The Impact of Chronic Inflammation in Ulcerative Colitis

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Contents

Risks Associated With Chronic Inflammation

Chronic Inflammation and Severe UC Complications

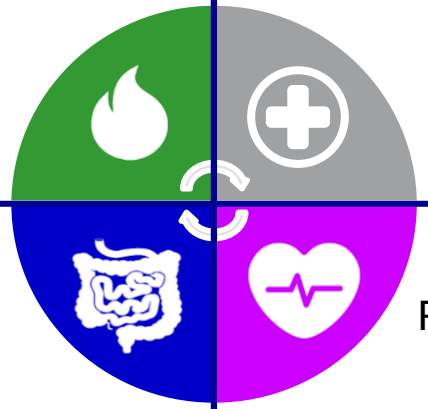
- UC is a chronic disease characterized by relapsing and remitting episodes of inflammation of the colonic mucosa[1]
  - Colonoscopy is used to assess extent, location, and severity of colonic inflammation[2]
  - Biomarkers (eg, CRP, albumin, fecal calprotectin) may be used to monitor inflammation[3,4]
- Chronic inflammation can lead to serious consequences, including increased risk of:

Hospitalizations due to severe, acute flare

Up to 25% of patients are hospitalized for severe UC[5]

Colectomy

Approximately 30% of patients require colectomy, which may be associated with morbidity and persistent quality-of-life issues[6,7]



Colorectal cancer

Risk is 2.4-fold greater in patients with UC[8]

Cardiovascular outcomes

Risk of thromboembolism, MI, stroke, and cardiovascular mortality is increased, especially during flares[9,10]

CRP=C-reactive protein; UC=ulcerative colitis.

1. Sedano R, et al. *Expert Rev Gastroenterol Hepatol.* 2019;13(10):943-955. **2.** Ordas I, et al. *Lancet*. 2012;380(9853):1606-1619. **3.** Darr U, Khan N. *Curr Treat Options Gastroenterol*. 2017;15(1):116-125. **4.** Ho GT, et al. *Am J Gastroenterol*. 2009;104(3):673-678. **5.** Pola S, et al. *Clin Gastroenterol Hepatol*. 2012;10(12):1315-1325. **6.** Hefti MM, et al. *Dis Colon Rectum*. 2009;52(2):193-197. **7.** Brown C, et al. Springerplus. 2015;4:573. **8.** Jess T, et al. *Clin Gastroenterol Hepatol*. 2012;10(6):639-645. **9.** Filimon AM, et al. *World J Gastroenterol*. 2015;21(33):9688-9692. **10.** Cheng K, et al. *World J Gastroenterol.* 2020;26(12):1231-1241

Inflammation and Flares

- UC is characterized by recurrent episodes of flare and remission[1]
- Flares can be accompanied by a rise in systemic markers of inflammation[2]
  - A case-control study (N=134) investigating factors that trigger flare in patients with IBD found that patients experiencing flare had significantly higher levels of CRP and ESR compared with patients in remission[1,a]

CRP and ESR in Patients With IBD[1,a]

Disease indices	Flares (n=66)	Remission (n=68)	*P* value
CRP, mg/dL (normal range 0-1.0)	3.48±5.5	1.19±1.7	0.0002
ESR, mm/h (normal range 0-30)	29.9±25.6	16.6±17.5	0.001

Note: This case-control study relied on medical records and/or patient-reported data and may be limited by recall or information bias.[1]

- Fecal calprotectin, a marker of intestinal inflammation, can also be predictive of flare[3]
  - In a cohort of 149 patients with IBD, it was found that the fecal calprotectin baseline levels were a strong independent predictor for disease flare (HR for 100µg/g: 1.75; 95% CI:1.28-2.39, *P*=0.001)[3]

Note: This retrospective study in patients with IBD had a small population, which did not allow for distinguishing between UC and CD in patients.[3]

[a]Patients with IBD were identified at the Dallas VA Medical Center; a total of 66 patients with flares of IBD (cases) were identified between 2009 and 2012. These cases were matched with 68 control individuals. This study was conducted in both UC and CD.

