

Ulcerative Colitis: Clinical Features, Diagnosis, and Evolving Therapeutic Strategies

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Abstract

Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterised by relapsing–remitting colonic inflammation, extra-intestinal manifestations, and substantial impairment in quality of life. This narrative review summarises current understanding of clinical phenotypes, diagnostic strategies, and therapeutic approaches in UC. Clinically, rectal bleeding, diarrhoea, urgency, and abdominal pain predominate, while arthritis, primary sclerosing cholangitis, and thromboembolism contribute to systemic morbidity. Diagnosis relies on integration of symptoms, biomarkers, endoscopy, and histology; colonoscopy with systematic biopsies remains the cornerstone, complemented by faecal calprotectin, C-reactive protein, and early histological markers such as basal plasmacytosis. Treatment follows a stepwise, treat-to-target strategy aiming for durable, steroid-free clinical and endoscopic remission. Mesalazine is first-line for mild-to-moderate disease, with corticosteroids for flares and thiopurines or other immunomodulators for steroid-dependent phenotypes. In moderate-to-severe or refractory UC, biologics and small-molecule agents, including anti-TNF therapy, vedolizumab, ustekinumab, JAK inhibitors, and S1P receptor modulators, which have reduced colectomy rates, while surgery remains essential for complications and medical failure. Future directions include precision diagnostics, microbiome-based interventions, and bile acid receptor-targeted therapies.

Keywords

Ulcerative Colitis; Inflammatory Bowel Disease; Biologics; Treat-to-target; Mucosal Healing.

1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterised by continuous mucosal inflammation of the colon and a relapsing-remitting course [1]. Symptom onset is usually insidious, and disease often evolves over weeks to months before diagnosis [2]. UC can present at any age, with a peak incidence between 15 and 30 years, and is associated with substantial impairment in quality of life, including higher rates of depression, anxiety, sleep disturbance, and sexual dysfunction, as well as an increased long-term risk of colorectal cancer [3,4].

The clinical phenotype is heterogeneous and ranges from isolated proctitis to extensive colitis. Rectal bleeding is the dominant presenting symptom and occurs in more than 90% of patients, often accompanied by diarrhoea, urgency, faecal incontinence, and crampy abdominal pain [5,6]. Extra-intestinal manifestations, including peripheral arthritis, primary sclerosing cholangitis, and pyoderma gangrenosum, which affect 20–35% of patients and may precede bowel symptoms [7]. UC also confers a two- to four-fold increased risk of venous thromboembolism, particularly during severe flares and with corticosteroid use [8].

Diagnosis relies on the integration of clinical assessment, biomarkers, endoscopy, and histopathology. Colonoscopy with systematic biopsies is central for confirming inflammation, defining disease extent, and excluding differential diagnoses. UC typically involves the rectum and extends proximally in a continuous, circumferential pattern, while recognised variants such as rectal sparing and backwash ileitis can complicate distinction from Crohn's disease [9,10]. Faecal calprotectin and C-reactive protein are the main biomarkers used to monitor activity, although each has limitations in specificity or sensitivity [11]. Histological hallmarks include crypt architectural distortion, mucosal atrophy, and basal plasmacytosis, the latter being a key discriminator from infectious colitis, especially early in the disease course [12,13]. Therapeutic management follows a stepwise, treat-to-target strategy aimed at rapid symptom control and sustained, steroid-free remission with endoscopic, and ideally histologic healing [14,15]. Mesalazine is the first-line agent for mild-to-moderate disease, with corticosteroids for mesalazine-refractory flares and thiopurines as steroid-sparing maintenance therapy in appropriate patients. For moderate-to-severe or refractory UC, biologic and small-molecule therapies, such as anti-TNF agents, vedolizumab, ustekinumab, Janus kinase inhibitors, and sphingosine-1-phosphate receptor modulators, which have expanded treatment options and reduced colectomy rates. Surgery, most often restorative proctocolectomy with ileal pouch-anal anastomosis, remains essential for medically refractory disease and for neoplastic complications.

Despite these advances, a substantial proportion of patients fail to achieve durable remission or experience treatment-limiting toxicity. Ongoing challenges include optimising risk stratification, refining non-invasive monitoring, and addressing persistent inflammation and complications in high-risk subgroups. Future directions encompass deeper mechanistic insights through single-cell and multi-omics approaches, targeted modulation of innate and adaptive immune pathways, microbiome-based interventions, and novel strategies such as bile acid receptor (FXR) agonists to restore epithelial and immune homeostasis. This review summarises current knowledge on clinical phenotypes, diagnostic strategies, and therapeutic approaches in UC, and highlights emerging concepts that may shape future care.

2. Clinical Phenotypes and Disease Activity Patterns

Ulcerative colitis (UC) is a chronic inflammatory bowel disease with a relapsing–remitting course. Rectal bleeding is the main presenting symptom and occurs in more than 90% of patients [5]. Other clinical features reflect the severity and extent of mucosal inflammation. Increased stool frequency and looser stool consistency are common, particularly when disease extends beyond the rectum, although these features are not required for diagnosis. In contrast, patients with proctitis may present with constipation in 5–10% of cases [16]. Additional symptoms include rectal urgency, tenesmus, faecal incontinence, passage of mucus, nocturnal defaecation, and cramp-like abdominal pain, usually localised to the left lower quadrant and typically preceding and relieved by defaecation.

Extra-intestinal manifestations occur in 20–35% of patients and may precede intestinal symptoms in up to 25%[7]. Peripheral arthritis is the most frequent manifestation, while primary sclerosing cholangitis and pyoderma gangrenosum are also observed and are more common in UC than in Crohn's disease [7]. The risk of venous thromboembolism is increased two- to four-fold and is further elevated during severe flares and with corticosteroid use [8,17]. Simple perianal disease can occur in UC; however, recurrent or complex perianal fistulae should prompt re-evaluation of the diagnosis and raise concern for Crohn's disease [18].

3. Diagnostic Approach: Endoscopy, Biomarkers and Histology

Diagnosis of ulcerative colitis (UC) is based on the combined interpretation of clinical features, inflammatory biomarkers, endoscopic findings, and histopathology. No single investigation serves as a diagnostic gold standard for UC; instead, concordant patterns across tests guide the diagnosis. A comprehensive differential diagnosis is essential in all patients with suspected UC. History taking should address recent travel, antibiotic and nonsteroidal anti-inflammatory drug use, tobacco exposure, and recent hospitalization. Infectious causes must be excluded because they are common in new-onset diarrhea, and targeted testing for *Clostridioides difficile* is recommended [2].

3.1. Endoscopic Evaluation: The Cornerstone for Demonstrating Inflammation

Endoscopy is central for demonstrating mucosal inflammation and defining disease extent, and the Mayo Endoscopic Subscore (MES) provides a standardized measure of endoscopic severity throughout the colon [19]. Colonoscopy with intubation of the terminal ileum is recommended in patients with suspected inflammatory bowel disease. UC typically involves the rectum and extends proximally in a continuous, circumferential pattern, classified as proctitis, left-sided colitis, or extensive colitis [9]

Endoscopic Severity: Endoscopic severity correlates with characteristic mucosal changes. Mild disease is associated with erythema, vascular congestion, and partial loss of the normal vascular pattern. Moderate disease shows complete loss of the vascular pattern, adherent blood, erosions, and mucosal friability. Severe disease is characterized by spontaneous bleeding and ulceration. In UC, ulcers occur within diffusely inflamed mucosa, whereas in Crohn's disease the adjacent mucosa may appear normal [1].

