Medical management of ulcerative colitis

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Patients with ulcerative colitis have no increased mortality compared to population controls and the disease can be cured be colectomy. This review concentrates on the medical management of ulcerative colitis including the management of active colitis, acute severe colitis and first presentation of colitis, maintenance of remission and long-term complications.

Ulcerative colitis (UC) affects about 0.1% of the population with an incidence of about 10–20/100 000/year. The incidence of UC is stable unlike that of Crohn's disease which is increasing. UC is a chronic, idiopathic relapsing-remitting inflammatory disorder of colonic mucosa. Inflammation involves the rectum, is generally continuous and extends proximally for a variable extent. The predominant symptoms of UC are diarrhoea and rectal blood loss. With left-sided disease or proctitis (rectal inflammation) the predominant symptom is blood or mucus per rectum with infrequent or formed stool; with more extensive disease the predominant symptom is bloody diarrhoea.

There is a strong negative association between UC and smoking and an even stronger negative association between appendicectomy and UC. The extent of disease varies with time and in 50% of patients the extent changes, either increasing or decreasing (Moum et al, 1999). Most patients show few clinical signs except during a severe exacerbation when they may be systemically unwell. Extraintestinal manifestations of UC occur in 10–20% of patients, some of which relate to disease activity: these include skin lesions (erythema nodosum, pyoderma gangrenosa), arthralgia, iritis, sacroiliitis and liver disease (sclerosing cholangitis). Endoscopically there may be diffuse mucosal changes with loss of the normal vascular pattern, increased erythema and granularity, ulceration, and spontaneous or contact bleeding (*Figure 1*). Characteristic histological changes include a chronic inflammatory cell infiltrate, distorted glandular architecture, crypt abscesses and goblet cell depletion (*Figure 2*).

TREATING AN ACUTE EXACERBATION

Treatment options are shown in *Table 1* based on disease extent and severity. There are no clinically useful disease activity scores available, although the most widely used is the Truelove–Witts scale (*Table 2*) (Truelove and Witts, 1955). Clinical assessment consists of investigating whether disease is left-sided or extensive and severity based on stool frequency, presence of blood and endoscopic appearances (usually by unprepared rigid sigmoidoscopy).

Oral aminosalicylates

Oral 5-aminosalicylates (5-ASA) are the mainstay of therapy for mild disease. Sulphasalazine 2–6 g/day can achieve remission rates of up to 80% in mild disease. However, side effects occur in about 30%, particularly at higher doses, includ-

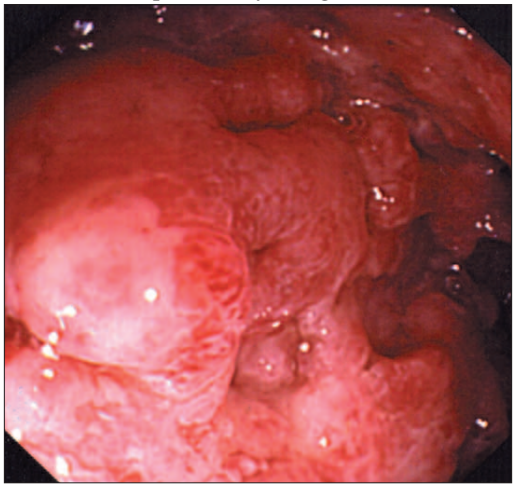

Figure 1. Endoscopic appearance of severely active ulcerative colitis with marked oedema, confluent erythema and extensive ulceration.

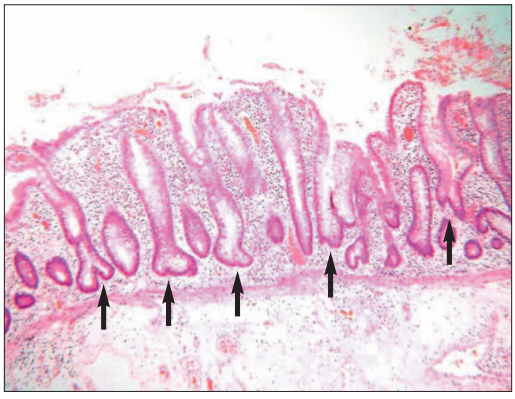

Figure 2. Histology of ulcerative colitis: low power view. There is crypt architectural distortion with shortened and branching crypts (black arrows) together with a transmucosal inflammatory infiltrate and depletion of goblet cells.