CI=confidence interval; CRP=C-reactive protein; CD=Crohn's disease; ESR=erythrocyte sedimentation rate; HR=hazard ratio; IBD=inflammatory bowel disease; UC=ulcerative colitis.

1. Feagins LA, et al. *World J Gastroenterol*. 2014;20(15):4329-4334. **2.** Peyrin-Biroulet L, et al. *Clin Gastroenterol Hepatol*. 2016;14(3):348-354. **3.** Kostas A, et al. *World J Gastroenterol.* 2017;23(41):7387-7396.

Flares and Hospitalizations

- Hospitalizations are a common consequence of flares[1]
- Approximately 20% of patients with UC will develop an episode of acute severe ulcerative colitis (ASUC), and 15%-25% will have a severe exacerbation requiring hospital admission at some point[2]
- The rate of colectomy after an ASUC episode (urgent or elective) has historically ranged 20% to 30%, with a mortality rate of 5% in those who required urgent procedure[2]
  - Rate of colectomy can be as high as 38.2% for patients who require multiple admissions[2]
  - A clinical evaluation should be done at admission to rule out complications and to assess disease severity[2]

Clinical Evaluation Following First ASUC[2]

Clinical evaluation
• Hemodynamics: temperature, blood pressure, heart rate, signs of dehydration
• Neurological examination
• Bowel movement: number, characteristics, presence and amount of blood in stool
• Risk factors: HIV, HBV or HCV, TB, previous use of antibiotics or hospitalizations (*C. diff*)
• Current and previous therapy for IBD
Laboratories
• Complete blood count
• Biomarkers of disease activity: CRP and fecal calprotectin
• Liver enzymes
• Albumin levels
• Anticipate eventual need for calcineurin inhibitors: magnesium and lipid profile
• Anticipate eventual need for TNFi therapy: quantiferon TB, varicella zoster titers, hepatitis serologies
Infection stool studies
• *Clostridium difficile*
• Stool culture – ideally multiplex GI pathogen PCR panel (Filmarray)
Imaging
• Chest X-ray
• Supine abdominal X-ray (to evaluate colonic dilation and megacolon)
Endoscopic evaluation
• Flexible sigmoidoscopy with no bowel lavage
• Obtaining biopsies for histologic analysis and to rule out cytomegalovirus

ASUC=acute severe ulcerative colitis; *C. diff*=*Clostridium difficile*; CRP=C-reactive protein; GI=gastrointestinal; HIV=human immunodeficiency virus; HBV=hepatitis B virus; HCV=hepatitis C virus; IBD=inflammatory bowel disease; PCR=polymerase chain reaction; TB=tuberculosis; TNFi=tumor necrosis factor inhibitor; UC=ulcerative colitis.

1. Feagins LA, et al. *World J Gastroenterol*. 2014;20(15):4329-4334. **2.** Sedano R, et al. *Expert Rev Gastroenterol Hepatol.* 2019;13(10):943-955

Inflammation and Risk of Colectomy

- Colectomy is often pursued when medical treatment fails to adequately control colonic inflammation in UC[1]
- Per the American College of Gastroenterology clinical guideline, elevated CRP and ESR are associated with higher rates of colectomy[2]

A Prospective Single-Center Cohort Study (N=90) Found That Selected Inflammatory Biomarkers Are Elevated in Patients With UC Who Undergo Colectomy[3,a]

	Colectomy	No colectomy	*P* value
CRP, mg/dL	53.0	32.0	0.029
ESR, mm/h	36.0	20.0	0.090

Note: This cohort study may be limited by patient selection bias. Larger prospective studies may be required to validate the results of this study.[3]

- Although colectomy can be lifesaving in UC, it has notable disadvantages[1]
  - Up to 46% of patients report detrimental effects on quality of life within 10 years of colectomy
  - Complications of colectomy include pouchitis, small bowel obstruction, fecal incontinence, sexual dysfunction, infections, and nerve damage[1,4,5]

[a]Patients undergoing colectomy were nonresponders to corticosteroids or infliximab therapy.
CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; UC=ulcerative colitis.