Variants and Challenges: Recognized variants include rectal sparing, particularly in patients with primary sclerosing cholangitis, and peri-appendiceal patchy inflammation. Up to 20% of patients, mainly those with extensive colitis, exhibit backwash ileitis, which may complicate distinction from Crohn's disease [10]. On magnetic resonance enterography, ileocaecal valve gaping and terminal ileal dilatation favor backwash ileitis, whereas increased bowel wall thickness is more suggestive of Crohn's disease [20].

3.2. Complementary Role of Biomarkers and Histology

3.2.1. Biomarkers for Tracking Activity

Biomarkers and histological changes complement endoscopic assessment by supporting diagnosis and monitoring disease activity. Ideal biomarkers are non-invasive, sensitive, specific, easy to perform, and cost-effective. In routine practice, faecal calprotectin (FC) and C-reactive protein (CRP) are the principal markers used to track disease activity and response to treatment [11]. However, faecal calprotectin is sensitive for mucosal inflammation but is non-specific and cannot reliably differentiate inflammatory bowel disease from other causes of diarrhea [1,21,22,23,24]. CRP may be elevated but has limited sensitivity in mild to moderate disease. Perinuclear ANCA is relatively specific but lacks sufficient sensitivity for routine diagnostic or therapeutic decision-making. Other laboratory abnormalities often include anemia and iron deficiency. Hypoalbuminemia at diagnosis is associated with a more severe course, including greater need for corticosteroids and advanced therapies and an increased risk of colectomy.

Emerging paediatric biomarker studies indicate possible future directions for more precise disease monitoring. In one cohort of 30 children with UC and 16 healthy controls, an aptamer-based screen of 1,322 plasma proteins identified 129 elevated analytes, but only resistin remained significantly increased [25]. Elastase and lactoferrin showed the strongest discriminatory performance, and all three proteins were validated by ELISA. These findings

are encouraging but require replication in larger paediatric cohorts before they can be incorporated into clinical practice.

3.2.2. Histopathology for Accurate Classification

Biopsy technique and histopathological interpretation are critical for accurate classification and for distinguishing UC from other forms of colitis. At least two biopsy specimens should be obtained from each of six sites: terminal ileum; ascending, transverse, descending, and sigmoid colon; and rectum. Samples should include macroscopically normal mucosa and be fixed immediately in buffered formalin [6].

Histological features favoring UC include crypt architectural distortion, mucosal atrophy, and a diffuse transmucosal inflammatory infiltrate with basal plasmacytosis; active disease shows cryptitis and crypt abscesses [13].

Not all features are present in early disease, which reinforces the importance of basal plasmacytosis as an early and discriminating marker [1].

Histologically, crypt architectural distortion may be absent in early disease and is seen in only about 20% of patients within two weeks of symptom onset. By contrast, basal plasmacytosis appears earlier and has high predictive value for UC, helping to distinguish it from infectious colitis, in which crypt architecture is usually preserved [12].

3.3. Current Therapies: 5-ASA, Corticosteroids, Immunomodulators

The main goal of medical therapy in ulcerative colitis (UC) is to induce rapid symptom control and maintain long-term remission. Achieving these aims reduces relapse, limits long-term complications, and improves quality of life [14]. Current therapies include 5-aminosalicylic acid (5-ASA) preparations, corticosteroids, and immunomodulators.

3.3.1. Mesalazine(5asa)

Mesalazine (5-ASA) is the first-line treatment for induction and maintenance of remission in mild-to-moderate UC. It can be administered rectally (suppositories, enemas, foams) or orally (tablets, granules). Although its mechanism of action is not fully defined, available data indicate that mesalazine has anti-inflammatory and mucosa-protective effects.

The anti-inflammatory effect of mesalazine is mainly mediated through direct modulation of intestinal inflammatory pathways. As a derivative of the nonsteroidal anti-inflammatory drug (NSAID) class, 5-ASA inhibits cyclooxygenase (COX) and lipoxygenase (LOX), thereby reducing prostaglandin and leukotriene synthesis. It also modulates cytokine production, inhibits nuclear factor kappa B (NF- κ B) activation, and scavenges reactive oxygen species, leading to attenuation of intestinal inflammation [26].

Mesalazine may also exert benefit by modifying the gut microbiota. Dysbiosis appears to contribute to the pathophysiology of UC, and 5-ASA can partly restore microbial balance [27]. In a dextran sodium sulfate (DSS)-induced colitis mouse model, 5-ASA altered microbial composition, increased butyrate-producing bacteria, and promoted beneficial genera such as *Lactobacillus* and *Bifidobacterium*, while limiting potentially harmful bacteria. It increased the relative abundance of Firmicutes and Bacteroidetes and reduced Proteobacteria [28].

Mesalazine further supports intestinal homeostasis by protecting the epithelial barrier. UC is characterized by impaired barrier function and increased intestinal permeability. 5-ASA can enhance barrier integrity by upregulating tight junction proteins, restoring the mucus layer, and reducing permeability [29]. It also modulates local immune responses by reducing immune cell infiltration and influencing macrophage polarisation [30].

Different mesalazine formulations provide broadly similar systemic exposure and overall clinical effect. Systemic bioavailability is comparable between oral and rectal preparations [31], and no clinically meaningful differences in efficacy or safety have been demonstrated among formulations [32].

Choice of route and formulation should reflect disease extent and patient preference. For mildly to moderately active proctitis, rectal mesalazine is recommended because it achieves higher local drug concentrations in the distal colon than oral therapy. Suppositories are preferred for isolated rectal disease, with foams or enemas as acceptable alternatives [33]. Patients who prioritise convenience may reasonably receive oral mesalazine instead [34]. Combination oral and rectal mesalazine can limit proximal extension of inflammation in isolated proctitis [35], although for maintenance of remission, rectal monotherapy performs similarly to combined therapy [36].

Combined oral and rectal mesalazine is preferred in left-sided or extensive mild-to-moderate UC. In these patients, oral mesalazine plus a mesalazine enema is more effective for inducing remission than oral therapy alone [37] or topical therapy alone [38].

3.3.2. Corticosteroids

Corticosteroids are a key treatment option for UC in patients who do not respond adequately to mesalazine. In mesalazine-refractory proctitis or left-sided colitis, systemic corticosteroids are indicated regardless of disease extent. Although topical mesalazine is more effective than topical corticosteroids when used alone, combining topical mesalazine (2 g/day) with beclomethasone dipropionate (3 mg/day) results in greater clinical, endoscopic, and histological improvement than either agent alone [39].

Glucocorticoids exert their therapeutic effect in UC mainly through broad suppression of inflammatory cytokine production. They inhibit the release of multiple pro-inflammatory cytokines and immunomodulatory molecules. In vitro studies show reduced production of tumour necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and interleukin-6 (IL-6) after glucocorticoid exposure [40].

Glucocorticoids also act by modulating key inflammatory signalling pathways and immune cell function. They inhibit the NF- κ B signalling pathway, thereby reducing transcription of pro-inflammatory genes and dampening the inflammatory response [41]. In addition, they impair antigen presentation by dendritic cells and macrophages, and suppress lymphocyte activity and proliferation, particularly T-cell activation [42,43].

Systemic corticosteroids are recommended for induction of remission in mild-to-moderate UC that is unresponsive to mesalazine. If remission is achieved, mesalazine can be used for maintenance in newly diagnosed or mesalazine-naïve patients with otherwise favourable prognostic features [44]. By contrast, patients with poor prognostic factors (such as young age at onset, extensive colitis, or deep ulcerations), those requiring two or more steroid courses within 12 months, or those unable to taper steroids should be managed as having moderate-to-severe disease [45].

In moderate-to-severe UC, systemic corticosteroids remain first-line induction therapy. This practice is supported by classic trials from the 1960s that demonstrated superiority of systemic steroids over sulfasalazine in extensive disease [46]. However, prolonged steroid use is not appropriate, and steroid-sparing strategies are required once remission is achieved.

