

A Comprehensive Review on Ulcerative Colitis

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ABSTRACT

Ulcerative colitis (UC) is a refractory, chronic, and nonspecific disease occurred usually in the rectum and the entire colon. Ulcerative colitis always involves the rectum (i.e., proctitis), and it may extend proximally in a contiguous pattern to involve the sigmoid colon (i.e., proctosigmoiditis), the descending colon (i.e., left-sided colitis), or the entire colon (i.e., pancolitis). The etiopathology is probably related to dysregulation of the mucosal immune response toward the resident bacterial flora together with genetic and environmental factors. In Western Europe and in the USA, UC has an incidence of approximately 6 to 8 cases per 100.000 populations and an estimated prevalence of approximately 70 to 150 per 100.000 populations. The leading initial symptom of UC is diarrhea with blood and mucus, sometimes with pain. Fever and weight loss are less frequent. Treatment is based on the extent and severity of the disease. Rectal therapy with 5-aminosalicylic acid compounds is used for proctitis. More extensive disease requires treatment with oral 5-aminosalicylic acid compounds and oral corticosteroids. Herbal medicine includes a wide range of practices and therapies outside the realms of conventional Western medicine. However, there are limited controlled evidences indicating the efficacy of traditional Chinese medicines. The given epidemiology, pathogenesis and treatment are easily understandable to get a clear picture. Yet, precise studies has to be done to uncover the most opt recipe for the management of ulcerative colitis.

Keywords: ulcerative colitis, pathogenesis, therapy, herbal medicines.

INTRODUCTION

Ulcerative colitis, also known as chronic ulceration of the intestines characterized by diffuse mucosal inflammation limited to colon¹. Intermittent exacerbations are typical, with symptoms characterized by bloody diarrhea associated with urgency and tenesmus². Various factors contribute to the disease's clinical manifestations, including psychiatric and physical components, but the etiology of the disease remains poorly understood³⁻⁵. The clinical presentation of UC is characterised by abdominal pain, diarrhoea with or without hematochezia, and mucosa ulcerations⁶. The etiology of colitis is multifaceted. Prostaglandins are dramatically increased in the mucosa, serum and stools of the patients. Research indicates that an imbalance of the gastrointestinal (GI) mucosal immune system of colitis patients causes an overproduction of inflammatory cytokines and leukocytes into the colon⁷. Patients with ulcerative colitis display defects in the intestinal epithelial barrier function⁸. The interaction of food and the GI mucosal immune system is an important factor in intestinal inflammation. Patients with UC demonstrate increased mucosal eosinophils and IgE in relation to certain foods^{9,10}.

Although there has been much research, the cause of UC is still uncertain. Currently, the most widely accepted hypothesis implicates a combination of the following factors: immune deregulation (caused by genetic or environmental factors), abnormal gastrointestinal (GI) tract luminal factors, (such as microorganisms constituting the GI tract flora, oxidative stress, and tumour necrosis factor (TNF) -alpha) and defects in the GI mucosal barrier that allow luminal factors to penetrate into the mucosa^{11,12}. The genes a person has inherited and an abnormal reaction of the immune system to certain bacteria in the intestines, triggered by something in the environment. The immune system is the body's protection system against harmful substances. So it could be that something in the environment may stimulate the body's defences to produce inflammation that continues without control: once the immune system of someone with UC is 'switched on' it does not know how to 'switch off' properly at the right time. Viruses, bacteria, the use of antibiotics, diet and stress have all been suggested as environmental triggers, but there is no definite evidence that any one of these is the cause of UC¹³.

EPIDEMIOLOGY

Ulcerative colitis affects approximately 250,000 to 500,000 persons in the United States, with an annual incidence of two to seven per 100,000 persons¹⁴. The overall incidence of the disease has remained constant over the past five decades¹⁵. Although the condition most commonly affects people between the ages of 10 - 20, with a smaller peak at 50 - 80 years of age, infants and children may also develop the disease¹⁶. Ulcerative colitis occurs 5 times more frequently in those with a Jewish heritage than it does in the general population. There is no cure for ulcerative colitis, but diet and medications can help control the disease¹⁷. The disease occurs more frequently in non-smokers than smokers however, compared with those who have never smoked, former smokers are approximately 1.7 times more likely to develop the disease.¹⁸

CLASSIFICATION

The Montreal classification¹⁹ has categorised the extent of UC into three subgroups:

- Ulcerative proctitis: involvement limited to the rectum (50 per cent at presentation).
- Left-sided UC (distal UC): involvement limited to a proportion of the colorectum distal to the splenic flexure (30 per cent at presentation).
- Extensive UC (pancolitis): involvement extends proximal to the splenic flexure (20 per cent at presentation).