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ing headache, nausea, vomiting, haemolytic anaemia, bone marrow suppression and infertility in men. Meta-analysis is particularly difficult in UC because of the lack of standardized scoring systems, but the newer 5-ASAs (mesalazine, olsalazine, balsalazide) are better tolerated at higher doses than sulphasalazine. Remission or improvement rates are comparable to sulphasalazine at doses of 2–4.8 g/day but at a higher relative cost (Sutherland and MacDonald, 2003).

Topical 5-ASAs as foam or liquid enemas (or suppositories for rectal disease) are the most effective therapy for active distal UC: 10–20% better than steroid enemas. Meta-analyses show remission in symptoms (52%), endoscopic appearance (41%) and histology (32%) (Cohen et al, 2000). The optimum dose is 1 g/day, usually only needed once a day. Combined oral and per rectum 5-ASA seems to be better at inducing earlier and complete remission than either therapy alone (Safdi et al, 1997). The effect of combination treatment is greater than that expected from merely the increased total dose of 5-ASA (Cohen et al, 2000). Generally, if left-sided disease of mild to moderate severity is not responding to oral 5-ASA then rectal 5-ASA should be started. If the disease remains mild to moderately active rectal steroids can be tried, although there is no strong evidence to support this.

TABLE 1.
Treatment options in acute disease depending on severity and extent

	Oral 5-ASA	Topical 5-ASA/ steroids	Oral steroids	IV steroids
Mild distal	√	√	x	x
Mild extensive	√	x	x	x
Moderate distal	√	√	√	x
Moderate extensive	√	x	√	x
Severe distal	√	√	√	√
Severe extensive	?√	x	√	√

5-ASA= 5-aminosalicylates; IV= intravenous

TABLE 2.
Truelove–Witts ulcerative colitis severity scale

	Stool frequency	Rectal bleeding	Temperature (°C)	Pulse rate/min	Haemoglobin (g/dl)	ESR (mm/hr)
Mild	< 4	Small	<37.2	Normal	Normal	<20
Moderate	4–6	Moderate	37.2–37.8	Intermediate	Intermediate	20–30
Severe	>6	Large	>37.8	>90	<10.5	>30

ESR= erythrocyte sedimentation rate

TABLE 3.
Acute exacerbation: suggested steroid regimen

Week 0–2	Prednisolone 40 mg/day + calcium and vitamin D
Week 2–4	Prednisolone 30 mg/day + calcium and vitamin D
Week 4–8	Prednisolone 20 mg/day then reduce by 5 mg every 5–7 days and continue calcium and vitamin D until stopped prednisolone

Oral steroids

For patients with mild to moderately active disease not responding to oral 5-ASA and not responding to topical 5-ASA or steroid enemas, oral corticosteroids are indicated. Groundbreaking trials in the 1950s and 60s showed remission rates of 50–65% and remission or improvement rates up to 95% (Truelove and Witts, 1955; Baron et al, 1962). Optimum dosage and administration regimens for prednisolone are not well defined but the plateau of effect is between 25 and 60 mg of prednisolone and there are more side effects on 60 mg than 40 mg. Therapy needs to last for more than 1 month, with a high dose for 1 month then a tapering dose in the second month. A practical regimen is shown in *Table 3*. The decision to start oral corticosteroids must be balanced against potential side effects, in particular the long-term increased risk of osteoporosis (see below). Calcium and vitamin D should be administered concurrently throughout oral steroid therapy.

MANAGEMENT OF ACUTE SEVERE UC

About 15% of UC patients have a severe episode of colitis, defined by Truelove–Witts, and should be managed as an inpatient. There are few randomized controlled trials (RCTs) in severe colitis and evidence is generally 'expert opinion' based. Clinical examination is important and localized tenderness is an ominous sign of possible perforation. Plain abdominal X-rays are important to estimate the extent of disease and exclude toxic megacolon (non-obstructive large bowel dilatation >5.5 cm associated with systemic toxicity).

