# Therapeutic Strategy for Recurrent Ulcerative Colitis

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## ABSTRACT

*Ulcerative Colitis (UC) is a chronic idiopathic inflammation that appears from the rectum and can extend to colon causing diffuse friability and superficiality. In this case report, Woman, 44 years old, admitted to hospital because of bloody diarrhea, frequency of 4-6 times daily with mucous, malaise, and history of weight loss. Patient already had oral sulfasalazine and oral corticosteroid to maintain her condition, but she stopped the medication at will. On physical examination, showed anemic conjunctiva and increasing in bowel sound, fecal examination showed brown to red, porridge-like consistency, blood, mucous, and positive Benzidine test. Colonoscopy examination revealed, normal anus; in the sigmoid rectum, colon descendent found small swellings, an ulcer, and few bloody. On histopathology, epithelial surface with mucin depletion distortion of crypt architecture, dilatation and elongation of crypt, as well as shortening of the crypt that does not reach muscular mucous and lamina propria contains solid aggregate inflammation cells, dominated by plasma cells. The patient was given combination of 5-aminosalicylates and glucocorticoids. On re-evaluation in week 8 of therapy, frequency of defecation becomes 1-2 times daily with no blood occurring and improvement on colonoscopy, rectal mucous, colon sigmoid improved, no bleeding and clean mucous. 5-aminosalicylates is the first treatment in UC, it also helps to achieve remission and prevent carcinoma development. UC is a disease that also causes extra-intestinal manifestation, so the treatment should be done holistically. Compliance and regular monitoring will help to improve the quality of life.*

***Keywords:*** *Gastrointestinal, irritable bowel syndrome, ulcerative colitis*

## ABSTRAK

*Kolitis ulseratif didefinisikan sebagai inflamasi kronik yang terjadi berawal dari rectum mencapai kolon yang menyebabkan kerapuhan yang difus dan superfisial. Pada kasus ini, Wanita 44 tahun mengeluhkan diare berdarah dengan frekuensi 4-6x sehari dengan lendir, lemas dan riwayat penurunan berat badan. Pasien sudah mendapat sulfasalasin oral dan kortikosteroid oral sebagai terapi pencegahan kekambuhan, namun menghentikan pengobatan atas kemauannya sendiri. Pemeriksaan fisik menunjukkan konjungtiva mata anemis dan peningkatan bising usus, pada pemeriksaan feses lengkap didapatkan warna coklat kemerahan, konsistensi*

*bubur, ditemukan darah dan lendir dengan hasil benzidine tes positif. Pada pemeriksaan penunjang endoskopi ditemukan anus normal, rectum sigmoid, kolon descenden terdapat beberapa benjolan kecil-kecil, ulkus, beberapa segmen berdarah; pada pemeriksaan histopatologi ditemukan epitel permukaan dengan deplesi musin, distorsi arsitektur kripte berupa dilatasi kripte, elongated kripte, serta pemendekan kripte yang tidak mencapai muskularis mukosa, serta lamina propia mengandung agregat padat sel radang yang didominasi oleh sel plasma. Pasien diberikan terapi kombinasi 5-aminosalicylates dan glukokortikoid. Evaluasi paska 8 minggu terapi, frekuensi defekasi pasien berkurang menjadi 1-2kali/hari tanpa darah dan dari pemeriksaan kolonoskopi menunjukkan perbaikan; mukosa rectum, sigmoid berangsur mulai normal, tidak dijumpai perdarahan, mukosa bersih. 5-aminosalicylates merupakan terapi lini satu untuk UC, selain untuk mencapai remisi juga memiliki kemampuan untuk pencegahan terjadinya karsinoma. UC merupakan penyakit yang dapat menyebabkan gejala ekstraintestinal, sehingga tatalaksana harus dilakukan secara holistik. Kepatuhan minum obat dari evaluasi rutin dari kolon akan mempengaruhi peningkatkan kualitas hidup pasien.*

