Regular review

Ulcerative colitis

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Ulcerative colitis is a relapsing and remitting disease characterised by acute non-infectious inflammation of the colorectal mucosa. In the United Kingdom the annual incidence is around 7 cases per 100 000 population.¹ The rectal mucosa is invariably affected. Confluent inflammation and shallow ulceration extend proximally from the anal margin. A patient may have proctitis, left sided colitis (the proximal limit being below the splenic flexure), extensive colitis (involving the transverse colon), or pan colitis. At any point in time, 50% of patients are asymptomatic, 30% have mild symptoms, and 20% have moderate to severe symptoms.² Many patients have long periods of complete remission, but the cumulative probability of remaining free from relapse at two years is only 20%, decreasing to less than 5% at 10 years.³ Later relapses generally affect the same region of the colon as previous episodes.

Several of the current clinical and therapeutic issues in ulcerative colitis include: (a) medical treatment options for relapse and for maintenance of remission; (b) management of the minority of patients who develop a severe life threatening relapse or chronic unremitting disease; (c) surgical treatment of ulcerative colitis; and (d) long term complications in patients with extensive disease—namely, colonic and biliary cancers and sclerosing cholangitis.

Methods

We have based this review on our clinical and research experience in gut immunology and inflammatory diseases together with information from comprehensive monographs^{3,4,5} and UK and US guidelines on management.^{6,7} We also searched Medline from 1985 to July 1999 using the search terms “ulcerative colitis” and “sclerosing cholangitis,” which yielded 6116 and 889 citations respectively and other seminal papers.

Clinical features and diagnosis

Ulcerative colitis may present at any age. Men and women are equally affected. In adults at presentation about 55% have proctitis, 30% left sided colitis, and 15% extensive colitis or pan colitis. In children, only 25% present with proctitis alone, 30% have left sided colitis, and in 45% the disease extends to the transverse colon or beyond.

Box 1 lists typical symptoms at presentation. Virtually all patients with ulcerative colitis have rectal

Summary points

Ulcerative colitis may present at any age, but the anatomical distribution of involvement at presentation is different between children and adults

All patients with bloody diarrhoea need to have infection excluded

Outpatient rigid sigmoidoscopy is the best method of diagnosing the nature of inflammation

The extent of inflammation may be established by total colonoscopy (or a double contrast barium enema)

The mainstays of treatment are rectal and systemic 5-aminosalicylic acid derivatives and corticosteroids, with azathioprine in steroid dependent or resistant cases

Restorative proctocolectomy with ileal pouch-anal anastomosis should be considered in every patient in whom colectomy is contemplated

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bleeding or bloody diarrhoea. Delays in presentation are common through such diverse reasons as fear of cancer or a general reluctance to discuss matters relating to bowel habit (box 2). Many patients may complain of pain of colonic origin, often left sided and related to defecation. There are no specific clinical signs on general examination, but inflammation of the rectal mucosa (proctitis) can readily be seen at proctoscopy (fig 1).

Patients with bloody diarrhoea need careful clinical evaluation. After infection has been excluded in patients with colitis the nature and extent of inflammation should be established by sigmoidoscopy and biopsy and either total colonoscopy or double contrast barium enema examination (fig 2). Sedation may be necessary for appraisal of the rectal mucosa in an anxious child presenting for the first time. The patient should be informed that rectal examination and sigmoidoscopy are safe and usually painless and that they are performed routinely at appointments to allow sensible treatment decisions to be made. Sigmoidoscopy may be

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Box 1: Symptoms of ulcerative colitis**Colonic symptoms**

- Diarrhoea with blood and mucus
- Urgency, tenesmus
- Incontinence
- Lower abdominal cramps and pain with defecation

Systemic symptoms

- Tiredness, weight loss
- Malaise, fever

Extraintestinal*Related to activity of colitis*

- Peripheral arthritis
- Erythema nodosum
- Iritis, uveitis
- Thromboembolism

Unrelated to activity of colitis

- Sclerosing cholangitis
- Ankylosing spondylitis, sacroileitis
- Pyoderma gangrenosum (see fig A on website)

performed safely during pregnancy if considered essential for management, but never total colonoscopy.

Differential diagnosis

The most difficult decision may be to establish whether the diagnosis is ulcerative colitis or Crohn's disease. It may be several years after presentation that the clinical evolution allows a firm decision to be made. Fortunately, unless surgery is contemplated the management of colonic Crohn's disease is broadly similar to that of ulcerative colitis. The table summarises the differences between ulcerative colitis and Crohn's disease. In our view these are different diseases. Otherwise the differential diagnosis includes anal fissure (seen with proctoscopy), infectious colitis (stool cultures for bacterial pathogens, and careful examination of stools and biopsy material for viral, parasitic, and protozoal infection are mandatory), and pseudomembranous colitis (history of antibiotic exposure, toxin assay for *Clostridium difficile*). Food sensitive colitis should be considered in infants⁸ and ischaemic colitis, diverticulitis, and colonic tumours in adults.