Stool samples should be examined for superadded infective diarrhoea and are positive in about 20% of cases, particularly *Clostridium difficile* toxin diarrhoea. Patients should receive intravenous (IV) fluid and electrolyte replacement, high calorie low fibre oral nutrition and prophylactic low molecular weight heparin, as there is a moderate risk of thromboembolic disease. Treatment that can exacerbate colitis such as non-steroidal anti-inflammatory drugs (NSAIDs) and loperamide should be discontinued, as should oral 5-ASA which can worsen diarrhoea and has no evidence of a beneficial effect in fulminant UC.

The mainstay of therapy is IV corticosteroid generally given as hydrocortisone 100 mg four times a day which achieves remission or significant improvement in 60–75%. A joint

medical–surgical approach should be used to identify complications and to decide on the timing of surgical intervention. If there is no clinical response after 5–7 days, the patient is clinically deteriorating, has developed toxic megacolon or if perforation is suspected then colectomy is indicated. A useful clinical guide is that 85% of patients passing >8 stools/day or >3 stools/day and with C-reactive protein level >45 mg/litre on day 3 of IV steroids fail to respond to medical treatment and require colectomy (Travis et al, 1996). People with UC have a normal life expectancy and colectomy in fulminant colitis is life-saving; any delay in colectomy can induce unacceptable mortality.

Cyclosporin has been evaluated as a 'rescue therapy' for steroid-unresponsive fulminant UC. The only RCT is of continuous IV cyclosporin 4 mg/kg *vs* placebo in steroid-unresponsive UC (Lichtiger et al, 1994). An unvalidated scoring system was used and the trial was terminated early by a predetermined interim efficacy analysis. After 7 days' therapy 9 out of 11 in the cyclosporin group *vs* 0 out of 9 in the placebo group responded. Uncontrolled trials have suggested a two-thirds response rate. Long-term cyclosporin is not effective as maintenance therapy in responders and 45–70% of initial responders to cyclosporin need colectomy in the following year.

The main concern over the use of cyclosporin relates to deaths associated with the use of cyclosporin in fulminant UC, together with life-threatening side effects with long-term sequelae such as opportunistic infections (particularly *Pneumocystis carinii*, for which cotrimoxazole prophylaxis should be considered), nephrotoxicity, seizures, hypertension, hypokalaemia and hypomagnesaemia. Anecdotal evidence suggests that lower dose IV or oral cyclosporin may be as effective and have less frequent side effects (Rayner et al, 2003). Initiation of rescue therapy with cyclosporin in fulminant colitis needs full and frank discussion with the patient, in particular the balance between risk and benefit. It is certainly an option in the patient with new-onset UC presenting with fulminant colitis who refuses colectomy. In this situation cyclosporin can buy time by avoiding colectomy in the short-term and allowing the patient to consider the implications of surgical intervention.

First presentation of colitis

About 10% of patients present with acute fulminant colitis as their first presentation of UC. The main differential diagnoses are acute infective colitis (bacterial, viral, protozoal), ischaemic colitis, Beçhet's syndrome or NSAID-induced colitis. An accurate clinical history can usually differentiate between these, particularly with UC being more likely than infective colitis if the symptoms have lasted more than a week. Patients should be treated as for acute severe colitis with the addition of oral ciprofloxacin to cover bacterial colitis, pending the results of multiple stool cultures. Unprepared flexible sigmoidoscopy with biopsies for histology and microbiological culture should be performed as early as possible. It must be borne in mind that up to 60% of patients with infective colitis will have negative cultures. Histological features that suggest UC are architectural distortion and a prominent increase in cellularity in the lamina propria (Jenkins et al, 1997).

MAINTENANCE OF REMISSION

The ideal maintenance therapy should be effective, have a low incidence of adverse effects and easy dosage regimens to maximize compliance.

5-aminosalicylates

Regular oral sulphasalazine reduces yearly relapse rate from 75% to about 20%. Daily oral 5-ASA reduces the yearly relapse rate by approximately the same amount. Oral sulphasalazine is probably superior to the newer 5-ASAs (odds ratio = 1.29; 95% confidence interval = 1.05–1.57) and has similar adverse event profiles (Sutherland et al, 2003). Adverse effects are common with higher doses of sulphasalazine and the newer 5-ASAs allow higher doses to be used for maintenance of remission with less adverse effects.