***Kata Kunci:*** *Saluran pencernaan, sindrom iritasi usus, kolitis ulserativa*

## INTRODUCTION

Inflammatory Bowel Disease (IBD) is an inflammation of the gastrointestinal tract that is repetitive in episodes and caused by abnormal immune response to gut microbiota. IBD has two forms, Crohn's Disease (CD) and Ulcerative Colitis (UC) that are differentiated by their location and depth of involvement in the bowel wall.[1] Ulcerative Colitis (UC), is an idiopathic inflammatory disease that starts from the rectum to the colon, that causes friability on the colonic wall and causing erosion-associated bleeding. A genetic factor is one of the risk factors that cause UC, 8-14% of patients had UC in their family history, and in first-degree relatives, the risk is higher to 4 fold. Other risk factors such as autoimmune, environmental factors, food and lifestyle, and gut microbiota.[1,2]

IBD is expected to occur because of the Westernized environment and lifestyle, with the highest incidence found in Northern Europe and North America. In the UK, UC incidence was reported at 126/100,000 person-years;[3] European population had a lower incidence of UC when compared with the second-generation South Asian (7 *vs* 17.2 per 100,000 population/year). Compared to CD, UC had a higher prevalence that appears in 2 incidence peaks, the age of 20-30 years and the second peak at 50-80 years old. [2,4]

The finding in UC is bloody diarrhea with or without mucous, tenesmus, defecation urgency dan abdominal pain, the pain can occur along the colon and may relieved by defecation. Other associated symptoms may weight loss, malaise, fever, and based on the severity of the disease.[5] In Diagnosing UC, endoscopic findings, biopsy, and histology need to be performed. [2] The severity of the disease, grade of inflammation, and mucous that is affected need to be assessed to give proper treatment based on the patient condition.[6] Although UC had a low rate of mortality, it affecting the quality of life of patients. [7]

## CASE ILLUSTRATION

Woman, 44 years old, was admitted to the hospital complaining of malaise and bloody diarrhea for a week, the patient was diagnosed with UC 2 years ago. The frequency of bloody diarrhea was 4-6 times daily, with mucous. The patient also complained of abdominal pain, and tenesmus and had weight loss. But for the last 2 weeks, didn't take any medication on the patient's will. She before had oral sulfasalazine and oral corticosteroid, but she stopped taking the medication at her will, because she already felt no bloody diarrhea and no abdominal pain. The patient denied having a history of another disease and has no history of the same complaint in her family.

On physical examination, the vital signs were within normal limits, with anemic conjunctiva +/+, and increasing of bowel sound. Lab examination reveals WBC 8,81 10^3/ul, Hb 10,9 g/dL, PLT 288 10^3/ul, HCT 33,7%, CRP<5, SGPT 10 U/L, SGOT 14 U/L, Ur 18 mg/dl, Cr 0.6mg/dL, Na 140 mmol/L, K 3.3 mmol/L, Cl 107 mmol/L. PT 10 s, INT 0,93 s, APTT 26,0 s. On fecal examination, in macroscopy, color: brown to red, porridge-like consistency, blood, and mucous were found; in microscopy: leucocyte 25-30/ field and erythrocyte 45-50/field and no parasite. The benzidine test was positive. The patient then undergoes a colonoscopy **(Figure 1A)** and histopathology examination **(Figures 2A and 2B)**, which suggests ulcerative colitis.

Based on anamnesis, physical examination, and supportive diagnosis, the patient is diagnosed with UC. The patient was given oral budesonide 3x3 mg dan oral mesalamine 3x500 mg, IV lansoprazole 2x30 mg, IV tranexamic acid 3x500 mg, oral methylprednisolone 2x8 mg, dan oral ciprofloxacin 2x200 mg. After 4 weeks, patient came to the clinic, and the frequency of diarrhea became 1-2 times daily, with no mucous and minimal blood seen. On the first 8 weeks of therapy, the patient had no complaint of bloody diarrhea, and feeling no malaise; an endoscopy was performed again **(Figure 2B)** and showed repairment.