Causal and immunological aspects

The cause remains unresolved, but current interest is focused on defects in the mucous gel barrier, either primary or acquired by bacterial sulphatases,⁹⁻¹¹ low appendectomy rates in ulcerative colitis¹² (even when smoking is controlled for),¹³ and colonic sulphate reducing bacteria.¹⁴ The existence of true autoimmunity

in ulcerative colitis is uncertain, and the evidence is conflicting.^{15 16} The balance between Th1 and Th2 phenotypes of T lymphocytes determines the characteristics of a chronic inflammatory process. Th1 cells secrete proinflammatory cytokines such as interleukin 2 and γ interferon, whereas Th2 cells express regulatory cytokines such as interleukin 4 and interleukin 10. Th2 responses have been shown to be important in atopy, a condition in which altered humoral immunity is present, and existing data suggest that ulcerative colitis more closely resembles a Th2 type disease.¹⁷

Fig 1 Appearance of rectum in proctitis with erythematous friable mucosa, loss of vascular pattern, and mucopus

Fig 2 Double contrast barium enema showing granularity and continuous involvement with ulcerations

Box 2: Atypical symptoms at presentation or relapse

- Bleeding not recognised because of colour blindness
- Constipation proximal to severe proctitis—blood and mucus several times daily, hard stool once or twice a week (olsalazine frequently causes diarrhoea and may be a useful drug)
- Late stage tubular colon with failure of the capacity to concentrate stool so the patient has watery diarrhoea without inflammation or bleeding
- Faecal incontinence—at least 50% of patients with diarrhoea due to ulcerative colitis are occasionally incontinent
- The patient does not recall an earlier episode of colitis but presents with sclerosing cholangitis or colon cancer and dysplasia (even if there are no current symptoms of ulcerative colitis, biopsies usually show evidence of a previous total colitis)
- Chronic iron deficiency anaemia—usually there is a history of diarrhoea on direct questioning

Management

Analysis of the patient's illness

As in many chronic diseases, an appropriate plan of management must be tailored to the patient's current anatomical, functional, and "disease activity" status. Anatomical extent of grossly affected colon, symptomatic disease activity, local and remote complications, iatrogenic illnesses, nutrition, growth variables, social and psychological factors, and coexistent diseases should all be considered within a comprehensive management strategy.

Symptoms are the best guide towards disease activity¹⁸ and their relief is the main treatment aim. It may be difficult to decide whether remission has been achieved, and this is a major problem in the design of clinical trials. Various clinical indices have been devised, mainly based on subjective data. The Powell-Tuck index¹⁹ is widely employed and is of particular use in clinical trials where objective, reproducible assessment of symptoms is vital. In practice, the Crohn's disease activity index²⁰ gives similar values to the Powell-Tuck index (see fig B on website). Symptoms may remit but endoscopically there may still be evidence of mucosal inflammation; histology often remains abnormal long after complete clinical remission. Blood tests indicating inflammatory activity, such as platelet and leucocyte counts, erythrocyte sedimentation rate, or concentrations of C reactive protein, although a useful adjunct, often merely confirm the overall clinical impression. A new objective measure of gut inflammation (gut protein loss measured by lavage fluid from the whole gut) measures the same symptomatic, acute inflammatory component of overall illness as the Crohn's disease activity index, both in ulcerative colitis and Crohn's disease in adults (see fig C on website).²¹ Tests based on whole gut lavage offer a different approach for assessing the contribution of "disease activity" to overall illness, as well as measuring the efficacy of treatment.

Medical treatment of typical relapse

In practice, rectal and systemic derivatives of 5-aminosalicylic acid and corticosteroids form the basis of medical treatment (see table on website). Azathioprine may be used as a steroid sparing agent. There is little to choose between the various 5-aminosalicylic acid preparations available. The use of sulphasalazine, the oldest (and least expensive) of these, has become less popular because of side effects including nausea, skin rashes, and reversible oligospermia. Balsalazide, a colonic release preparation that is azo bonded may be more effective and better tolerated than mesalazine.²² Topical treatment is usually effective for proctitis. Patients may need to be taught how to use formulations given through the rectum. Rectal 5-aminosalicylic acid preparations and corticosteroids are both effective in relieving symptoms and inducing remission but the former is more effective.²³ Patients tolerate foam enema preparations better than liquid enemas,²⁴ but the new mesalazine gel enema may be better still.²⁵

There is no evidence that elemental diets or other dietary intervention have any specific therapeutic effect in ulcerative colitis. However, the support of a dietician in the management of patients is invaluable for monitoring daily nutritional intake and educating patients on the principles of good nutrition. Many patients are