5-ASA suppositories are effective in maintaining remission in left-sided colitis. D'Albasio et al (1997) compared mesalazine suppositories 500 mg once or twice a day against placebo. Cumulative relapse rates at 12 months were 10%, 32% and 47% respectively (P=0.007 mesalazine *vs* placebo). The combination of oral 5-ASA and twice-weekly 5-ASA enemas has been shown to be more effective than oral 5-ASA alone in maintaining remission in left-sided UC with relapse rates at 12 months of 39% in the combined group against 69% in the oral only therapy group (P = 0.036). Most patients understandably find it difficult to comply with regular maintenance enema therapy but it is a good option in patients with frequent relapses of left-sided colitis.

Corticosteroids

Prednisolone has no effect on maintaining remission in UC (Leonard-Jones et al, 1965). There are no data on newer corticosteroids such as budesonide but it is unlikely that any corticosteroids will be useful long-term therapy.

Thiopurines

Although widely used and clearly effective, there is little RCT evidence of the effect of the thiopurines, azathioprine and 6-mercaptopurine, on the maintenance of remission in UC. A withdrawal study has shown the efficacy of maintenance azathioprine with a 1-year relapse rate of 61% for placebo compared to 31% maintained on therapy (number needed to treat =3) (Hawthorne et al, 1992). A retrospective case review spanning 30 years of patients receiving azathioprine showed an overall remission rate of 58%. Patients who received more than 6 months of therapy had a remission rate of 87%. The efficacy of azathioprine was sustained over at least 5 years with minimal toxicity (Fraser et al, 2002). Current opinion suggests that it is justified to discontinue azathioprine after a relapse-free interval of 5 years.

Patients need to be informed of the risk of neutropenia (3%) and have full blood counts checked weekly for a month, monthly for 3 months and then every 2–3 months long term.

Cyclosporin

The seriousness and frequency of side effects make oral cyclosporin unsuitable for maintenance of remission. In patients who initially responded to IV cyclosporin and were converted to oral cyclosporin, only 40% avoided colectomy after a mean follow up of 19 months (Hyde et al, 1998).

Novel therapies

A single RCT has not shown any benefit of methotrexate over placebo in the maintenance of remission, although the dose used may have been too low (Oren et al, 1996). Likewise, nicotine patches have not been shown to be effective in maintaining remission (Thomas et al, 1995). It is very likely that substances other than nicotine in cigarette smoke protect against UC and a minority of patients smoke to control their colitis. However, this approach cannot be encouraged.

Antibiotics, probiotics and prebiotics

There is no evidence to support the use of antibiotics in UC. Because of the role of enteric flora in the pathogenesis of UC, there is considerable interest in the use of probiotics and prebiotics in the treatment of UC. A probiotic is 'a preparation of or a product containing viable, defined microorganisms in sufficient numbers, which alter the microflora in a compartment of the host and by that exert beneficial health effects'. Prebiotics are food ingredients that are not digested and alter the growth or activity of enteric bacteria. It is not clear whether viable bacteria are needed or whether bacterial protein or DNA alone is sufficient.

Three trials have examined the probiotic *Escherichia coli* strain Nissle 1917 against standard mesalazine in the maintenance of remission in UC. These have shown highly variable rates of relapses in both groups but taken together suggest that *E. coli* strain Nissle 1917 has a similar effect as oral mesalazine in maintaining remission in UC (Rembacken et al, 1999). Further trials of different probiotic and prebiotic regimens in the maintenance of remission in UC are eagerly awaited.

Epidermal growth factor

Epidermal growth factors (EGF) are salivary gland peptides which stimulate several components of the healing response. A recent small RCT provides preliminary data that EGF enemas may be effective in UC. Patients with active left-sided disease were randomized to EGF or placebo enemas for 2 weeks. Significantly more patients entered remission (83%) with EGF enemas than placebo (8%) ($P<0.001$) (Sinha et al, 2003). Unfortunately the scoring system was non-validated and there was no significant difference using a validated UC disease activity score. However, these preliminary data are exciting as they provide some evidence that targeted biological therapy may be effective in UC. Further larger studies are required to confirm these findings and examine whether there is an increased risk of colonic dysplasia, as EGF is a potent mitogen.