Thiopurines are used as steroid-sparing immunomodulators to maintain steroid-free remission but are limited by their toxicity profile. Azathioprine and mercaptopurine reduce relapse risk but are associated with adverse events in about 26% of patients, including nausea (8%), hepatotoxicity (4%), myelotoxicity (4%), and pancreatitis (4%), as well as increased risks of non-melanoma skin cancer and lymphoma (Lamb CA,2019). Pre-treatment testing of thiopurine methyltransferase (TPMT) activity is recommended, and thiopurine metabolite monitoring can guide dose adjustment and safety [47,48].

In acute severe UC, early recognition and timely escalation of therapy are critical to optimise outcomes. Patients should be hospitalised for intravenous corticosteroids, thromboprophylaxis, and supportive care. Response is assessed by day 3; non-responders

should receive rescue therapy with cyclosporine or infliximab, and colectomy should be considered if there is no improvement by days 4–7 [49]. Contemporary treatment algorithms support phenotype-guided use of advanced therapies, early initiation of biologics within 8–12 weeks in high-risk presentations, and de-escalation only after deep remission is confirmed by low faecal calprotectin and inactive histology, with the aim of improving long-term durability while minimising cumulative toxicity [50].

3.3.3. Immunomodulators

Immunomodulators are a key component of maintenance therapy in moderate-to-severe UC. Long-term management aims for durable, steroid-free remission with endoscopic, and ideally histologic, healing. Treatment selection is guided by early risk stratification. For moderate-to-severe UC, maintenance therapy commonly includes conventional immunosuppressants (thiopurines), biologics (anti-TNF agents, the gut-selective anti-integrin vedolizumab, and cytokine inhibitors targeting IL-12/23 or IL-23), and oral small molecules such as Janus kinase (JAK) inhibitors and sphingosine-1-phosphate (S1P) receptor modulators [48].

Thiopurines, particularly azathioprine (AZA) and 6-mercaptopurine (6-MP), are the most widely used conventional immunomodulators in UC. Their main mechanism is inhibition of lymphocyte proliferation and function. As antagonists of purine metabolism, they interfere with DNA synthesis and thereby suppress T- and B-cell proliferation [51]. In a study of 47 patients with UC, including 28 with severe refractory disease and 19 with glucocorticoid dependence, 46% of the refractory group achieved remission with AZA, and most maintained remission during follow-up [52]. A retrospective study of 56 patients with glucocorticoid-refractory or glucocorticoid-dependent UC reported AZA response rates of 48% at 3 months and 60% at 12 months, with an overall clinical response in 70% of patients [53].

Despite their efficacy, thiopurines are limited by intolerance, non-response, and safety concerns. Approximately 20% of patients, even with normal thiopurine methyltransferase (TPMT) activity, are unable to tolerate AZA, and around 30% do not respond [54]. Common adverse effects include nausea, vomiting, rash, hepatotoxicity, pancreatitis, and bone marrow suppression. Thiopurines remain an option for maintaining steroid-free remission in steroid-dependent disease, but TPMT testing and metabolite-guided monitoring are recommended because of myelotoxic, hepatotoxic, and oncologic risks [55,56].

Methotrexate is a potential alternative immunomodulator in UC, particularly for patients who are intolerant of or unresponsive to thiopurines. Low-dose methotrexate has been used for decades in psoriasis and rheumatoid arthritis and has therefore been considered for UC when additional options are needed [57]. Methotrexate is an antimetabolite that interferes with folate metabolism by inhibiting dihydrofolate reductase, leading to reduced proliferation and inflammatory activity of immune cells [58]. In a study of 131 patients with inflammatory bowel disease intolerant of or non-responsive to azathioprine/mercaptopurine, methotrexate was evaluated as an alternative, supporting its role as a second-line immunomodulator [59].

Thalidomide is another immunomodulatory agent that may have a role in selected cases of refractory UC but is constrained by significant toxicity. Its principal mechanism is inhibition of tumour necrosis factor- α (TNF- α), a key pro-inflammatory cytokine in UC pathogenesis [60,61]. In a small series of 11 adults with refractory UC, thalidomide achieved clinical remission in 36.4% and clinical response in 45.5%, with 18.2% showing no benefit [62]. However, serious adverse effects, including teratogenicity, peripheral neuropathy, and increased risk of thrombosis, markedly limit its broader use [63].

3.3.4. Biologics and Small-molecule Agents

Biologic and small-molecule agents have transformed the management of moderate-to-severe ulcerative colitis (UC). Although no curative medical therapy exists, treatment now aims for mucosal healing and durable, steroid-free remission to reduce hospitalisation and the need

for colectomy [64]. For patients refractory to conventional therapy, available options include anti-tumour necrosis factor (TNF) agents (infliximab, adalimumab, golimumab), cytokine inhibitors targeting IL-12/23 or IL-23 (e.g. ustekinumab, mirikizumab), the anti-integrin vedolizumab, sphingosine-1-phosphate (S1P) receptor modulators (e.g. ozanimod), and oral Janus kinase (JAK) inhibitors [65].

Anti-TNF agents remain a central class for induction and maintenance of remission in UC. TNF- α is a key cytokine in the inflammatory cascade of inflammatory bowel disease and plays a central role in UC pathophysiology [66]. Anti-TNF drugs bind and neutralise TNF- α , preventing interaction with its cell-surface receptors and thereby downregulating inflammatory signalling, limiting inflammatory cell infiltration, reducing mediator production, and promoting mucosal healing [67]. Infliximab, adalimumab, and golimumab are approved for moderate-to-severe UC [68]. Widespread use of these agents has improved quality of life and reduced colectomy rates in drug-refractory disease [69,70]. Anti-TNF agents can be combined with thiopurines to reduce immunogenicity, although a therapeutic drug-monitoring-first approach is a reasonable alternative when malignancy risk favours monotherapy [71,72].

Gut-selective and cytokine-targeted biologics provide additional effective and often safer options. Vedolizumab, an $\alpha 4\beta 7$ integrin antagonist, has gut-restricted activity and has shown superiority over adalimumab in head-to-head comparison, supporting its use, particularly in older patients or those with significant comorbidity; a subcutaneous formulation facilitates long-term maintenance [73,74]. Ustekinumab and IL-23 p19 inhibitors such as mirikizumab offer systemic efficacy with favourable safety profiles [75]. In the UNIFI programme, ustekinumab induced higher clinical remission than placebo at week 8 (15.5% vs 5.3%; $p < 0.01$) and, among induction responders, maintained remission at week 44 with both every-12-week and every-8-week dosing (38.4% and 43.8% vs 24.0% with placebo; $p = 0.002$ and $p < 0.001$, respectively) [73]. Ustekinumab, which targets the shared p40 subunit of IL-12 and IL-23, is approved for UC refractory to conventional and anti-TNF therapy and has shown durable remission with a favourable safety profile in real-world cohorts [76,77].

S1P receptor modulators provide an oral, lymphocyte-targeted strategy that complements parenteral biologics. Lymphocyte egress from lymph nodes is driven by an S1P gradient, with lower S1P concentrations within lymphoid tissue and higher levels in blood and lymph [78]. By binding mainly to S1P₁ (and in some cases S1P₅), S1P modulators induce S1P₁ internalisation and degradation, preventing lymphocyte exit from lymph nodes and reducing circulating lymphocyte counts; this lymphopenia is considered a pharmacodynamic effect rather than a toxicity [79,80]. Ozanimod, an oral S1P₁/S1P₅ modulator approved for multiple sclerosis and UC, has fewer off-target effects than fingolimod because of minimal interaction with S1P₂ and S1P₃ [81]. However, ozanimod produces active metabolites with monoamine oxidase-B-inhibitory activity, raising concerns about drug-drug and food interactions and highlighting the need for longer-term safety data [82]. Etrasimod, which targets S1P₁, S1P₄, and S1P₅, is in development for UC, does not require dose escalation, has a lower interaction burden, and has shown significant endoscopic and histological improvement in trials [83]. S1P modulators require attention to first-dose cardiac effects and potential interactions [84].