The same group also proposed a classification system for the severity of UC:

- Clinical remission (S0): asymptomatic.
- Mild UC (S1): ≤four bowel movements daily, absence of any systemic illness and normal inflammatory markers (ESR).
- Moderate UC (S2): >four bowel movements daily but with minimal signs of systemic toxicity.
- Severe UC (S3): passage of ≥six bloody stools per day, pulse rate ≥90bpm, temperature ≥37.5 degrees, haemoglobin <10.5g/dl and ESR ≥30mm/h.

PATHOGENESIS

While the cause of UC remains unknown, a number of findings in recent years point to an over stimulation or inadequate regulation of the mucosal immune system as a major pathophysiologic pathway, and particular emphasis has been given to either the study of mucosal inflammation or immunologic reactions.

When the disease is active, the lamina propria of the mucosa becomes heavily infiltrated with a mixture of acute and chronic inflammatory cells. There is a predominant increase in mucosal IgG production, evidence of complement activation, and activation of macrophages and T cells. This immunological activity is associated with the release of a vast array of cytokines, kinins, leukotrienes, platelet activating factor (PAF) and reactive oxygen metabolites. These mediators not only serve to amplify the immune and inflammatory response, but they also have direct effects on epithelial function, on endothelial function (which may increase permeability and lead to ischaemia), and on repair mechanisms, thus increasing collagen synthesis. In addition, many of the cytokines (interleukins 1 and 6, tumor necrosis factor) will activate an acute phase response, resulting in fever and a rise in serum acute phase proteins. Some of the clinical features of acute ulcerative colitis may explain by these mechanisms. It follows, therefore, that any treatment which is able to inhibit the activation of these immunological and inflammatory effector mechanisms is likely to lead to an improvement in the patient's symptoms and to a decrease in the inflammatory activity.^{20,21}

SYMPTOMS AND DIAGNOSIS

Ulcerative colitis symptoms can vary, depending on the severity of inflammation and which parts of the colon are inflamed. Symptoms range from painless bleeding with bowel movements to frequent bloody diarrhea. Painful abdominal cramping, an inability to have a bowel movement in spite of the urge to do so, unintended weight loss and fatigue may also be experienced. Typically, people with ulcerative colitis experience periods of exacerbated symptoms alternating with periods with very few symptoms (remission)²². General physical findings are unspecific and directly related to the duration and presentation of the disease. Anorexia, weight loss, growth retardation, anaemia, general debility, abdominal pain, and fever are associated with a long-standing or fulminant course of the disease²³.

People with ulcerative colitis are at increased risk for malnutrition. The condition is also associated with other health problems, including arthritis, eye infections, liver disease, skin rashes, blood clots, or gallstones. No one is sure why such problems occur outside the colon. But some researchers think they may be linked to a faulty immune system response. The diagnosis of UC is made on clinical suspicion and confirmed by biopsy,

stool examinations, sigmoidoscopy or colonoscopy, or barium radiographic examination. The presence of extracolonic manifestations such as arthritis, and uveitis may also aid in establishing the diagnosis²⁴.

TREATMENT

Three main types of drugs are most commonly used to treat UC: aminosalicylates, corticosteroids (steroids) and immunosuppressants. Aminosalicylates are

the first treatment option for mild to moderate UC. If the condition is more severe or is not responding to aminosalicylates, then steroids may be used. If the condition is still not responding to treatment or if you wish to stop steroids because of side effects, you may be offered immunosuppressants. Occasionally, a fourth type of drug – biologics – is used for severe cases of UC. These are also known as Anti-TNF (Tumour Necrosis Factor) drugs²⁵.

