffiths AM. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. *Clin Gastroenterol Hepatol.* 2007;5:103–10.
[140]. Laharie D, Bourreille A, Branche J, et al. for the Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial. *Lancet.* 2012;380:1909–15.
[141]. Duijvis NW, Ten Hove AS, Ponsioen CIJ, et al. Similar short- and long-term colectomy rates with ciclosporin and infliximab treatment in hospitalised ulcerative colitis patients. *J Crohns Colitis.* 2016;10:821–27.
[142]. Kaplan GG, McCarthy EP, Ayanian JZ, Korzenik J, Hodin R, Sands BE. Impact of hospital volume on postoperative morbidity and mortality following a colectomy for ulcerative colitis. *Gastroenterology.* 2008;134:680–87.

[143]. Randall J, Singh B, Warren BF, Travis SPL, Mortensen NJ, George BD. Delayed surgery for acute severe colitis is associated with increased risk of postoperative complications. *Br J Surg.* 2010;97:404–09.
[144]. Laine L, Kaltenbach T, Barkun A, et al. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. *Gastroenterology.* 2015;148:639–51.e28.
[145]. Øresland T, Bemelman WA, Sampietro GM, et al. European evidence based consensus on surgery for ulcerative colitis. *J Crohns Colitis.* 2015;9:4–25.
[146]. Burns EM, Bottle A, Aylin P, et al. Volume analysis of outcome following restorative proctocolectomy. *Br J Surg.* 2011;98:408–17.
[147]. Fazio VW, Kiran RP, Remzi FH, et al. Ileal pouch anal anastomosis: analysis of outcome and quality of life in 3707 patients. *Ann Surg.* 2013;257:679–85.
[148]. Waljee A, Waljee J, Morris AM, Higgins PDR. Threefold increased risk of infertility: a meta-analysis of infertility after ileal pouch anal anastomosis in ulcerative colitis. *Gut.* 2006;55:1575–80.
[149]. Bartels SAL, D'Hoore A, Cuesta MA, Bensdorp AJ, Lucas C, Bemelman WA. Significantly increased pregnancy rates after laparoscopic restorative proctocolectomy: a cross-sectional study. *Ann Surg.* 2012;256:1045–48.
[150]. Beyer-Berjot L, Maggiori L, Birnbaum D, Lefevre JH, Berdah S, Panis Y. A total laparoscopic approach reduces the infertility rate after ileal pouch-anal anastomosis: a 2-center study. *Ann Surg.* 2013;258:275–82.
[151]. Kani HT, Shen B. Male issues of the ileal pouch. *Inflamm Bowel Dis.* 2015;21:716–22.
[152]. Biancone L, Michetti P, Travis S, et al. European evidence-based consensus on the management of ulcerative colitis: special situations. *J Crohns Colitis.* 2008;2:63–92.
[153]. Shen B. Pouchitis: what every gastroenterologist needs to know. *Clin Gastroenterol Hepatol.* 2013;11:1538–49.
[154]. Shen B, Achkar JP, Lashner BA, et al. A randomized clinical trial of ciprofloxacin and metronidazole to treat acute pouchitis. *Inflamm Bowel Dis.* 2001;7:301–05.
[155]. Colombel JF, Ordás I, Ullman T, et al. Agreement between rectosigmoidoscopy and colonoscopy analyses of disease activity and healing in patients with ulcerative colitis. *Gastroenterology.* 2016;150:389–95.e3.
[156]. Sandborn WJ, Panés J, Zhang H, Yu D, Niezychowski W, Su C. Correlation between concentrations of fecal calprotectin and outcomes of patients With ulcerative colitis in a phase 2 trial. *Gastroenterology.* 2016;150:96–102.
[157]. Schoepfer AM, Beglinger C, Straumann A, et al. Fecal calprotectin more accurately reflects endoscopic activity of ulcerative colitis than the Lichtiger Index, C-reactive protein, platelets, hemoglobin, and blood leukocytes. *Inflamm Bowel Dis.* 2013;19:332–41.
[158]. Mosli MH, Zou G, Garg SK, et al. C-reactive protein, fecal calprotectin, and stool lactoferrin for detection of endoscopic activity in symptomatic inflammatory bowel disease patients: a systematic review and meta-analysis. *Am J Gastroenterol.* 2015;110:802–19.
[159]. Yarur AJ, Abreu MT, Deshpande AR, Kerman DH, Sussman DA. Therapeutic drug monitoring in patients with inflammatory bowel disease. *World J Gastroenterol.* 2014;20:3475–84.
[160]. Roblin X, Marotte H, Rinaudo M, et al. Association between pharmacokinetics of adalimumab and mucosal healing in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol.* 2014;12:80–84.e2.
[161]. Adedokun OJ, Sandborn WJ, Feagan BG, et al. Association between serum concentration of infliximab and efficacy in adult patients with ulcerative colitis. *Gastroenterology.* 2014;147:1296–1307.e5.