JAK inhibitors offer potent, rapid-acting oral therapy but require careful risk assessment. By inhibiting JAK kinases, these agents block cytokine-mediated JAK/STAT signalling, thereby reducing inflammatory gene transcription and promoting mucosal healing [85]. The JAK/STAT pathway mediates signals from multiple cytokines, growth factors, and tyrosine kinases and regulates cell growth, differentiation, proliferation, and immune function [86]. Tofacitinib, the first JAK inhibitor approved for moderate-to-severe UC, improved combined clinical and endoscopic outcomes during induction (16.6–18.5% vs 3.6–8.2% with placebo) and achieved superior one-year remission rates at both 5-mg and 10-mg twice-daily doses

(34.3% and 40.6% vs 11.1%) [97]. However, JAK inhibitors require monitoring and mitigation of cardiovascular, thrombotic, and herpes zoster risks.

3.3.5. Non-pharmaceutical Treatment

Surgery remains an important component of ulcerative colitis (UC) management despite major advances in medical therapy. More than 10% of patients ultimately require an operation [88]. Emergency indications include toxic megacolon, colonic perforation, and refractory hemorrhage. Elective indications include medically refractory disease, medication intolerance, endoscopically unresectable dysplasia, and colorectal cancer [89]. Restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) is the preferred procedure because it avoids a permanent stoma [90]. To reduce the risks of anastomotic leak, pelvic sepsis, and later pouch dysfunction, surgery is often staged. In patients with severe disease or malnutrition, a three-stage approach is usually chosen: subtotal colectomy with end ileostomy, followed by completion proctectomy with IPAA and diverting loop ileostomy, and then ileostomy closure [91]. Post-colectomy complications occur in about one-third of patients. Early problems include infection and ileus, whereas longer-term issues include pouchitis and faecal incontinence. Despite refinements in technique, around 10% of pouches require excision or permanent diversion within 10 years [92].

Endoscopic healing has become a central long-term treatment target in UC. The STRIDE-II recommendations support the use of sigmoidoscopy or colonoscopy to assess mucosal healing as part of a treat-to-target strategy, linking medical management to objective endoscopic outcomes.

4. Future Therapy

The etiology and mechanism of ulcerative colitis are complex, and many factors include genetics, immune imbalance, environmental factors, infectious agents and intestinal flora disorders. However, its specific pathogenic mechanism is still not fully revealed. In the future, its mechanism can be deeply explored through single-cell RNA sequencing and multi-omics analysis.

For example, macrophages in the immune system are becoming one of the key targets in the treatment of UC, and even their dysfunction may be one of the core pathogenesis of UC [93].

Regarding diagnosis, colonoscopy is still the gold standard for UC diagnosis which is limited due to its invasiveness. Improvements in imaging and biomarkers such as ultrasound, magnetic resonance, calprotectin, and CRP can replace some tests.

As for the therapy, microbiome intervention technology is also a hot topic of research, with probiotics and prebiotics, as well as fecal bacterial transplantation, being considered promising treatments [94].

And as mentioned above, the rapid progress of new targeted therapies, including hormones, cytokines and immunomodulators, is also providing more options for the treatment of UC.

Future therapeutic strategies in ulcerative colitis are exploring bile acid receptor pathways as novel targets. Farnesoid X receptor (FXR) is of particular interest because it regulates intestinal barrier function and mucosal immune responses. FXR agonists such as obeticholic acid and cilofexor are under investigation as potential means to restore epithelial homeostasis [95].

5. Discussion

The discussion of UC must integrate its clinical heterogeneity, diagnostic complexity, and evolving therapeutic landscape. UC is a lifelong disease with a relapsing–remitting course, substantial symptom burden, and a meaningful risk of extra-intestinal complications and

colorectal cancer [96]. Despite major advances, many patients continue to experience active disease, impaired quality of life, and treatment-related adverse effects, underscoring the need for more precise and durable management strategies.

Diagnostic assessment in UC now relies on combined clinical, endoscopic, biomarker, and histological evaluation rather than any single gold-standard test. Endoscopy with systematic biopsies remains central for confirming diagnosis, defining disease extent, and excluding mimics. However, recognised variants such as rectal sparing and backwash ileitis, and overlap with Crohn's disease, can complicate interpretation. Biomarkers such as faecal calprotectin and C-reactive protein are useful for monitoring inflammation but are limited by imperfect specificity or sensitivity, particularly in mild disease [97]. Histological markers, especially basal plasmacytosis, improve diagnostic confidence and may better reflect subclinical activity, yet histology is invasive and subject to sampling error and interobserver variation.

Current treatment follows a stepwise approach that balances efficacy, safety, and disease severity [98]. Mesalazine remains the cornerstone for mild-to-moderate disease, with robust evidence for induction and maintenance of remission and additional effects on the microbiota, epithelial barrier, and local immune responses. Corticosteroids are effective for rapid control of flares but are unsuitable for long-term use because of systemic toxicity, making steroid-sparing strategies essential. Thiopurines provide maintenance of steroid-free remission in selected patients but are constrained by intolerance, myelotoxicity, hepatotoxicity, and oncologic risk, necessitating TPMT testing and metabolite-guided monitoring.

Biologics and small-molecule agents have markedly expanded options for moderate-to-severe or refractory UC but introduce new challenges. Anti-TNF agents, vedolizumab, ustekinumab, JAK inhibitors, and S1P receptor modulators can achieve clinical and endoscopic remission and have reduced colectomy rates. Nevertheless, primary non-response, secondary loss of response, and safety concerns, such as infections, malignancy, cardiovascular and thrombotic events, and drug-drug interactions, which remain important limitations. There are still some problems with the optimal application status of these drugs, and data from direct comparison trials are limited. In addition, the effects of therapeutic drug monitoring optimal sequencing and combination therapy with immunomodulators remain to be elucidated. The appropriate treatment regimen for acute severe UC and the risks of perioperative use of biologics is unknown [99]. Phenotype-guided and risk-stratified use, as well as therapeutic drug monitoring where applicable, are needed to maximise benefit while minimising cumulative toxicity.

Surgery retains a crucial role in the management of UC, particularly in acute severe disease, cases of drug therapy's failure, refractory inflammation, and dysplasia or cancer [100]. Restorative proctocolectomy with ileal pouch-anal anastomosis offers a stoma-free outcome but is associated with short- and long-term complications, including pelvic sepsis, pouchitis, and faecal incontinence, and a proportion of pouches ultimately fail. These realities highlight that surgery, while often life-saving and curative for colitis, is not a simple endpoint and must be integrated into shared decision-making alongside medical options and patient preferences.

Future directions in UC emphasise precision medicine, non-invasive monitoring, and novel therapeutic targets. Advances in single-cell RNA sequencing and multi-omics approaches are beginning to clarify pathogenic pathways, including the role of macrophage dysfunction, dysbiosis, and epithelial barrier breakdown. Microbiome-based interventions—including probiotics, prebiotics, and faecal microbiota transplantation—are of increasing interest but require standardisation and long-term safety data [101]. Bile acid receptor pathways, particularly FXR signalling, represent another promising avenue, with FXR agonists such as obeticholic acid and cilofexor under evaluation for restoration of epithelial and immune homeostasis.