1. Brown C, et al. *Springerplus*. 2015;4:573. **2.** Rubin DT, et al. *Am J Gastroenterol*. 2019;114(3):384-413. **3.** Ho GT, et al. *Am J Gastroenterol*. 2009;104(3):673-678. **4.** De Silva S, et al. *Clin Gastroenterol Hepatol*. 2011;9(11):972-980. **5.** Parray FQ, et al. *Int J Prev Med.* 2012;3(11):749-763.

Chronic Inflammation and Risk of Colorectal Neoplasia (CRN)

Endoscopic and Histologic Inflammation Increases the Risk of CRN[a]

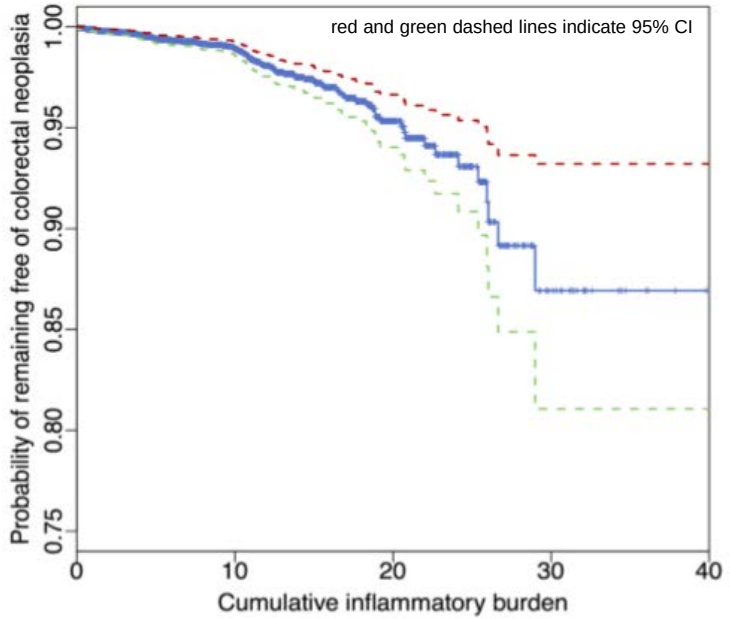
- A retrospective single-center study[b] found cumulative endoscopic inflammatory burden[c] to be strongly associated with CRN risk in patients with UC (N=987; *P*<0.001)[1]
  - There was a 2-fold increase in risk of CRN for approximately 10, 5, and 3.3 years of continuously mild, moderate, and severe active microscopic inflammation, respectively

Note: Limitations of this retrospective single-center study may include interobserver variability, as well as assumptions made in statistical analyses performed.[1]

- A US case-control study identified patients with UC-related CRN (N=59) and demonstrated an association between histologic inflammation and risk of CRN (OR: 2.56 per unit increase; 95% CI: 1.45-4.54)[2,d]
  - Prolonged inflammation, as opposed to a single severe episode, increased the risk of CRN

Note: This case-control study relied on medical records and may be limited by recall or information bias and/or patient selection bias.[2]

Cumulative Risk of CRN by Endoscopic Cumulative Inflammatory Burden[1]



[a]CRN is defined as development of high-risk low-grade dysplasia, high-grade dysplasia, or CRC. [b]Patients with extensive UC who were under colonoscopic surveillance between 2003 and 2012 were studied. [c]Cumulative inflammatory burden was calculated using endoscopic analyses and length of surveillance interval in years. Each 10 units of cumulative inflammatory burden is equivalent to 10, 5, and 3.3 years of continuous mild, moderate, and severe active inflammation, respectively. [d]Patients were identified from the IBD Endoscopy Database and IBD Registry, databases that include all patients with IBD seen at the University of Chicago; a total of 59 patients with CRN (cases) were identified between 1994 and 2005. These cases were matched with 141 control individuals.

