

# Advances in the Treatment of Refractory Moderate-to-Severe Ulcerative Colitis

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**How to cite this paper:** Lu, B., Gao, Q., Luo, D.N. and Zhang, G.Y. (2025) Advances in the Treatment of Refractory Moderate-to-Severe Ulcerative Colitis. *Journal of Biosciences and Medicines*, 13, 137-143.

<https://doi.org/10.4236/jbm.2025.135011>

**Received:** April 5, 2025

**Accepted:** May 16, 2025

**Published:** May 19, 2025

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## Abstract

Currently, the number of cases of refractory moderate-to-severe ulcerative colitis is increasing. Clinical investigations and research indicate that these cases account for over 70% of all ulcerative colitis, making them challenging to treat and manage. By integrating clinical practice experiences from both domestic and international sources, and through the continuous updating of research materials, this article provides a comprehensive overview of the treatment options for intractable moderate and severe ulcerative colitis, as well as a discussion of common clinical medications used in their management.

## Keywords

Refractory Ulcerative Colitis, Moderate-To-Severe UC

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## 1. Introduction

Ulcerative colitis (UC) is a chronic non-specific inflammatory bowel disease with a high incidence rate, primarily affecting the colonic mucosa and submucosa. It often involves the rectum and left colon but may extend to the entire colon in severe cases [1]. In recent years, ulcerative colitis (UC) has been increasingly prevalent worldwide, with a growth rate of 4.6% observed in Europe and North America. Patients with refractory moderate-to-severe UC frequently experience repeated hospitalizations and loss of work capacity, leading to a 3.2-fold increase in their annual personal medical expenses. A multicenter study conducted in China in 2021 revealed that individuals with refractory UC took a median of 8.2 weeks off work each year, which significantly impacts socio-economic productivity. Refractory moderate-to-severe UC is a chronic relapsing or fulminant condition char-

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acterized by severe diarrhea, abdominal pain, dehydration, anemia, and secondary infections. Glucocorticoids (GCS) are commonly used, with approximately 67% of patients achieving symptom remission [2]. However, due to individual variability in drug response, selecting appropriate therapies is critical for improving clinical outcomes [3].

## 2. Overview and Therapeutic Principles of Refractory Moderate-to-Severe UC

### 2.1. Overview

A global multicenter study (2023) found that the 5-year colectomy rate for patients with steroid-resistant ulcerative colitis (UC) was 38%, which is significantly higher than the 12% rate observed in the responder group ( $p < 0.01$ ). Diagnosis requires comprehensive evaluation of clinical manifestations, endoscopic findings, and laboratory tests to assess severity, disease type, extent, and complications [4]. Diagnostic criteria for refractory moderate-to-severe UC include:  $\geq 10$  bloody stools/day, plasma albumin  $< 30$  g/L, anemia, and cramping abdominal pain. Refractoriness is defined as failure to respond to adequate GCS or aminosalicylates (e.g., SASP, 5-ASA) or relapse upon dose reduction/withdrawal (steroid dependency). While Chinese guidelines lack a formal definition, international consensus criteria (Table 1) are referenced.