[162]. Vande Casteele N, Ferrante M, Van Assche G, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. *Gastroenterology.* 2015;148:1320–29.e3.
[163]. Ben-Horin S, Kopylov U, Chowers Y. Optimizing anti-TNF treatments in inflammatory bowel disease. *Autoimmun Rev.* 2014;13:24–30.
[164]. Annese V, Beaugerie L, Egan L, et al. European evidence-based consensus: inflammatory bowel disease and malignancies. *J Crohns Colitis.* 2015;9:945–65.
[165]. Soetikno RM, Lin OS, Heidenreich PA, Young HS, Blackstone MO. Increased risk of colorectal neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis: a meta-analysis. *Gastrointest Endosc.* 2002;56:48–54.
[166]. Sinclair JA, Wasan SK, Farraye FA. Health maintenance in the inflammatory bowel disease patient. *Gastroenterol Clin North Am.* 2012;41:325–37.
[167]. Singh S, Nagpal SJS, Murad MH, et al. Inflammatory bowel disease is associated with an increased risk of melanoma: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol.* 2014;12:210–18.
[168]. Long MD, Martin CF, Pipkin CA, Herfarth HH, Sandler RS, Kappelman MD. Risk of melanoma and nonmelanoma skin cancer among patients with inflammatory bowel disease. *Gastroenterology.* 2012;143:390–99.e1.

[169]. Peyrin-Biroulet L, Khosrotehrani K, Carrat F, et al. Increased risk for nonmelanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. *Gastroenterology.* 2011;141:1621–28.e1.
[170]. Khanna R, Jairath V, Vande Casteele N, et al. Efficient early drug development for ulcerative colitis. *Gastroenterology.* 2016;150:1056–60.
[171]. Sandborn WJ, Ghosh S, Panes J, et al. Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. *N Engl J Med.* 2012;367:616–24.
[172]. Vermeire S, O'Byrne S, Keir M, et al. Etrolizumab as induction therapy for ulcerative colitis: a randomised, controlled, phase 2 trial. *Lancet.* 2014;384:309–18.
[173]. Yoshimura N, Watanabe M, Motoya S, et al. safety and efficacy of ajm300, an oral antagonist of α4 integrin, in induction therapy for patients with active ulcerative colitis. *Gastroenterology.* 2015;149:1775–83.e2.
[174]. Sandborn WJ, Feagan BG, Wolf DC, et al. ozanimod induction and maintenance treatment for ulcerative colitis. *N Engl J Med.* 2016;374:1754–62.
[175]. Lang A, Salomon N, Wu JCY, et al. Curcumin in combination with mesalamine induces remission in patients with mild-to-moderate ulcerative colitis in a randomized controlled trial. *Clin Gastroenterol Hepatol.* 2015;13:1444–49.e1.
[176]. Farkas K, Rutka M, Golovics PA, et al. Efficacy of infliximab biosimilar CT-P13 induction therapy on mucosal healing in ulcerative colitis. *J Crohns Colitis.* 2016 doi: 10.1093/ecco-jcc/jjw085. published online April 21.
[177]. Danese S, Gomollon F, Governing Board and Operational Board of ECCO ECCO position statement: the use of biosimilar medicines in the treatment of inflammatory bowel disease (IBD) *J Crohns Colitis.* 2013;7:586–89.
[178]. Rossen NG, Fuentes S, van der Spek MJ, et al. Findings from a randomized controlled trial of fecal transplantation for patients with ulcerative colitis. *Gastroenterology.* 2015;149:110–18.e4.
[179]. Moayyedi P, Surette MG, Kim PT, et al. Fecal microbiota transplantation induces remission in patients with active ulcerative colitis in a randomized controlled trial. *Gastroenterology.* 2015;149:102–09.e6.
[180]. Paramsoth S, Kamm M, Walsh A, et al. Multi-donor intense faecal microbiota transplantation is an effective treatment for resistant ulcerative colitis: a randomised placebo-controlled trial. 11th Congress of European Crohn's and Colitis Organisation; Amsterdam. March 16–19, 2016; p. OP017.
[181]. Kelly CR, Ihunnah C, Fischer M, et al. Fecal microbiota transplant for treatment of Clostridium difficile infection in immunocompromised patients. *Am J Gastroenterol.* 2014;109:1065–71.
[182]. Zenlea T, Yee EU, Rosenberg L, et al. Histology grade is independently associated with relapse risk in patients with ulcerative colitis in clinical remission: a prospective study. *Am J Gastroenterol.* 2016;111:685–90.
[183]. Peyrin-Biroulet L, Bressenot A, Kampman W. Histologic remission: the ultimate therapeutic goal in ulcerative colitis? *Clin Gastroenterol Hepatol.* 2014;12:929–34.e2.