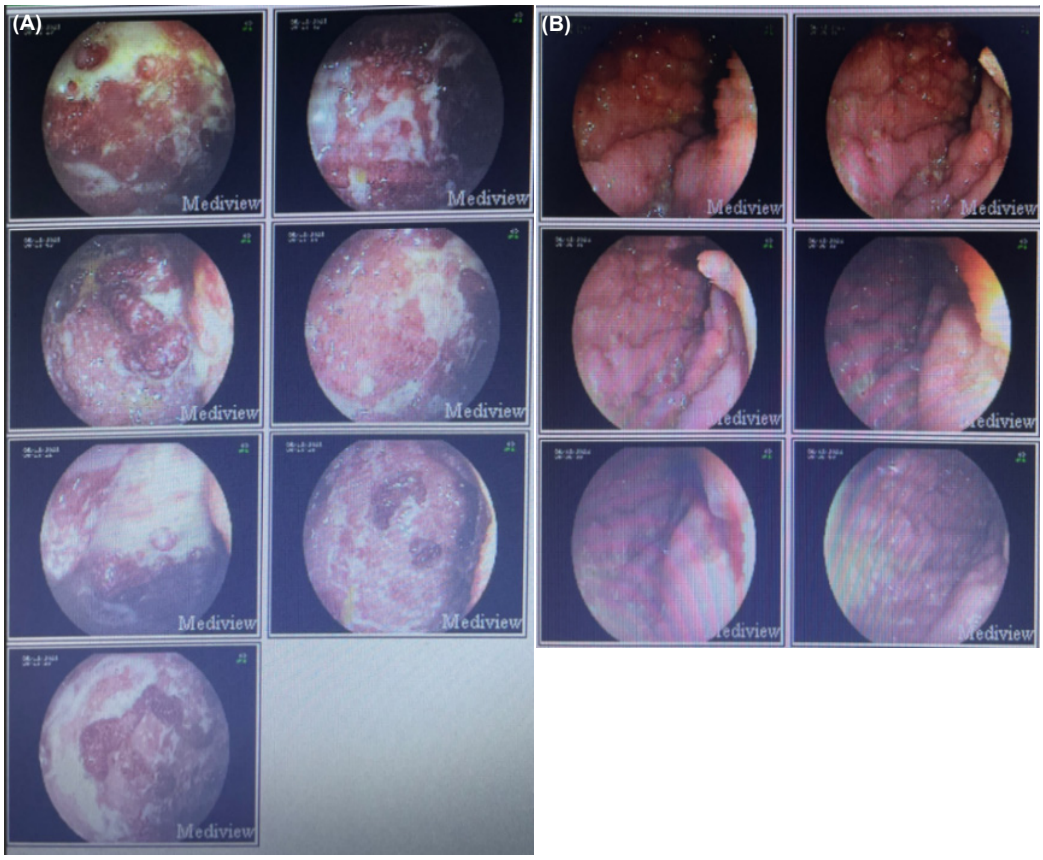


**Figure 1. Colonoscopy (A) anus normal; in the sigmoid rectum, the descendent colon found small swellings, ulcers, and few bloody. (B) Colonoscopy on week 8, showed improvement. Rectal mucous, colon sigmoid improved, no bleeding, and clean mucous**