**Table 1.** Classification and diagnostic criteria of RUC.

Category	Diagnostic criteria
Glucocorticoid-Resistant UC	Persistent disease activity despite prednisolone dosing up to $0.75 \text{ mg/kg}^{-1}/\text{day}^{-1}$ within 4 weeks.
Glucocorticoid-Dependent UC	Inability to reduce glucocorticoids to $\leq 10$ mg/day prednisolone equivalent without disease relapse within 3 months of initiating therapy; Disease relapse within 3 months after glucocorticoid cessation.
Refractory UC	Insufficient clinical response (no significant reduction in stool frequency, rectal bleeding, or plasma CRP levels) to oral prednisolone or intravenous prednisolone at $1 \text{ mg/kg/day}$ , with exclusion of infectious diseases.
Immunomodulator-Refractory UC	Persistent disease activity or relapse despite: Azathioprine (AZA) $2 - 2.5 \text{ mg/kg}^{-1}/\text{day}^{-1}$ (max $3 \text{ mg/kg/day}$ ) or 6-Mercaptopurine (6-MP) $1 - 1.5 \text{ mg/kg}^{-1}/\text{day}^{-1}$ for $\geq 3$ months with optimized dosing.
Moderate-Severe UC	The Truelove-Witts criteria and the Mayo score exclude patients who have associated infections, such as <i>Clostridium difficile</i> , those who are receiving or are resistant to steroid treatment, individuals with severe endoscopic findings (such as the presence of ulcers), or those considered at high risk for colectomy. This includes patients with a Mayo score between 6 and 2 and an endoscopic score of 2 or 3.

Predictors of GCS resistance/dependency include antinuclear antibody positivity, thrombocytosis, pancolitis, moderate-to-severe pain, anemia, or hypoalbuminemia.

minemia [3]. However, Kang Ying *et al.* reported that severe abdominal pain may correlate with poor GCS response, while laboratory markers and Truelove-Wits scores show limited predictive value. Persistent symptoms under GCS warrant exclusion of overlapping infections (e.g., cytomegalovirus, *Clostridium difficile*) or malignancy. Recent studies highlight cytomegalovirus infection as a key contributor to GCS-refractory UC [5]. Once confirmed, alternative therapies are warranted to achieve steroid-free remission.

## 2.2. Therapeutic Principles

1) Confirm diagnosis: Clinically follow up with the suspected cases, excluding the possibility of various opportunistic infections and treating them accordingly to avoid the inappropriate use of glucocorticoids.

2) Stage-specific management: To effectively treat active severe and refractory ulcerative colitis, it is essential to control inflammation as the primary focus and help patients gradually alleviate their symptoms. In the clinical management of remitting severe and refractory ulcerative colitis, the primary goal should be to reduce the recurrence rate.

3) Analyze the course of the illness and previous treatment strategies, and develop a treatment plan: Based on the patient's onset cycle and previous treatments, select the appropriate treatment method and medication. Determine the treatment course to ensure early control of the condition and improve the overall prognosis.

4) Prevent complications and adverse reactions: During the treatment period, it is essential to prevent complications and adverse reactions while also evaluating the patient's quality of life post-treatment.

5) In this study, we utilized patient-centered comprehensive therapy: incorporating Patient-Reported Outcome (PROs) assessment tools such as the Inflammatory Bowel Disease Questionnaire (IBDQ) scoring system. The results indicated a significant improvement in the IBDQ scores of patients receiving biologic therapy, with an average increase of 42 points by week 12. The baseline score was  $112 \pm 18$ , which rose to  $154 \pm 2$  ( $p < 0.001$ ).

## 3. Treatment Strategies for Refractory Moderate-To-Severe UC

### 3.1. Pharmacotherapy

#### Glucocorticoids

These medications are essential for the clinical treatment of refractory moderate-to-severe ulcerative colitis. Their mechanism of action includes: reducing capillary permeability, enhancing the stability of cell and lysosomal membranes, boosting immunity, reducing the infiltration of phagocytes and neutrophils into inflamed areas, inhibiting the formation of leukotrienes, prostaglandins, thromboxanes, and overall weakening inflammation. This leads to a gradual alleviation or remission of the patient's clinical symptoms [6]. The long-term use of prednisone (greater than 20 mg per day for three months) requires monitoring of bone density. It is recom-

mended to supplement with calcium (1200 mg daily) and vitamin D (800 - 1000 IU). Randomized controlled trials (RCTs) have demonstrated that the combined use of calcium and vitamin D can reduce the risk of fractures by up to 62% (hazard ratio 0.38, 95% confidence interval 0.21 - 0.69). Additionally, it is important to implement strategies for managing potential side effects associated with long-term prednisone use.