Heparins

Several uncontrolled trials have suggested that anti-inflammatory properties of unfractionated and low molecular weight heparins may be useful in active UC. However, a good quality trial of heparin monotherapy against standard corticosteroids conclusively showed no beneficial effect (Panes et al, 2000). Further trials of low molecular weight heparins as monotherapy have shown no effect. It may be that heparins may have a beneficial role as adjuvants to steroid therapy and further data are awaited.

Anti-TNFα antibodies

Pilot trials suggested some benefit from infliximab in steroid-resistant patients with UC. A randomized double-blind placebo controlled trial showed no benefit of two infusions in 2 weeks of infliximab 5 mg/kg over placebo (Probert et al, 2003). This trial was small and powered for a large difference over placebo. Further studies are ongoing with repeated infusions of infliximab in active steroid-resistant UC. A pilot trial on another anti-tumour necrosis factor (TNF)-α antibody (CDP571) showed some benefit (Evans et al, 1997) but as yet there are no randomized trial data.

SURVEILLANCE FOR DISEASE COMPLICATIONS

Colon cancer

UC increases the risk of developing colorectal cancer. The risk is highest in patients with the most extensive disease and longest duration of disease with a risk of colon cancer of 2% at 10 years, 8% at 20 years and 18% at 30 years (Eaden et al, 2001). Current guidelines recommend surveillance colonoscopy and biopsies (a minimum of 33 per colonoscopy) to start 8–10 years after onset for extensive colitis and 15–20 years after onset for left-sided colitis. Colonoscopy should be every 3 years for the first decade of surveillance, every 2 years for the second decade and then annually long-term (Eaden and Mayberry, 2002). Case-control studies have demonstrated a 75% reduction in the risk of colorectal cancer in UC patients taking regular 5-ASA compared to patients not on maintenance therapy, thus providing an added incentive for long-term therapy with a 5-ASA drug (Eaden et al, 2000).

CONCLUSIONS

The current most effective treatments for active UC are 5-ASA either topically or orally with the addition of corticosteroids for more severe or extensive disease. Azathioprine should be added if UC is relapsing frequently. The possible benefit of EGF enemas is one of the few biological therapies that have shown to be effective in UC. However, as the pathogenesis of UC is elucidated, it is likely that there will be new and effective therapies, particularly targeting the autoimmune basis of UC. The long-term risk of cancer requires colonoscopic surveillance. In future it is hoped that advances in faecal DNA analysis may improve detection of dysplasia. There is some evidence that long-term 5-ASA may reduce the risk of colon cancer and the authors recommend continuing treatment long-term in UC with 5-ASA. HM

Conflict of interest: none.

Baron JH, Connell AM, Kanaghinis TG et al (1962) Outpatient treatment of ulcerative colitis: comparison between three doses of oral prednisone. *Br Med J* **ii:** 441–3

Cohen RD, Woseth DM, Thisted RA, Hanauer SB (2000) A meta-analysis and overview of the literature on treatment options for left-sided ulcerative colitis and ulcerative proctitis. *Am J Gastroenterol* **95:** 1263–76

D'Albasio G, Pacini F, Camarri E et al (1997) Combined therapy with 5-aminosalicylic acid tablets and enemas for maintaining remission in ulcerative colitis: a randomized double-blind study. *Am J Gastroenterol* **92:** 1143–7

Eaden J, Abrams K, Ekbom A et al (2000) Colorectal cancer prevention in ulcerative colitis: a case-control study. *Aliment Pharmacol Ther* **14:** 145–53

Eaden JA, Abrams K, Mayberry JF (2001) The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut* **48:** 526–35

Eaden JA, Mayberry JF (2002) Guidelines for colorectal cancer screening in high risk groups. *Gut* **51**(suppl V): v10–12

Evans RC, Clarke L, Heath P et al (1997) Treatment of ulcerative colitis with an engineered human anti-TNFalpha antibody CDP571. *Aliment Pharmacol Ther* **11:** 1031–5