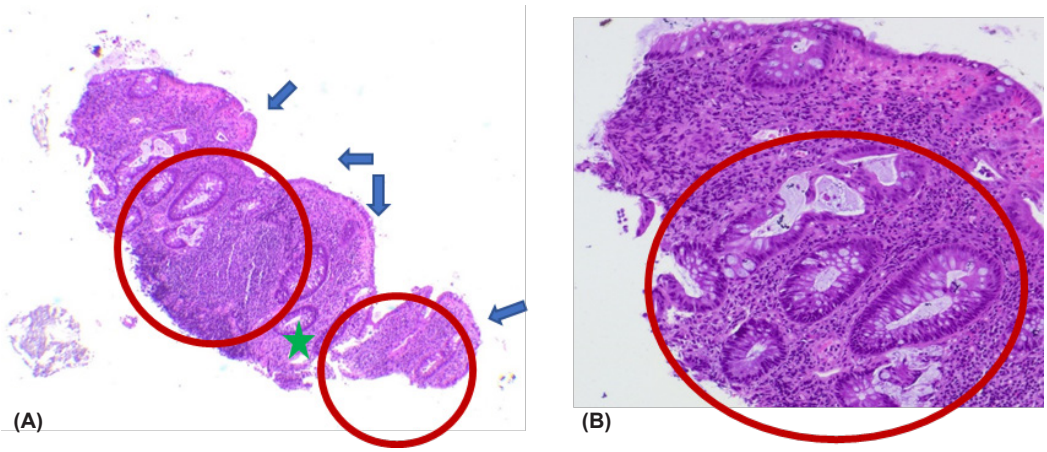


**Figure 2. Histopathology examination. (A) blue arrow, surface epithelial with mucin depletion, red circle, distortion of crypt architecture; green star, lamina propria contain solid aggregate inflammation cell, dominated by plasma cell. (B) distortion of crypt architecture, dilatation of crypt, elongated crypt, as well as shortening of the crypt that does not reach muscular mucous**

## DISCUSSION

UC is a chronic idiopathic inflammatory bowel disorder that starts from the rectum extending to the colon that occur chronically. UC finding is bloody diarrhea with or without mucous, Other associated symptoms may weight loss, malaise, fever and based on the severity of the disease. The symptoms may be relapsing and remitting. [2,6] In CD, the inflammation may extend to any part of the gastrointestinal tract, this is characterized as a "skipping lesion".

UC incidence has a higher rate in the industrial county, but in the last few years, there have been reported increasing incidents in Asian countries. Geographic variation has also been observed, with higher incidence reported in northern latitudes than in southern latitudes. Other studies have reported the risk of UC is more related to intake habits, lifestyle, and environmental influences than true genetics. [1,8] UC has a bimodal age distribution with an incidence peak at 20-30 years old and a second peak between 50-80 years old, with male predominance in UC. Genetics account for 8-14% of incidence. "western" style diet, increasing risk of developing IBD, immunologic response to food antigens expected to be the cause.[2]

The most frequent symptoms of UC is bloody diarrhea (>90%), combined with other symptoms like constipation, fecal urgency, abdominal pain, and tenesmus that may be along the entire length of the colon that is relieved by defecation. Other associated symptoms reported anemia, having >4 bowel movements daily, and weight loss of >5 kg in the past year (likelihood ratio 14.6).(2,5) On laboratory examination, leukocyte and CRP may be within normal limits, unless the inflammatory activity of UC is very intense. Fecal calprotectin may also be a marker of remission. Other laboratory results may reveal, iron deficiency anemia, thrombosis, hypoalbuminemia, positive antibody goblet cells, and anti-neutrophil cytoplasmic antibodies (ANCA).[2] UC also may affect, extra-intestinal involvement, pancreas, and hepatobiliary system are the two key areas. Prevalence of PSC and cholelithiasis also increasing the incidence of UC by 0.76%-5.4% and 4.6%-36.4%.[9] Other study also find higher incidence of hepatobiliary system in UC patient when compared to control group.[10]

Definitive diagnosis of UC is defined by ileocolonoscopy with biopsy, the finding is the inflammation is continuously affecting the colonic, characterized by redness, granularity, lower of normal vascular pattern , bleeding and ulceration that differentiated between normal and inflamed bowel. [8] To ensure the diagnosis, biopsies should be taken at least two samples from six different areas of colon; normal appearing mucosa also need to be examined, biopsies also help to assess the disease severity and finding cancer or dysplasia lesion; when Ileocolonoscopy can be used for monitoring disease. [11] in Histological examination, cellular infiltrate with plasma cells (basal plasmacytosis), in lamina propria there increased of lymphocytes , mucin depletion and Paneth cell metaplasia irregular mucosal surface, crypt architecture is distorded, shortened, and abscessed and also absence of genuine granuloma causing heavy diffuse transmucosal inflammation. [12] Other examination, such as Advanced endoscopic procedures, help in assessing submucosal vasculature. EGD can also performed when the patient had upper GI tract symptoms.[6,8]