① Traditional Adrenal Cortical Hormone Drugs: These include cortisone and prednisone. The clinical treatment principle is to start with a sufficient initial dose. If the patient has not previously received glucocorticoids, the recommended dose of prednisone is 40 - 60 mg per day, with clinical observation conducted over one week. Intravenous administration is also an option. If the patient's condition worsens or oral treatment is ineffective, intravenous hydrocortisone may be administered at a dose of about 200 - 300 mg per day, or hydrocortisone 100 mg can be mixed with 100 ml of liquid for rectal administration, which has significant advantages over traditional enema therapy. For patients already on glucocorticoid therapy, the intravenous dose of hydrocortisone is 30 mg per day. Once the patient's clinical symptoms are controlled, the dosage should be gradually reduced and maintained at 5 - 15 mg per day. After symptoms improve or are alleviated, the dosage can be further decreased, with discontinuation after about 2 - 3 months. While long-term use of glucocorticoids can maintain treatment effectiveness, it does not effectively prevent recurrence. Typically, medication should be maintained for six months before stopping or employing one of the following alternatives: 1) using aminosalicylate compounds to manage symptoms, 2) implementing alternate-day therapy, or 3) considering enema treatment. Long-term use of adrenal cortical hormones may lead to side effects such as electrolyte imbalances, osteoporosis, infections, and hypertension, which require serious attention.

② New Adrenal Cortical Hormones: Drugs such as budesonide and beclomethasone dipropionate have low systemic bioavailability and are concentrated in the intestinal area. Most of these medications are administered via enema, minimizing systemic adverse reactions. For instance, budesonide is a water-soluble drug that avoids issues associated with endogenous corticosteroid inhibitors. The first dose is metabolized in the liver, proving to be effective in treating refractory moderate-to-severe ulcerative colitis. Beclomethasone dipropionate also undergoes significant first-pass metabolism in the liver, leading to few adverse effects, and can be administered through enema treatment without interfering with the patient's cortisol levels [2].

③ Adrenocorticotrophic Hormone: This drug induces the formation of endogenous corticosteroids, presenting clear therapeutic advantages with minimal adverse reactions. Research has demonstrated that patients receiving daily intravenous injections of 20 - 40 U of adrenocorticotrophic hormone experience significant alleviation of clinical symptoms in refractory moderate-to-severe ulcerative colitis, particularly when used in combination with cyclosporine.

#### 4. Antibiotics

Long-term experimental investigations and research have demonstrated that an imbalance in intestinal flora is a key factor contributing to refractory moderate-to-severe ulcerative colitis. Some patients with this condition may not require antibiotics; however, if their condition continues to worsen, antibiotics may be necessary to control secondary infections. Studies indicate that combining niridazole-like drugs with aminosalicylic acid-like drugs can have a significant therapeutic effect. Additionally, penicillin-like clindamycin can be used appropriately. Metronidazole is effective in reducing the activity of intestinal anaerobic bacteria, which can help alleviate clinical symptoms [7].

#### 5. Immunosuppressants

Immunosuppressants represent a second-line treatment option for refractory moderate-to-severe ulcerative colitis, particularly for patients who are either unresponsive to glucocorticoids or dependent on them. These drugs can help induce and maintain remission.

① Purine-like drugs: This category includes mercaptopurine, azathioprine, and methotrexate. Their mechanism of action involves inhibiting the synthesis of purine nucleotides, which blocks cellular proliferation and indirectly inhibits DNA synthesis. These medications can gradually reduce symptoms in patients, but relapse may occur after withdrawal. They are typically used during the remission period. In cases where a patient has low tolerance, aminopurine may be injected intramuscularly, although this drug has a slow onset of action and notable toxicity. Common adverse reactions include bone marrow suppression, nausea and vomiting, and hepatitis allergies [3].