Fraser AG, Orchard TR, Jewell DP (2002) The efficacy of azathioprine for the treatment of inflammatory bowel disease: a 30 year review. *Gut* **50:** 485–9

Hawthorne AB, Logan RFA, Hawkley CJ et al (1992) Randomised control trial of azathioprine-withdrawal in ulcerative colitis. *Br Med J* **305:** 20–2

Hyde GM, Thillainayagam AV, Jewell DP (1998) Intravenous cyclosporin as rescue therapy in severe ulcerative colitis: time for a reappraisal? *Eur J Gastroenterol Hepatol* **10:** 411–13

Jenkins D, Balsitis M, Gallivan S et al (1997) Guidelines for the initial biopsy diagnosis of suspected chronic idiopathic inflammatory bowel disease. The British Society of Gastroenterology Initiative. *J Clin Pathol* **50:** 93–105

Leonard-Jones JE, Misiewicz JJ, Connell AM et al (1965) Prednisolone as a maintenance treatment of ulcerative colitis in remission. *Lancet* **i:** 188–9

Lichtiger S, Present DH, Kornbluth A et al (1994) Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med* **330:** 1841–5

Moum B, Ekbom A, Vatn MH et al (1999) Change in the extent of colonoscopic and histological involvement in ulcerative colitis over time. *Am J Gastroenterol* **94:** 1564–9

Panes J, Esteve M, Cabre E et al (2000) Comparison of heparin and steroids in the treatment of moderate and severe ulcerative colitis. *Gastroenterology* **119:** 903–8

Probert CS, Hearing SD, Schreiber S et al (2003) Infliximab in moderately severe glucocorticoid resistant ulcerative colitis: a randomised controlled trial. *Gut* **52:** 998–1002

Oren R, Arber N, Odes S et al (1996) Methotrexate in chronic active ulcerative colitis: a double-blind, randomized, Israeli multicenter trial. *Gastroenterology* **110:** 1416–21

Rayner CK, McCormack G, Emmanuel AV, Kamm MA (2003) Long-term results of low-dose intravenous ciclosporin for acute severe ulcerative colitis. *Aliment Pharmacol Ther* **18:** 303–8

Rembacken BJ, Snelling AM, Hawkey PM, Chalmers DM, Axon AT (1999) Non-pathogenic *Escherichia coli* versus mesalazine for the treatment of ulcerative colitis: a randomised trial. *Lancet* **354:** 635–9

Safdi M, DeMicco M, Sninsky C et al (1997) A double-blind comparison of oral versus rectal mesalamine versus combination therapy in the treatment of distal ulcerative colitis. *Am J Gastroenterol* **92:** 1867–71

Sinha A, Nightingale JMD, West KP, Berlanga-Acosta J, Playfer RJ (2003) Epidermal growth factor enemas with oral mesalamine for mild-moderate left-sided ulcerative colitis or proctitis. *N Engl J Med* **349:** 350–7

Sutherland L, MacDonald JK (2003) Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. In: The Cochrane Library, Issue 4. John Wiley & Sons, Chichester

Sutherland L, Roth D, Beck P, May G, Makiyama K (2003) Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. In: The Cochrane Library, Issue 4. John Wiley & Sons, Chichester

Thomas AOT, Rhodes J, Mani V et al (1995) Transdermal nicotine therapy as maintenance therapy for ulcerative colitis. *N Engl J Med* **332:** 988–92

Travis SPL, Farrant JM, Ricketts C et al (1996) Predicting outcome in severe ulcerative colitis. *Gut* **38:** 905–10

Truelove SC, Witts LJ (1955) Cortisone in ulcerative colitis. Final report on a therapeutic trial. *Br Med J* **ii:** 1041–8

KEY POINTS

- Ulcerative colitis (UC) has a strong negative correlation with smoking and appendicitis.
- Acute severe colitis should be treated with intravenous corticosteroids and early colectomy if medical therapy fails.
- Moderately severe exacerbations of UC can be treated with oral and rectal 5-aminosalicylates in left-sided disease and oral steroids in more extensive disease.
- Long-term 5-aminosalicylates are effective in maintaining remission and may reduce the risk of colon cancer.
- The risk of colon cancer is increased in UC and regular surveillance colonoscopy with multiple biopsies is recommended.