CI=confidence interval; CRC=colorectal cancer; CRN=colorectal neoplasia; IBD=inflammatory bowel disease; OR=odds ratio; UC=ulcerative colitis.

1. Choi CR, et al. *Gut*. 2019;68(3):414-422. **2.** Rubin DT, et al. *Clin Gastroenterol Hepatol*. 2013;11(12):1601-1608.

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Inflammation and Risk of Colorectal Cancer

- Patients with IBD are at increased risk for CRC, associated with the pro-neoplastic effects of chronic intestinal inflammation[1]
- A 40-year UK prospective observational study in patients with UC (N=1375, PY=15,234) found an increased incidence rate of dysplasia and early CRC over time[2]
  - 37.5% of CRC cases were accompanied by synchronous CRC or spatially distinct dysplasia

    Note: This study was limited by the relatively small number of CRC cases. Additionally, it was conducted on a population at a tertiary referral center with more patients who had more severe or complex disease. Finally, this was an ex-US study, and therefore, results may not be directly applicable to the US patient population.
- Particular risk factors include extensive colonic disease, long disease duration, severity of colonic disease, and presence of PSC[3]
  - Elevated CRP or ESR has been reported to be associated with increased risk of CRC in patients with IBD[4]

Summary of Risk Factors for CRC in IBD[1]

Risk factor	Risk of CRC	Study design
Disease duration		
Annual incidence	0.06–0.20%	Meta-analyses
Cumulative incidence, 20 y	2.5–8.0%	Meta-analyses
Cumulative incidence, 30 y	7.5–18.0%	Meta-analyses
Extent of inflammation		
Pancolitis	SIR: 5.6–14.8	Meta-analyses
Left-sided colitis	SIR: 2.1–2.8	Meta-analyses
Primary sclerosing cholangitis	OR: 4.0	Meta-analyses
Pseudopolyposis	OR: 2.1–2.5	Case–controls
Family history of CRC	RR: 2.4–9.2	Case–controls

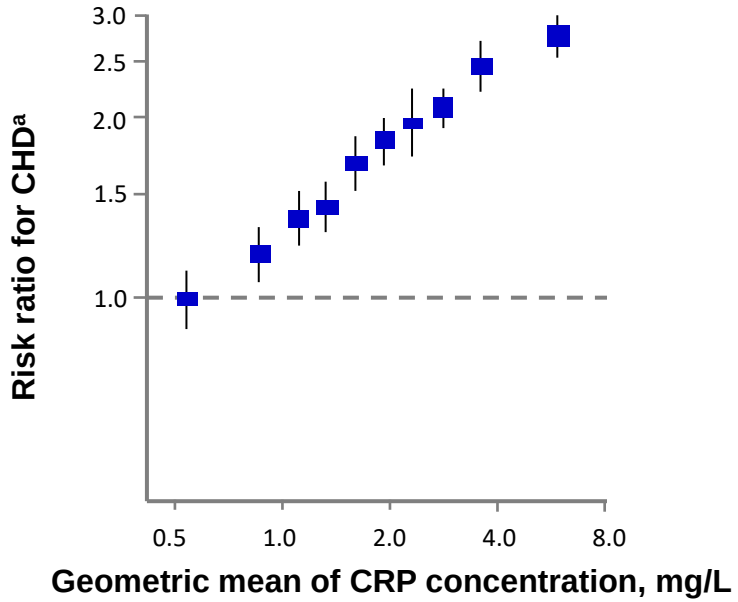
CRC=colorectal cancer; CRP=C-reactive-protein; ESR=erythrocyte sedimentation rate; IBD=inflammatory bowel disease; OR=odds ratio; PSC=primary sclerosing cholangitis; PY=patient-years; RR=risk ratio; SIR=standardized incidence ratio; UC=ulcerative colitis.