Focus treatment in UC is aiming in improving the quality of life achieve steroid-free remission and decreasing the risk of cancer. In deciding treatment, data on disease severity and disease duration and extra-intestinal manifestation need to be assessed.. systemic therapy can be given, when the inflammation below splenic flexure in endoscopy. Assessment tool such as truelove and witts index is used to assess UC severity. Remission is reached when there is rectal bleeding, endoscopic healing and improvement in frequent of defecation. [2] Inpatients, who achieve endoscopic healing, will decrease their risk of undergoing colectomy limit corticosteroid use, and improve long-term clinical remission. [13]

First-line treatment in managing UC is sulfasalazine and 5-aminosalicylates (5-ASA), which have a remission rate of about 50%. In proctitis where the disease is isolated in the distal, topical application in the rectal mucosa is better when compared to oral regimen to achieve higher concentration. But, combination with systemic therapy can help to decrease tenesmus.[7,14]

Glucocorticoids therapy, can be given in patient who fail to get remission within to weeks, the use of glucocorticoid can be orally or rectally can be added; optimizing the oral 5-ASA dosing is also recommended. A higher dosage of 5-ASA (≥4g daily) has been recommended to achieve clinical remission;[2] Other management that also studied for UC is the use of probiotics to help remission, and transplantation of fecal microbiota in order to establish healthy gut microbiota. [7]

The use thiopurines or biological drugs in moderate to severe disease can be added, in Patients with refractory to glucocorticoids. Thiopurines are immunosuppressants such as azathioprine or 6-mercaptopurine; have a role in maintaining remission but not inducing remission. Thiopurine takes 2 to 12 weeks to achieve therapeutic effect, so prolonged use of corticosteroids needs to be started when taking it. [1,2,11] Biological drugs like anti-TNF-alpha, can both induction and maintenance of remission in UC. In severe cases that need hospitalization, one may consider using anti-NTF therapy without taking corticosteroids to induce remission; but in most cases, anti-TNF is used in conjunction with corticosteroids. For now, Infliximab, adalimumab, and golimumab are the 3 anti-TNF agents approved for UC and Infliximab is the most biological that is used for UC. Anti-adhesion molecule inhibitors, such as vedolizumab, work by blocking alpha-4-beta-7 integrin is the latest class of biological, such as vedolizumab. [15,16] Therapeutic response to anti-TND may take 3 days to 12 weeks to achieve initial response and mucosal healing.[1,16]

Surgical intervention is decreasing because of the advances in medical therapy, approximately 10% of UC patient require surgery in the first year of diagnosis, and up to 30% in their lifetime.[2] Proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the most common surgical technique used for improving patient quality of life. however, proctocolectomy with ileostomy is a choice in patients who cannot undergo IPAA.[2,6,12]

The prognosis is often generally good, and most patients go into remission in the first decade of diagnosis. An estimated 15% of IBD deaths are because of colorectal carcinoma, the risk factors for the development are duration of disease, extent of disease, simultaneous PSC, and history of colon cancer in the family. Endoscopy must be performed at regular intervals, risk of colon cancer become higher in UC, and all patients need maintenance therapy to prevent relapse.[2,17]

## CONCLUSION

Ulcerative colitis is a chronic inflammatory disease with no cure and it has several extra-intestinal involvement beside in colon. As medical treatments become more advanced, they enable the treatment aims not only to achieve symptomatic relief to endoscopic and histological healing but also to attain better long-term outcomes. Despite this improvement, a regular interval of monitoring needs to be performed; people with UC have a risk of colorectal cancer development, a regular colonoscopy should be performed every 1-2 years. Individualize each patient assessment and treatment plan is necessary to achieve remission and improve their quality of life.

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