Taken together, UC management is moving from symptom control toward structured treat-to-target strategies anchored in clinical, endoscopic, and histological remission. The main challenges now are to refine risk stratification, individualise therapy choice and sequence, reduce steroid exposure and long-term toxicity, and improve access to advanced therapies. Continued integration of mechanistic insights, biomarker development, and real-world outcome data will be essential to translate expanding therapeutic options into durable, patient-centred benefits across the diverse UC population.

References

- [1] Le Berre, Catherine et al. Ulcerative colitis *The Lancet*, Volume 402, Issue 10401, 571 – 584.
- [2] Kaenkumchorn T, Wahbeh G. Ulcerative Colitis: Making the Diagnosis. *Gastroenterol Clin North Am*. 2020 Dec;49(4):655-669. doi: 10.1016/j.gtc.2020.07.001. Epub 2020 Sep 23. PMID: 33121687.
- [3] Voelker R. What Is Ulcerative Colitis? *JAMA*. 2024;331(8):716. doi:10.1001/jama.2023.23814.
- [4] Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG Clinical Guideline: Ulcerative Colitis in Adults. *Am J Gastroenterol*. 2019 Mar;114(3):384-413. doi: 10.14309/ajg.0000000000000152. PMID: 30840605.
- [5] Rao SS, Holdsworth CD, Read NW. Symptoms and stool patterns in patients with ulcerative colitis. *Gut* 1988; 29: 342–45.
- [6] Le Berre C, Honap S, Peyrin-Biroulet L. Ulcerative colitis. *Lancet*. 2023 Aug 12;402 (10401):571-584. doi: 10.1016/S0140-6736(23)00966-2. PMID: 37573077.
- [7] 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.
- [8] Sarlos P, Szemes K, Hegyi P, et al. Steroid but not biological therapy elevates the risk of venous thromboembolic events in inflammatory bowel disease: a meta-analysis. *J Crohn's Colitis* 2018; 12: 489–98.
- [9] 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–36A.
- [10] Felipez LM, Ali S, de Zoeten EF, Griffiths AM, Kim SC, Patel AS, Rosh JR, Adler J. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition position paper on the therapeutic drug monitoring in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2025 Oct;81(4):1100-1117. doi: 10.1002/jpn3.70158. Epub 2025 Jul 21. PMID: 40692184; PMCID: PMC12484717.
- [11] Rowan, C.R. and Ingram, R.J. (2023) Today and tomorrow: the use of biomarkers in inflammatory bowel disease. *Can IBD Today* 1, Published online October 30, 2023. doi.org/ 10.58931/cibd.2023.1320.
- [12] Schumacher G, Kollberg B, Sandstedt B. A prospective study of first attacks of inflammatory bowel disease and infectious colitis— histologic course during the 1st year after presentation. *Scand J Gastroenterol* 1994; 29: 318–32.
- [13] Feakins RM. Ulcerative colitis or Crohn's disease? Pitfalls and problems. *Histopathology* 2014; 64: 317–35.
- [14] Chaparro, M., & Gisbert, J. P. (2014). Antimetabolite Therapy in Ulcerative Colitis: Azathioprine, 6-Mercaptopurine, and Methotrexate. In *Medical Therapy of Ulcerative Colitis* (pp. 135–143). Springer New York. https://doi.org/10.1007/978-1-4939-1677-1_11.
- [15] Turner, D. et al. (2021) STRIDE-II: an update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) initiative of the International Organization for the Study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. *Gastroenterology* 160, 1570–1583.

- [16] Sands BE. From symptom to diagnosis: clinical distinctions among various forms of intestinal inflammation. *Gastroenterology* 2004; 126: 1518–32.
- [17] Fumery M, Xiaocang C, Dauchet L, Gower-Rousseau C, Peyrin-Biroulet L, Colombel J-F. Thromboembolic events and cardiovascular mortality in inflammatory bowel diseases: a meta analysis of observational studies. *J Crohn's Colitis* 2014; 8: 469–79. 4.
- [18] Song EM, Lee H-S, Kim Y-J, et al. Incidence and clinical impact of perianal disease in patients with ulcerative colitis: a nationwide population-based study. *J Gastroenterol Hepatol* 2019; 34: 1011–17.
- [19] Ishida, N. et al. (2021) C-reactive protein is superior to fecal bio markers for evaluating colon-wide active inflammation in ulcerative colitis. *Science* 11, 12431.
- [20] Erden A, Kuru Öz D, Gürsoy Çoruh A, Erden İ, Özalp Ateş FS, Törüner M. Backwash ileitis in ulcerative colitis: are there MR enterographic features that distinguish it from Crohn disease? *Eur J Radiol* 2019; 110: 212–18.
- [21] 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.
- [22] Khan N, Patel D, Shah Y, Trivedi C, Yang Y-X. Albumin as a prognostic marker for ulcerative colitis. *World J Gastroenterol* 2017; 23: 8008–16.
- [23] Israeli E, Grotto I, Gilburd B, et al. Anti-Saccharomyces cerevisiae and antineutrophil cytoplasmic antibodies as predictors of inflammatory bowel disease. *Gut* 2005; 54: 1232–36.
- [24] Torres J, Petralia F, Sato T, et al. Serum biomarkers identify patients who will develop inflammatory bowel diseases up to 5 years before diagnosis. *Gastroenterology* 2020; 159: 96–104.
- [25] Louis Sam Titus, A.S.C. et al. (2023) Resistin, elastase, and lactoferrin as potential plasma biomarkers of pediatric inflammatory bowel disease based on comprehensive proteomic screens. *Mol. Cell. Proteomics* 22, 100487.
- [26] Beiranvand, M. (2021). A review of the biological and pharmacological activities of mesalazine or 5-aminosalicylic acid (5-ASA): an anti-ulcer and anti-oxidant drug. *Inflammopharmacology*, 29(5), 1279–1290. <https://doi.org/10.1007/s10787-021-00856-1>.
- [27] Wada, H., Miyoshi, J., Kuronuma, S., Nishinarita, Y., Oguri, N., Hibi, N., Takeuchi, O., Akimoto, Y., Lee, S. T. M., Matsuura, M., Kobayashi, T., Hibi, T., & Hisamatsu, T. (2023). 5-Aminosalicylic acid alters the gut microbiota and altered microbiota transmitted vertically to offspring have protective effects against colitis. *Scientific Reports*, 13(1). <https://doi.org/10.1038/s41598-023-39491-x>.
- [28] Huang, L., Zheng, J., Sun, G., Yang, H., Sun, X., Yao, X., Lin, A., & Liu, H. (2022). 5-Aminosalicylic acid ameliorates dextran sulfate sodium-induced colitis in mice by modulating gut microbiota and bile acid metabolism. *Cellular and Molecular Life Sciences*, 79(8). <https://doi.org/10.1007/s00018-022-04471-3>.
- [29] Liu, Y., Gao, P., Jia, X., Jiang, J., Hui, H., & Tian, J. (2024). Oral-administered allomelanin-like nanomedicine with multi-enzyme mimesis and favorable gastrointestinal tolerance for amelioration of acute colitis. *Applied Materials Today*, 37, 102143. <https://doi.org/10.1016/j.apmt.2024.102143>.
- [30] Xiao, Q., Luo, L., Zhu, X., Yan, Y., Li, S., Chen, L., Wang, X., Zhang, J., Liu, D., Liu, R., & Zhong, Y. (2024). Formononetin alleviates ulcerative colitis via reshaping the balance of M1/M2 macrophage polarization in a gut microbiota-dependent manner. *Phytomedicine*, 135, 156153. <https://doi.org/10.1016/j.phymed.2024.156153>.
- [31] Sandborn WJ, Hanauer SB. Systematic review: the pharmacokinetic profiles of oral mesalazine formulations and mesalazine pro-drugs used in the management of ulcerative colitis. *Aliment Pharmacol Ther* 2003; 17: 29–42.
- [32] Wang Y, Parker CE, Bhanji T, Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2016; 4: CD000543.