The following table gives you details of the various types of drugs used to reduce inflammation²⁶

Drug	What they do	Possible side-effects
Aminosalicylates (5-ASAs) Aminosalicylates (5-ASAs) sulphasalazine (Salazopyrin) mesalazine (Asacol, Ipcol, Mesren, Mezavant XL, Pentasa, Salofalk) olsalazine (Dipentum) balsalazide (Colazide)	<ul style="list-style-type: none"> Reduce inflammation and maintain remission Do not have the side effects of corticosteroids, and therefore can be used for longer periods of time Continued use may help to protect against bowel cancer 	<ul style="list-style-type: none"> Headaches and skin rash Indigestion, nausea and diarrhoea Sulphasalazine may temporarily reduce fertility in men; colour urine orange; stain soft contact lenses.
Corticosteroids (steroids) hydrocortisone prednisolone budesonide (Budenofalk, Entocort) beclometasone dipropionate (BDP) (Clipper)	<ul style="list-style-type: none"> Reduce inflammation which stops pain, reduce diarrhoea and restore appetite May also help mineral (sodium) and water uptake Also reduce inflammation of eyes and joints (Except Entocort and BDP) 	<ul style="list-style-type: none"> Weight gain 'Mooning' of face Growth of facial hair and acne Increase in blood pressure Thinning of bones, muscle & skin Increase in sugar levels in blood, occasionally diabetes
<p><i>The adrenal glands may become suppressed by long-term use of steroids. This reduces the body's ability to cope with stress caused by an operation or accident. It is important to wear or carry a steroid bracelet or card, so that doctors can give you extra steroids if needed. These are not anabolic steroids used by bodybuilders.</i></p>		

Drug	What they do	Possible side-effects
Immunosuppressants azathioprine (Imuran) 6-mercaptopurine (6-MP)(Purinethol)	<ul style="list-style-type: none"> Suppress inflammation over longer periods of time 	<ul style="list-style-type: none"> Can reduce the number of red and white blood cells, so regular blood check ups are necessary Nausea, a flu-like illness, diarrhoea, abdominal pain and inflammation of the pancreas Increases skin's sensitivity to sun light Diarrhoea, nausea, headache, Difficulty sleeping, tingling of hands or feet, increased blood pressure
ciclosporin	<ul style="list-style-type: none"> Used intravenously in acute attacks 	<ul style="list-style-type: none"> A range including nausea, headache, swollen gums, growth of facial hair, increased blood pressure
Biologics Anti-TNF infliximab (Remicade)	<ul style="list-style-type: none"> Blocks an inflammatory agent in the blood – TNF-alpha – believed to cause chronic inflammation 	<ul style="list-style-type: none"> Nausea Headache Reaction to infusion Make infections worse

The following table describes drugs that may help to relieve symptoms^{27,28}

Drug	What they do	Possible side-effects
Antidiarrhoeals codeine phosphate diphenoxylate (Lomotil) loperamide (Imodium, Arret)	<ul style="list-style-type: none"> Reduce the contractions in the bowel, therefore reducing the number of stools Absorb excess water from the bowel 	<ul style="list-style-type: none"> Constipation Nausea/indigestion Codeine can cause drowsiness, also drug dependence if taken over a prolonged period
<i>If you are having an acute or severe flare up, it is best to check with your doctor before taking antidiarrhoeal drugs, as they can make your UC worse.</i>		
Analgesics (Pain killers) paracetamol	<ul style="list-style-type: none"> Relieve pain 	<ul style="list-style-type: none"> Constipation Dizziness Rashes
<i>Paracetamol is commonly used in people with UC, though some evidence suggests its use may precede a relapse. It may be better to avoid non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and diclofenac. Although they can be very effective for pain in the joints and spine, they can make UC symptoms worse or possibly trigger a flare up. Severe arthritis in IBD can be treated with a special type of anti-inflammatory called a cox-2 inhibitor. It is best to discuss this with your doctor.</i>		
Anaemia treatments Supplements of iron, folic acid and Vitamin B12	<ul style="list-style-type: none"> Enable body to rebuild the red blood cells lost during bleeding or damaged as a side effect of another drug 	<ul style="list-style-type: none"> Constipation Dizziness Rashes
Laxatives: osmotic (Movicol)	<ul style="list-style-type: none"> Softens stool by increasing the amount of water in the large bowel Considered safer than other laxatives, being slow acting and not absorbed into body 	<ul style="list-style-type: none"> Constipation Dizziness Rashes
bulking agent (Fybogel)	<ul style="list-style-type: none"> Contains husks that absorb water to bulk stools 	