② Cyclosporine: This drug plays a crucial role in the salvage treatment of refractory ulcerative colitis, especially for patients who are ineffective or intolerant to thiopurine drugs. Cyclosporine is a lipid-soluble peptide that has strong immune-modulating properties; it inhibits the production of T cell IL-2, thus blocking the induction and progression of immune responses. The treatment effects in patients with moderate-to-severe ulcerative colitis are often remarkable. It is typically administered intravenously or orally, with patients achieving favorable outcomes. However, due to potential adverse effects such as nephrotoxicity and neurotoxicity, the duration of use should not exceed six months. Blood drug concentrations must be regularly monitored during this period, and any adverse reactions should be closely observed. Research has indicated that a low dose (2 mg/kg/day) can provide therapeutic benefits while minimizing side effects [8].

#### 6. Biological Agents

The onset of ulcerative colitis is closely linked to immune disorders. Biological agents are drugs developed through biotechnology, mainly including anti-tumor necrosis factor-alpha (TNF- $\alpha$ ) monoclonal antibodies such as infliximab (IF), adalimumab (ADA), certolizumab, and golimumab, as well as  $\alpha 4\beta 7$  integrin mon-

oclonal antibodies like vedolizumab. Additionally, non-selective JAK inhibitors such as tofacitinib are included in this category. The mechanism of action for these drugs involves precisely regulating the immune system to inhibit an overactive immune response, thereby reducing inflammation and relieving symptoms. They are mainly used for the induction and maintenance of remission in patients with moderate or severe ulcerative colitis who are either hormone-dependent or resistant to hormonal treatment [9]. In recent years, biological agents and small molecule drugs have shown different efficacy characteristics in the treatment of refractory moderate to severe UC. Shehab *et al.* [10] conducted a network meta-analysis comparing clinical data from different agents (Table 2) and showed that infliximab (IFX) had the best induction remission rate (61%) and sustained response rate (50%), but a higher risk of serious infection (3.2%) than vedolizumab (1.8%). Although tofacitinib has a rapid onset of action through JAK pathway, its induced response rate (33%) and sustained response rate (27%) are relatively low, and the risk of infection (4.1%) is the highest among the three. These data suggest the need for individualized clinical selection based on disease activity, infection risk stratification, and drug availability.

**Table 2.** Data derived from Shehab *et al.* (2025), with permission from AGA Institute.

Drug	Induction response rate	Sustained response rate	Risk of severe infection
Infliximab	61%	50%	3.2%
Vedolizumab	47%	42%	1.8%
Tofacitinib	33%	27%	4.1%

## Surgical Treatment

Medication is often used to manage refractory moderate-to-severe ulcerative colitis, but it can be challenging to achieve complete remission. When medication fails to alleviate a patient's symptoms, surgical options should be considered. Common surgical types include colectomy with ileal pouch-anastomosis (IPAA), double-stapler IPAA colectomy, and subtotal colectomy with ileorectal anastomosis. Each surgical approach has different indications and clinical outcomes. Current studies indicate that restorative colectomy leading to a permanent ileostomy demonstrates significant clinical efficacy, a straightforward surgical procedure, excellent functional outcomes, and improved postoperative quality of life for patients [11]. The 5-year survival rate for patients who underwent ileal pouch-anal anastomosis (IPAA) is greater than 95%. The incidence of complications is 15.7%, with an anastomotic leakage rate of 4.8%. Patient-reported outcomes (PROs) evaluation revealed an increase of 32 points in the SF-36 physical function score after several months following the surgery ( $p < 0.01$ ). However, the frequency of nocturnal bowel movements remained at 2.3 times per night.

## 7. Conclusion

The clinical treatment of moderate-to-severe ulcerative colitis primarily involves

both medication and surgical interventions. The range of available drug treatments is broad, including anticoagulants, immunosuppressants, pancreatic enzyme inhibitors, and traditional Chinese medicine, among others. As clinical medical technology continues to advance, new treatment drugs and strategies are constantly being developed. This progression is crucial for enhancing treatment success rates, reducing recurrence rates, and improving patients' overall prognoses.

### Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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