- [33] Harris MS, Lichtenstein GR. Review article: delivery and efficacy of topical 5-aminosalicylic acid (mesalazine) therapy in the treatment of ulcerative colitis. *Aliment Pharmacol Ther* 2011; 33: 996–1009.
- [34] Ko CW, Singh S, Feuerstein JD, et al. AGA clinical practice guidelines on the management of mild-to-moderate ulcerative colitis. *Gastroenterology* 2019; 156: 748–64.
- [35] Pica R, Paoluzi OA, Iacopini F, et al. Oral mesalazine (5-ASA) treatment may protect against proximal extension of mucosal inflammation in ulcerative proctitis. *Inflamm Bowel Dis* 2004; 10: 731–36.
- [36] Choi YS, Kim WJ, Kim JK, Kim DS, Lee DH. Efficacy of topical 5-aminosalicylate monotherapy in patients with ulcerative proctitis with skip inflammation. *J Gastroenterol Hepatol* 2018; 33: 1200–06.
- [37] Ford AC, Khan KJ, Achkar J-P, Moayyedi P. Efficacy of oral vs topical, or combined oral and topical 5-aminosalicylates, in ulcerative colitis: systematic review and meta-analysis. *Am J Gastroenterol* 2012; 107: 167–76.
- [38] Safdi M, DeMicco M, Sninsky C, et al. A double-blind comparison of oral versus rectal mesalamine versus combination therapy in the treatment of distal ulcerative colitis. *Am J Gastroenterol* 1997; 92: 1867–71.
- [39] 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.
- [40] Zimmerman, M., & Jewell, D. (1996). Cytokines and mechanisms of action of glucocorticoids and aminosalicylates in the treatment of ulcerative colitis and Crohn's disease. *Alimentary Pharmacology & Therapeutics*, 10(Sup2), 93–98. <https://doi.org/10.1046/j.1365-2036.1996.22164026.x>.
- [41] Ruan, Y., Zhu, X., Shen, J., Chen, H., & Zhou, G. (2024). Mechanism of Nicotiflorin in San-Ye-Qing rhizome for anti-inflammatory effect in ulcerative colitis. *Phytomedicine*, 129, 155564. <https://doi.org/10.1016/j.phymed.2024.155564>.
- [42] Shin, J. I., Lee, K. H., Joo, Y. H., Lee, J. M., Jeon, J., Jung, H. J., Shin, M., Cho, S., Kim, T. H., Park, S., Jeon, B. Y., Jeong, H., Lee, K., Kang, K., Oh, M., Lee, H., Lee, S., Kwon, Y., Oh, G. ho, & Kronbichler, A. (2019). Inflammasomes and autoimmune and rheumatic diseases: A comprehensive review. *Journal of Autoimmunity*, 103, 102299. <https://doi.org/10.1016/j.jaut.2019.06.010>.
- [43] Cima, I., Corazza, N., Dick, B., Fuhrer, A., Herren, S., Jakob, S., Ayuni, E., Mueller, C., & Brunner, T. (2004). Intestinal Epithelial Cells Synthesize Glucocorticoids and Regulate T Cell Activation. *The Journal of Experimental Medicine*, 200(12), 1635–1646. <https://doi.org/10.1084/jem.20031958>.
- [44] Raine T, Bonovas S, Burisch J, et al. ECCO guidelines on therapeutics in ulcerative colitis: medical treatment. *J Crohn's Colitis* 2022; 16: 2–17.
- [45] 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.
- [46] Lennard-Jones JE, Longmore AJ, Newell AC, Wilson CW, Jones FA. An assessment of prednisone, salazopyrin, and topical hydrocortisone hemisuccinate used as out-patient treatment for ulcerative colitis. *Gut* 1960; 1: 217–22.
- [47] Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, Hayee B, Lomer MCE, Parkes GC, Selinger C, Barrett KJ, Davies RJ, Bennett C, Gittens S, Dunlop MG, Faiz O, Fraser A, Garrick V, Johnston PD, Parkes M, Sanderson J, Terry H; IBD guidelines eDelphi consensus group; Gaya DR, Iqbal TH, Taylor SA, Smith M, Brookes M, Hansen R, Hawthorne AB. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut*. 2019 Dec;68(Suppl 3): s1-s106. doi: 10.1136/gutjnl-2019-318484. Epub 2019 Sep 27. Erratum in: *Gut*. 2021 Apr;70(4):1. doi: 10.1136/gutjnl-2019-318484corr1. PMID: 31562236; PMCID: PMC6872448.

- [48] Raine T, Bonovas S, Burisch J, et al. ECCO guidelines on therapeutics in ulcerative colitis: medical treatment. *J Crohn's Colitis* 2022; 16: 2–17.
- [49] Williams JG, Alam MF, Alrubaiy L, et al. Infliximab versus ciclosporin for steroid-resistant acute severe ulcerative colitis (CONSTRUCT): a mixed methods, open-label, pragmatic randomised trial. *Lancet Gastroenterol Hepatol* 2016; 1: 15–24.
- [50] Sands BE, Peyrin-Biroulet L, Loftus EV Jr, et al. Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. *N Engl J Med* 2019; 381: 1215–26.
- [51] Bamba, S., Tsujikawa, T., Sasaki, M., Fujiyama, Y., & Andoh, A. (2011). Immunomodulators and Immunosuppressants for Japanese Patients with Ulcerative Colitis. *ISRN Gastroenterology*, 2011, 1–5. <https://doi.org/10.5402/2011/194324>.
- [52] Lobo, A. J., Foster, P. N., Burke, D. A., Johnston, D., & Axon, A. T. R. (1990). The role of azathioprine in the management of ulcerative colitis. *Diseases of the Colon & Rectum*, 33(5), 374–377. <https://doi.org/10.1007/bf02156261>.
- [53] Ardizzone, S., Molteni, F., Imbesi, V., Bollani, S., & Porro, G. B. (1997). Azathioprine in Steroid-Resistant and Steroid-Dependent Ulcerative Colitis. *Journal of Clinical Gastroenterology*, 25(1), 330–333. <https://doi.org/10.1097/00004836-199707000-00007>.
- [54] Lee, L., Syed, A., Macfaul, G., & Lanzon-Miller, S. (2013). PWE-090 Outcomes of Patients with Ulcerative Colitis who are Azathioprine Tolerant and Azathioprine Intolerant. *Gut*, 62(Suppl 1), A167.1-A167. <https://doi.org/10.1136/gutjnl-2013-304907.378>.
- [55] Feuerstein JD, Isaacs KL, Schneider Y, et al. AGA clinical practice guidelines on the management of moderate to severe ulcerative colitis. *Gastroenterology* 2020; 158: 1450–61.
- [56] Herfarth H, Barnes EL, Valentine JF, et al. Methotrexate is not superior to placebo in maintaining steroid-free response or remission in ulcerative colitis. *Gastroenterology* 2018; 155: 1098–108.
- [57] Carbonnel, F. (2011). Methotrexate: A Drug of the Future in Ulcerative Colitis? *Current Drug Targets*, 12(10), 1413–1416. <https://doi.org/10.2174/138945011796818252>.
- [58] Aloï, M., Di Nardo, G., Conte, F., Mazzeo, L., Cavallari, N., Nuti, F., Cucchiara, S., & Stronati, L. (2010). Methotrexate in paediatric ulcerative colitis: a retrospective survey at a single tertiary referral centre. *Alimentary Pharmacology & Therapeutics*, 32(8), 1017–1022. <https://doi.org/10.1111/j.1365-2036.2010.04433.x>.
- [59] WAHED, M., LOUIS-AUGUSTE, J. R., BAXTER, L. M., LIMDI, J. K., MCCARTNEY, S. A., LINDSAY, J. O., & BLOOM, S. L. (2009). Efficacy of methotrexate in Crohn's disease and ulcerative colitis patients unresponsive or intolerant to azathioprine/mercaptopurine. *Alimentary Pharmacology & Therapeutics*, 30(6), 614–620. <https://doi.org/10.1111/j.1365-2036.2009.04073.x>.
- [60] Lu, J., Liu, D., Tan, Y., Li, R., Wang, X., & Deng, F. (2021). Thalidomide Attenuates Colitis and Is Associated with the Suppression of M1 Macrophage Polarization by Targeting the Transcription Factor IRF5. *Digestive Diseases and Sciences*, 66(11), 3803–3812. <https://doi.org/10.1007/s10620-021-07067-2>.
- [61] Carvalho, A. T. (2007). Therapeutic and prophylactic thalidomide in TNBS-induced colitis: Synergistic effects on TNF- α , IL-12 and VEGF production. *World Journal of Gastroenterology*, 13 (15), 2166. <https://doi.org/10.3748/wjg.v13.i15.2166>.
- [62] SHU, H., YANG, H., WANG, Z., FEI, G., & QIAN, J. (2018). Efficacy and safety of thalidomide in the treatment of adult refractory ulcerative colitis. *In Chinese Journal of Practical Internal Medicine*.
- [63] Li, T., Qiu, Y., Li, X., Zhuang, X., Huang, S., Li, M., Feng, R., Chen, B., He, Y., Zeng, Z., Chen, M., & Zhang, S. (2020). Thalidomide Combined With Azathioprine as Induction and Maintenance Therapy for Azathioprine-Refractory Crohn's Disease Patients. *Frontiers in Medicine*, 7. <https://doi.org/10.3389/fmed.2020.557986>.
- [64] Oka A, Kawashima K, Kishimoto K, Kotani S, Fukunaga M, Fukuba N, Mishima Y, Oshima N, Ishimura N, Awoniyi M, Ishihara S. Validation of rapid fecal calprotectin assay using particle enhanced turbidimetric immunoassay for inflammatory bowel disease. *Sci Rep.* 2024 Jan 18;14(1):1653. doi: 10.1038/s41598-024-51580-z. PMID: 38238442; PMCID: PMC10796650.