1. Stidham RW, Higgins PDR. *Clin Colon Rectal Surg*. 2018;31(3):168-178. **2.** Choi CH, et al. *Am J Gastroenterol*. 2015;110(7):1022-1034. **3.** Greuter T, et al. *Digestion*. 2020;101(Suppl 1):136-145. **4.** Ananthakrishnan AN, et al. *Clin Gastroenterol Hepatol*. 2014;12(8):1342-1348.

Inflammation and Risk of Cardiovascular Disease

- Inflammation may be the most important driver of cardiovascular complications in IBD[1]
- Risk of CVD is elevated in patients with IBD compared with the general population, especially during flares, when inflammation is at its peak[1,2]
- Inflammation (indicated by elevated CRP) is associated with increased cardiovascular events[3]
  - In patients with persistently high systemic inflammation, reduction in inflammation as indicated by CRP was associated with a reduction in cardiovascular events, including MI, stroke, and cardiovascular-related death at 5 years[4]

Results From a Meta-analysis of 48 Studies in Patients (N=10,341) Without History of Heart Disease[5]



Note: This meta-analysis integrated the results of multiple studies and may be limited by clinical and statistical heterogeneity of studies included, treatment of covariates that may impact the outcome of the study, and selection bias.[4]

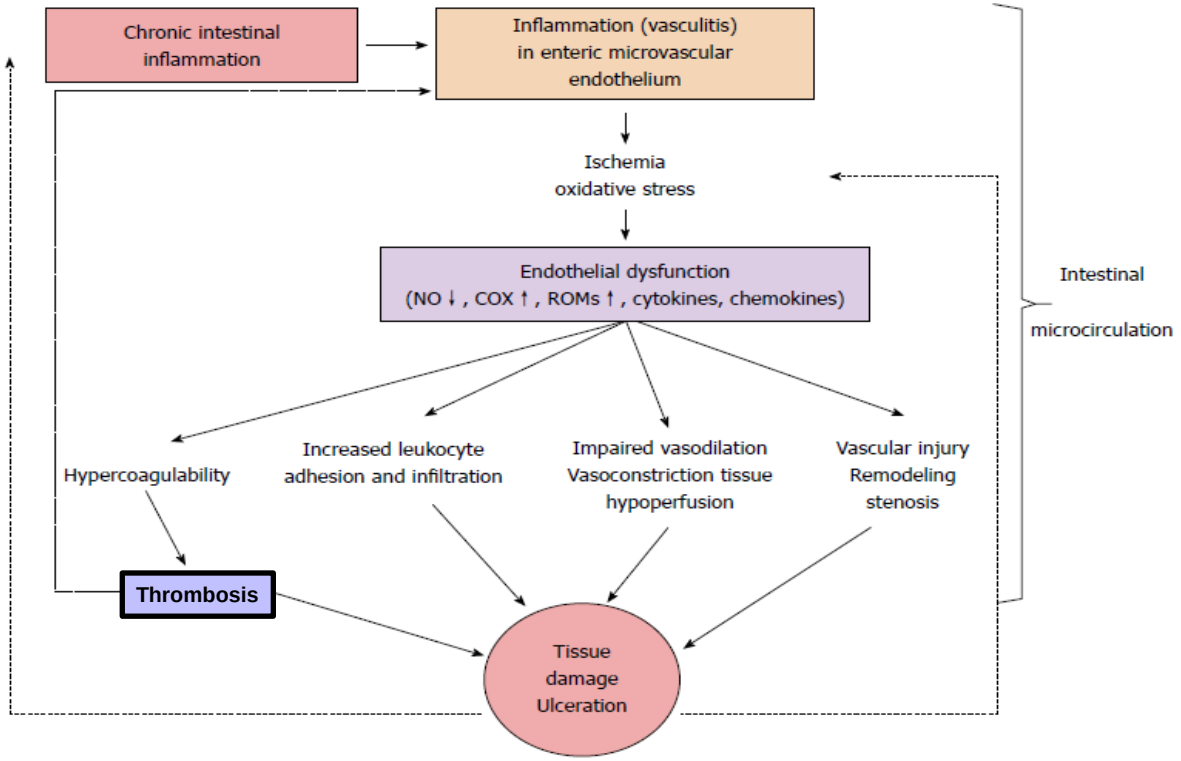
[a]Risk ratio adjusted for age and sex. Error bars indicate 95% confidence intervals.
CHD=coronary heart disease; CRP=C-reactive protein; CVD=cardiovascular disease; IBD=inflammatory bowel disease; MI=myocardial infarction.