Herbal medicine

Herbal medicine is one of the most common TCM (traditional Chinese medicine therapies) modalities. It has been estimated that 28.9% of US adults regularly use one or more TCM, 9.6%–12.1% of which are in the form of herbal products.²⁹

Aloe vera

A double-blind, randomized trial was undertaken to examine the effectiveness and safety of *aloe vera* gel for the treatment of mild-to-moderate active UC. Thirty patients took 100 mL of oral *aloe vera* gel and 14 patients had 100 mL of a placebo twice daily for 4 weeks. Clinical remission, improvement, and response occurred in 9 (30%), 11 (37%), and 14 (47%), respectively, in aloe vera-treated patients compared with 1 (7%), 1 (7%), and 2 (14%), respectively, in controls.³⁰

Boswellia serrata

Gupta *et al* studied the treatment of 30 patients with chronic UC, and gave 20 patients a *Boswellia* gum preparation (900 mg daily divided into 3 doses for 6 weeks), and 10 patients sulfasalazine (3 gm daily divided into 3 doses for 6 weeks). They concluded that

Boswellia was an effective treatment with few side effects, because 14 out of the 20 patients treated went into remission, and furthermore, 18 out of the 20 patients found an improvement in one or more parameters. In comparison, in the group taking sulfasalazine, 4 out of 10 went into remission, and 6 out of 10 showed improvement in one or more of the above parameters³¹

Licorice

Evidence has also reported that diammonium glycyrrhizinate could improve intestinal mucosal inflammation in rats and, importantly, reduce expression of NF- κ B, TNF- α , and ICAM-1 in inflamed mucosa. Clinical studies on licorice have also been performed in combination with other herbs and demonstrated to be effective in the management of UC³²

Slippery elm (*Ulmus fulva*)

A study has confirmed the antioxidant effects of slippery elm when used in patients with IBD. The research so far has been promising, but there is not enough to warrant the widespread use of slippery elm in the treatment of IBD³³

Tormentil extracts

Sixteen patients with active UC (clinical activity index ≥ 5) received *tormentil* extracts in escalating doses of 1200, 1800, 2400, and 3000 mg/day for 3 weeks each. Each treatment phase was followed by a 4-week washout phase. The outcome parameters were side effects, clinical activity index, C-reactive protein, and tannin levels in patient sera. Mild upper abdominal discomfort was experienced by 6 patients (38%), but did not require discontinuation of the medication. During therapy with 2400 mg of *tormentil* extracts per day, median clinical activity index, and C-reactive protein improved from 8 (6 to 10.75) and 8 (3 to 17.75) mg/L at baseline to 4.5 (1.75 to 6) and 3 (3 to 6) mg/L, respectively. During therapy, the clinical activity index decreased in all patients, whereas it increased during the washout phase³⁴.

CONCLUSIONS

Ulcerative colitis is a chronic inflammatory condition of the colon that does not shorten a patient's life span but can cause significant morbidity and lead to considerable expense. Before establishing the diagnosis of ulcerative colitis, a physician must carefully consider other inflammatory intestinal processes that resemble the disease. The primary goal in treating ulcerative colitis is to control acute flares of the disease and to maintain remission. The type of treatment often depends on how severe the disease is. For example, people with mild to moderate ulcerative colitis are usually treated with medications that reduce inflammation and suppress the immune system. More severe cases may require surgery.

There is no known way to prevent ulcerative colitis, but it is usually possible to manage the condition with a combination of medication, diet, and lifestyle changes. Preliminary studies indicate that the use of complementary and alternative remedies, lifestyle changes, including stress reduction; dietary adjustments (such as eating a variety of fruits and vegetables and avoiding saturated fat and sugar); specific herbs and supplements; and mind body techniques (such as hypnosis) may be useful additions to treatment and thus possible to prevent the recurrence of the disease.

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