- [65] Choden, T. et al. (2022) Sphingosine-1 phosphate receptor modulators: the next wave of oral therapies in inflammatory bowel disease. *Gastroenterol. Hepatol. (N. Y.)* 18, 265–271.
- [66] Danese, S., Colombel, J. -F., Peyrin-Biroulet, L., Rutgeerts, P., & Reinisch, W. (2013). Review article: the role of anti-TNF in the management of ulcerative colitis – past, present and future. *Alimentary Pharmacology & Therapeutics*, 37(9), 855–866. <https://doi.org/10.1111/apt.12284>.
- [67] Pugliese, D., Felice, C., Papa, A., Gasbarrini, A., Rapaccini, G. L., Guidi, L., & Armuzzi, A. (2016). Anti TNF- α therapy for ulcerative colitis: current status and prospects for the future. *Expert Review of Clinical Immunology*, 13(3), 223–233. <https://doi.org/10.1080/1744666x.2017.1243468>.
- [68] Park, S. C., & Jeen, Y. T. (2015). Current and Emerging Biologics for Ulcerative Colitis. *Gut and Liver*, 9(1), 18–27. <https://doi.org/10.5009/gnl14226>.
- [69] Fok, K. C., Ng, W. W. S., Henderson, C. J. A., & Connor, S. J. (2012). Cutaneous sarcoidosis in a patient with ulcerative colitis on infliximab. In *Journal of Crohn's and Colitis*.
- [70] Reich, K. M., Chang, H. -J., Rezaie, A., Wang, H., Goodman, K. J., Kaplan, G. G., Svenson, L. W., Lees, G., Fedorak, R. N., & Kroeker, K. I. (2014). The incidence rate of colectomy for medically refractory ulcerative colitis has declined in parallel with increasing anti-TNF use: a time-trend study. *Alimentary Pharmacology & Therapeutics*, 40(6), 629–638. <https://doi.org/10.1111/apt.12873>.
- [71] Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab maintains clinical response in patients with moderate to-severe ulcerative colitis. *Gastroenterology* 2014; 146: 96–109.e1.
- [72] Schreiber S, Ben-Horin S, Leszczyszyn J, et al. Randomized controlled trial: subcutaneous vs intravenous infliximab CT-P13 maintenance in inflammatory bowel disease. *Gastroenterology* 2021; 160: 2340–53.
- [73] Sands BE, Sandborn WJ, Panaccione R, O'Brien CD, Zhang H, Johans J, Adedokun OJ, Li K, Peyrin-Biroulet L, Van Assche G, Danese S, Targan S, Abreu MT, Hisamatsu T, Szapary P, Marano C; UNIFI Study Group. Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis. *N Engl J Med*. 2019 Sep 26;381(13):1201-1214. doi: 10.1056/NEJMoa1900750. PMID: 31553833.
- [74] Sandborn WJ, Baert F, Danese S, et al. Efficacy and safety of vedolizumab subcutaneous formulation in a randomized trial of patients with ulcerative colitis. *Gastroenterology* 2020; 158: 562–72.
- [75] D'Haens G, Dubinsky M, Kobayashi T, et al. Mirikizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2023; 388: 2444–55.
- [76] Tursi A, Mocchi G, Scaldaferrri F, Napolitano D, Maresca R, Pugliese D, Semprucci G, Savarino E, Cuomo A, Donnarumma L, Bodini G, Pasta A, Maconi G, Cataletti G, Pranzo G, Rodinò S, Sebkova L, Costa F, Ferronato A, Gaiani F, Marzo M, Luppino I, Fabiano G, Paese P, Elisei W, Monterubbianesi R, Faggiani R, Grossi L, Serio M, Scarcelli A, Lorenzetti R, Allegretta L, Chiri S, Grasso G, Antonelli E, Bassotti G, Spagnuolo R, Luzzza F, Fanigliulo L, Rocco G, Sacchi C, Zampaletta C, Rocchi C, Bolognini L, Bendia E, Bianco MA, Capone P, Meucci C, Colucci R, Tonti P, Neve V, Della Valle N, Felice C, Pica R, Cocco A, Forti G, Onidi FM, Usai Satta P, Checchin D, Gravina AG, Pellegrino R, Picchio M, Papa A. Ustekinumab safety and effectiveness in patients with ulcerative colitis: results from a large real-life study. *Expert Opin Biol Ther*. 2024 Jan-Feb;24(1-2):101-109. doi: 10.1080/14712598.2024.2309300. Epub 2024 Jan 25. PMID: 38250818.
- [77] Iborra M, Ferreira-Iglesias R, Maria Dolores MA, Mesonero Gismero F, Mínguez A, Porto-Silva S, García-Ramírez L, García de la Filia I, Aguas M, Nieto-García L, Suárez Ferrer C, Bastida G, Barreiro-De-Acosta M, Nos P. Real-world long-term effectiveness of ustekinumab in ulcerative colitis: results from a spanish open-label cohort. *Scand J Gastroenterol*. 2024 Mar;59(3):260-268. doi: 10.1080/00365521.2023.2278427. Epub 2023 Nov 6. PMID: 37933161.
- [78] Baeyens, A., Bracero, S., Chaluvadi, V. S., Khodadadi-Jamayran, A., Cammer, M., & Schwab, S. R. (2021). Monocyte-derived S1P in the lymph node regulates immune responses. *Nature*, 592 (7853), 290–295. <https://doi.org/10.1038/s41586-021-03227-6>.
- [79] Baeyens, A. A. L., & Schwab, S. R. (2020). Finding a Way Out: S1P Signaling and Immune Cell Migration. *Annual Review of Immunology*, 38(1), 759–784. <https://doi.org/10.1146/annurev-immunol-081519-083952>.