1. Fumery M, et al. *J Crohns Colitis*. 2014;8(6):469-479. **2.** Filimon AM, et al. *World J Gastroenterol*. 2015;21:9688-9692. **3.** Ridker PM. *Circulation*. 2003;107(3):363-369.
4. Ridker PM, et al. *N Engl J Med*. 2017;377(12):1119-1131. **5.** Kaptoge S, et al. *Lancet*. 2010;375(9709):132-140.

Inflammation and Risk of Thrombosis

- The etiology of thrombosis in IBD is multifactorial[1]
- Patients with IBD have prothrombotic risk factors such as inflammation, fluid depletion, immobility, surgery, steroid therapy, and use of central venous catheters[1]
- The presence of active inflammation and more extensive IBD resulting in hospitalization has been shown to increase risk of VTE, a known complication of IBD associated with significant cost, morbidity, and mortality[2]

Proposed Mechanism of Inflammation and Thrombosis in UC[3]



COX=cyclooxygenase; IBD=inflammatory bowel disease; NO=nitric oxide; ROM=reactive oxygen metabolite; UC=ulcerative colitis; VTE=venous thromboembolism.

1. Danese S, et al. *Am J Gastroenterol*. 2007;102(1):174-186. **2.** Cheng K, et al. *World J Gastroenterol.* 2020;26(12):1231-1241. **3.** Zezos P, et al. *World J Gastroenterol*. 2014;20(38):13863-13878.

A Treat-to-Target Approach to Control Inflammation

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Measures for Defining Remission

- The treatment goal in UC has traditionally been defined as the normalization of clinical symptoms such as stool frequency and rectal bleeding[1]
- There has been a shift from subjective to objective measures for defining remission, including clinical examinations, endoscopy, and biomarkers[1,2]
  - Each has advantages and disadvantages in the clinical setting[1-5]
  - A combination of these methods is recommended to accurately monitor intestinal inflammation[1,2,4]

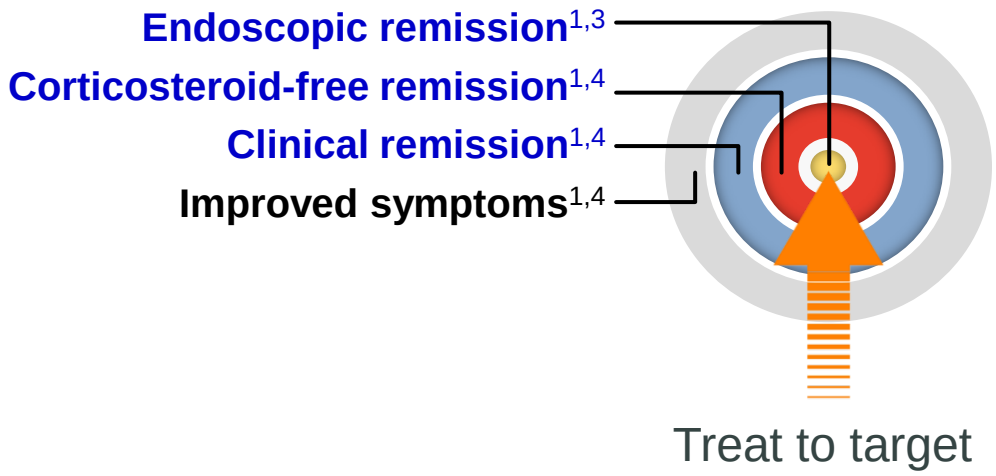
Objective parameters[1]	Clinical advantages	Clinical disadvantages
Endoscopic targets	• Most established therapeutic endpoint[2] • Can assess multiple aspects of disease activity (mucosal healing, eg, decreased bleeding, ulcerations, erosions, friability)[3,4]	• Invasive procedure[2]
Histologic targets	• Sensitive measure of inflammation; associated with hospitalization and neoplastic risk[1]	• No agreed-upon endpoint[2] • Relies on the quality of biopsies[5]
Noninvasive biomarkers (CRP, fecal calprotectin)	• Associated with endoscopic and histologic bowel inflammation[2]	• Lack of sensitivity and specificity for inflammation[2]

CRP=C-reactive protein; UC=ulcerative colitis.

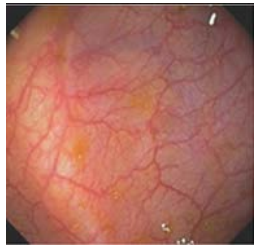
1. Peyrin-Biroulet L. *Am J Gastroenterol*. 2015;110(9):1324-1338. **2.** Darr U, Khan N. *Curr Treat Options Gastroenterol*. 2017;15(1):116-125. **3.** Ordas I, et al. *Lancet*. 2012;380(9853):1606-1619. **4.** Kim DB, et al. *Gastroenterol Res Pract.* 2016;2016:5832051. **5.** Bryant RV, et al. *J Crohns Colitis*. 2014;8(12):1582-1597.

The Treat-to-Target Approach

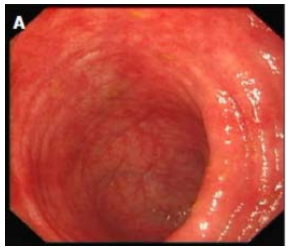
A "Treat-to-Target" Approach Using a Composite Remission Endpoint Has Been Proposed[1,2]



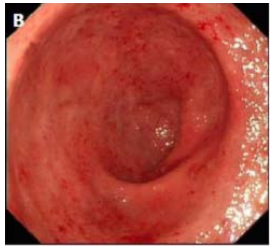
Mayo Endoscopic Subscore[5,6]



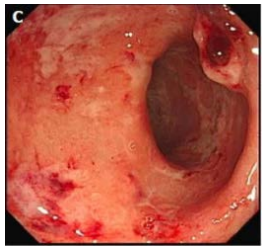
Subscore of 0: endoscopic remission



Subscore of 1: mild disease



Subscore of 2: moderate disease



Subscore of 3: severe disease

Objective measure of inflammation by endoscopic assessment is an important aspect of treat to target[1,2]

- Mayo endoscopic subscore of **0**: endoscopic remission[3]
- Mayo endoscopic subscore of **≤1**: improvement in endoscopic appearance of the mucosa[7]

1. Peyrin-Biroulet L, et al. *Am J Gastroenterol*. 2015;110(9):1324-1338. **2.** Darr U, *et al. Curr Treat Options Gastroenterol.* 2017;15:116-125. **3.** Ordas I, et al. *Lancet*. 2012;380(9853):1606-1619. **4.** Dubinsky MC. *Postgrad Med*. 2017;129(5):538-553. **5.** Moran CP, et al. *World J Gastrointest Endosc*. 2016;8(20):723-732. **6.** Pineton de Chambrun G, et al. *Nat Rev Gastroenterol Hepatol*. 2010;7(1):15-29. **7.** Sandborn WJ, et al. *N Engl J Med.* 2017;376(18):1723-1736.