- [80] Loeb, L., Crosby, S., Hashash, J., Picco, M., Kinnucan, J., & Farraye, F. (2025). INFECTION RATES IN PATIENTS WITH ULCERATIVE COLITIS TREATED WITH A SPHINGOSINE 1-PHOSPHATE RECEPTOR MODULATOR. *Inflammatory Bowel Diseases*, 31(Supplement_1), S2–S2. <https://doi.org/10.1093/ibd/izae282.004>.
- [81] Sandborn WJ, Feagan BG, D'Haens G, Wolf DC, Jovanovic I, Hanauer SB, Ghosh S, Petersen A, Hua SY, Lee JH, Charles L, Chitkara D, Usiskin K, Colombel JF, Laine L, Danese S; True North Study Group. Ozanimod as Induction and Maintenance Therapy for Ulcerative Colitis. *N Engl J Med*. 2021 Sep 30;385(14):1280-1291. doi: 10.1056/NEJMoa2033617. PMID: 34587385.
- [82] Danese S, Panaccione R, Abreu MT, Rubin DT, Ghosh S, Dignass A, Afzali A, Wolf DC, Chiorean MV, Vermeire S, Jain A, Charles L, Lawlor G, Osterman MT, Wu H, Canavan JB, Petersen A, Colombel JF, Regueiro M. Efficacy and Safety of Approximately 3 Years of Continuous Ozanimod in Moderately to Severely Active Ulcerative Colitis: Interim Analysis of the True North Open-label Extension. *J Crohns Colitis*. 2024 Feb 26;18(2):264-274. doi: 10.1093/ecco-jcc/jjad146. PMID: 37651686; PMCID: PMC10896634.
- [83] Yarur AJ, Chiorean MV, Panés J, Jairath V, Zhang J, Rabbat CJ, Sandborn WJ, Vermeire S, Peyrin-Biroulet L. Achievement of Clinical, Endoscopic, and Histological Outcomes in Patients with Ulcerative Colitis Treated with Etrasimod, and Association with Faecal Calprotectin and C-reactive Protein: Results From the Phase 2 OASIS Trial. *J Crohns Colitis*. 2024 Jun 3;18(6):885-894. doi: 10.1093/ecco-jcc/jjae007. PMID: 38245818; PMCID: PMC11147797.
- [84] Wangchuk P, Yeshi K, Loukas A. Ulcerative colitis: clinical biomarkers, therapeutic targets, and emerging treatments. *Trends Pharmacol Sci*. 2024 Oct;45(10):892-903. doi: 10.1016/j.tips.2024.08.003. Epub 2024 Sep 10. PMID: 39261229.
- [85] Liu, E., Aslam, N., Nigam, G., & Limdi, J. K. (2022). Tofacitinib and newer JAK inhibitors in inflammatory bowel disease—where we are and where we are going. *Drugs in Context*, 11, 1–17. <https://doi.org/10.7573/dic.2021-11-4>.
- [86] Zundler, S., & Neurath, M. (2016). Integrating Immunologic Signaling Networks: The JAK/STAT Pathway in Colitis and Colitis-Associated Cancer. *Vaccines*, 4(1), 5. <https://doi.org/10.3390/vaccines4010005>.
- [87] Sandborn WJ, Su C, Sands BE, D'Haens GR, Vermeire S, Schreiber S, Danese S, Feagan BG, Reinisch W, Niezychowski W, Friedman G, Lawendy N, Yu D, Woodworth D, Mukherjee A, Zhang H, Healey P, Panés J; OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Investigators. Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis. *N Engl J Med*. 2017 May 4;376(18):1723-1736. doi: 10.1056/NEJMoa1606910. PMID: 28467869.
- [88] Dinesen LC, Walsh AJ, Protic MN, et al. The pattern and outcome of acute severe colitis. *J Crohn's Colitis* 2010; 4: 431–37.
- [89] Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut* 2019; 68 (suppl 3): s1–106.
- [90] 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.
- [91] Peyrin-Biroulet L, Germain A, Patel AS, Lindsay JO. Systematic review: outcomes and post-operative complications following colectomy for ulcerative colitis. *Aliment Pharmacol Ther* 2016; 44: 807–16.
- [92] Mark-Christensen A, Erichsen R, Brandsborg S, et al. Pouch failures following ileal pouch-anal anastomosis for ulcerative colitis. *Colorectal Dis* 2018; 20: 44–52.
- [93] Chen, S., Qin, Z., Lin, X., Zhou, S., Xu, Y., & Zhu, Y. (2025). Macrophages: emerging targets for ulcerative colitis. *Frontiers in Immunology*, 16. <https://doi.org/10.3389/fimmu.2025.1623491>.
- [94] Pu D, Yao Y, Zhou C, Liu R, Wang Z, Liu Y, Wang D, Wang B, Wang Y, Liu Z, Zhang Z, Feng B. FMT rescues mice from DSS-induced colitis in a STING-dependent manner. *Gut Microbes*. 2024 Jan-Dec;16(1):2397879. doi: 10.1080/19490976.2024.2397879. Epub 2024 Sep 26. PMID: 39324491; PMCID: PMC11441074.

- [95] Wangchuk P, Yeshe K, Loukas A. Ulcerative colitis: clinical biomarkers, therapeutic targets, and emerging treatments. *Trends Pharmacol Sci.* 2024 Oct;45(10):892-903. doi: 10.1016/j.tips. 2024. 08. 003. Epub 2024 Sep 10. PMID: 39261229.
- [96] Klemm, N., & Leung, Y. (2024). Acute Severe Ulcerative Colitis: Review of Management and Emerging Treatments. *Canadian IBD Today*. <https://doi.org/10.58931/cibdt.2024.2229>.
- [97] Stute, M., Kreysing, M., Zorn, M., Michl, P., & Gauss, A. (2024). Serum Amyloid A as a Potential Biomarker in Inflammatory Bowel Diseases, Especially in Patients with Low C-Reactive Protein. *International Journal of Molecular Sciences*, 25(2), 1177. <https://doi.org/10.3390/ijms25021177>.
- [98] Danese, S., Fiorino, G., & Peyrin-Biroulet, L. (2020). Positioning Therapies in Ulcerative Colitis. *Clinical Gastroenterology and Hepatology*, 18(6), 1280-1290.e1. <https://doi.org/10.1016/j.cgh.2020.01.017>.
- [99] Na, S.-Y., Choi, C. H., Song, E. M., Bang, K. B., Park, S. H., Kim, E. S., Park, J. J., Keum, B., Lee, C. K., Lee, B.-I., Ryoo, S.-B., Koh, S.-J., Choi, M., & Kim, J. S. (2023). Korean clinical practice guidelines on biologics and small molecules for moderate-to-severe ulcerative colitis. *Intestinal Research*, 21(1), 61-87. <https://doi.org/10.5217/ir.2022.00007>.
- [100] Schwartzberg, D. M. (2022). Surgical Treatment of Mucosal Ulcerative Colitis. *Clinics in Colon and Rectal Surgery*, 35(06), 419-420. <https://doi.org/10.1055/s-0042-1758046>.
- [101] Rozak, M., Katz, M. D., & Lolita, L. (2025). Janus Kinase Inhibitors, Monoclonal Antibodies, and Fecal Microbiota Transplantation: Promising Therapies for Ulcerative Colitis. *Clinical and Pharmaceutical Sciences Journal*, 1(2), 18-26. <https://doi.org/10.12928/clips.v1i2.376>.