Reduction in Inflammation and Improved Outcomes

- Reduced inflammation, as indicated by endoscopic assessment, is associated with improved clinical outcomes in patients with UC[1-3]
  - Decreased rate of relapse[1]
  - Decreased rate of hospitalization[1,2]
  - Decreased rate of surgery[1,2]
- In patients without IBD, reduction in systemic inflammation (as indicated by CRP) was associated with a reduction in cardiovascular events, including MI, stroke, and cardiovascular-related death at 5 years[4,a]
- Large-scale studies are scant, but evidence suggests that long-term reduction of inflammation leads to a decreased risk of CRC in patients with UC[5]

[a]In a randomized controlled trial of patients with a history of myocardial infarction with persistently high CRP levels (≥2 mg/L) despite use of secondary prevention strategies.
CRC=colorectal cancer; CRP=C-reactive protein; IBD=inflammatory bowel disease; MI=myocardial infarction; UC=ulcerative colitis.

1. Ardizzone S, et al. *Clin Gastroenterol Hepatol.* 2011;9(6):483-489. **2.** Ordas I, et al. *Lancet*. 2012;380(9853):1606-1619. **3.** Rutgeerts P, et al. *N Engl J Med*. 2005;353:2462-2467.
4. Ridker PM, et al. *N Engl J Med*. 2017;377(12):1119-1131. **5.** Neurath MF, Travis SP. *Gut.* 2012;61(11):1619-1635.

Reduction in Inflammation and Long-lasting Response

Single-Center Cohort Study of Clinical Outcomes Stratified by Quality of Early Response to Therapy[a] (1981-2006; N=157)

Selected Clinical Outcomes at 5 Years	Clinical Outcome in Patients, n (%), Stratified By Quality of Response to Therapy[a]			
	No response Persistence of intestinal symptoms and endoscopic lesions	**Partial response** Only clinical remission (no endoscopic remission)	**Complete response** Both clinical and endoscopic remission	***P* value**
General relapse	58 (100.0%)	36 (92.3%)	50 (83.3%)	0.0019
Systemic relapse	53 (91.3%)	28 (71.8%)	33 (55.0%)	<0.0001
Hospitalization	37 (63.8%)	19 (48.7%)	15 (25.0%)	0.0001
Use of immunosuppressors	31 (53.5%)	10 (25.6%)	3 (5.0%)	<0.0001
Colectomy	10 (17.2%)	7 (18.0%)	2 (3.3%)	0.0191

- After 3 months of standard therapy with corticosteroids, patients with UC who achieved complete response (both clinical and endoscopic remission) had decreased rates of systemic relapse, hospitalization, use of immunosuppressive therapies, and colectomy at 5 years compared with patients with no or partial response to therapy

Note: This cohort study may be limited by patient selection bias. Randomized controlled trials may be required to further validate the results of this study.

[a]Early outcome was assessed at the end of a standardized course of corticosteroids (3 months). UC=ulcerative colitis.

Ardizzone S, et al. *Clin Gastroenterol Hepatol.* 2011;9(6):483-489.

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Summary

Overall Summary

Chronic intestinal inflammation underlies UC pathogenesis

- Inflammation of the intestinal mucosa is an important measure of disease severity

Chronic inflammation in UC is associated with increased risks

- Increased risks include flares, hospitalizations, colectomy, CRC, and cardiovascular outcomes

The treat-to-target approach should include objective measures to monitor inflammation

- Objective measures include noninvasive biomarkers and endoscopic assessment

Prompt treatment of intestinal inflammation may help prevent the potential complications associated with UC

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CRC=colorectal cancer; UC=ulcerative colitis.

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