Differences between ulcerative colitis and Crohn's disease

	Ulcerative colitis	Crohn's disease
Disease features		
Smoking	Non-smokers or ex-smokers	Smokers
Long latent period	No	Yes
Genetic susceptibility	+: HLA class II	++; non-major histocompatibility complex
Osteopenia at diagnosis	No	Yes
Oral and perianal disease	No	Yes
Growth failure	±	++
Anatomy of involvement	Colon	Entire gut; rectal sparing
Histology and immunology		
Granuloma, stricture, fistula	Generally no	Yes
Transmural inflammation	No	Yes
Cytokines	Increased interleukin 4 and interleukin 5; normal γ interferon and interleukin 12	Normal interleukin 4 and interleukin 5; increased γ interferon and interleukin 12
Associated autoimmune diseases	Yes	No
Mucosal IgG subclass	IgG1	IgG2
Autoantibodies	+++	+
Management		
Response to antibiotics	No	Yes
Nutritional therapy	Not effective	Effective
Maintenance with 5-aminosalicylic acid	Effective	Small benefit
Ileoanal pouch	Yes	Generally no
Recurrence after surgery	No (apart from pouchitis)	Yes
Extraintestinal manifestations		
Sclerosing cholangitis	+++	+
Autoimmune hepatitis	+++	+

±=Equivocal association; +=weakly associated; ++=moderately well associated; +++ strongly associated.

iron deficient and may require supplementation with oral iron preparations. Parenteral iron or recombinant human erythropoietin²⁶ has been used in cases where oral supplements are poorly tolerated.

Maintenance of remission

Since attacks recur, maintenance treatment is important. Sulphasalazine and the 5-aminosalicylic acid preparations are equally effective,²⁷ but the 5-aminosalicylic acid preparations are better tolerated. Intolerance to 5-aminosalicylic acid drugs occurs in about 10% of patients.²⁸ All 5-aminosalicylic acid preparations are potentially nephrotoxic and so regular monitoring of renal function is mandatory.²⁹ In patients with steroid resistant or dependent disease, immunosuppressive drugs such as azathioprine may maintain remission. Though the evidence supporting the use of azathioprine in ulcerative colitis is weaker than that in Crohn's disease, a recent survey confirmed its widespread use by British gastroenterologists.³⁰

Medical treatment of severe disease

Corticosteroids are the mainstay of treatment. These may be given orally or intravenously, usually in a daily dose of 60-80 mg methylprednisolone intravenously, or 40-60 mg prednisolone orally. The dose and form of corticosteroids used are not fully backed up by dose ranging trials in severe disease. Where corticosteroids are ineffective several alternative treatments have been tried. Noticeable clinical improvement has been reported in patients treated with intravenous unfractionated heparin.^{31,32} Cyclosporin, given intravenously (4 mg/kg)³³ or orally (4-9 mg/kg) has proved successful in inducing remission—for example, in a paediatric series 11 of 14 children responded.³⁴ Even lower doses may be effective, with fewer side effects. In many instances, however, colectomy is only delayed and not prevented—

seven of these cases needed colectomy within a year. The trend currently is to induce remission with cyclosporin and to maintain this with an immunosuppressive drug such as azathioprine. Over half of patients on this regimen may avoid colectomy in the longer term.³⁵ Avoiding colectomy, even for a short period, can be beneficial to some patients by providing time to think about surgery or allowing an elective rather than an emergency procedure. We believe that cyclosporin has a place in managing severe ulcerative colitis, a view supported by recent quality of life data.³⁶ Such treatment should, however, be confined to specialist centres.

The excellent results of, effectively curative, surgical treatment must always be taken into account when deciding whether to prolong medical treatment.

Failure of medical management and indications for surgery

Proctocolectomy or colectomy with rectal preservation may be an emergency procedure in fulminant colitis or toxic megacolon. More often, however, the procedure is elective after failure of medical treatment either through a lack of efficacy or unacceptable side effects (see fig D on website). Rarely, in a patient with long standing colitis, colectomy is necessary because of the development of severe dysplasia or carcinoma of the colonic epithelium. Until recently, surgical treatment implied permanent ileostomy, a prospect unacceptable to many patients. Now, advances in surgical technique have allowed the creation of an ileal reservoir or pouch, and with ileoanal anastomosis the need for permanent ileostomy is diminishing. Restorative surgery of this nature should be considered in every patient. Because of a child's small pelvis it may be technically advisable to delay pouch surgery until the mid teens, but often the best functional results after pouch surgery are seen in children.³⁷ Continent ileostomy has little use but may be considered in patients with existing conventional ileostomy or in pouch failures.

Ileal pouch-anal anastomosis and pouchitis

Restorative proctocolectomy with ileal reservoir has revolutionised surgery for ulcerative colitis, and with increasing confidence the indications have been widened to include those with more limited but refractory disease.³⁸ Pouchitis, a non-specific inflammation of the ileal reservoir, is the most frequent long term complication after ileal pouch-anal anastomosis for ulcerative colitis. This poorly understood condition may occur in up to one third of patients within 5 years of surgery, with two thirds of these having recurrent episodes.³⁹⁻⁴¹ Though faecal stasis is a popular explana-

Fig 3 Highly dysplastic mass lesion in caecum of patient with ulcerative colitis of 12 years' duration

tion of the cause of pouchitis, no difference in the faecal concentrations of bacteria, bile acids, and short chain fatty acids has been reported between patients with or without pouchitis. Complex interactions between an immunologically susceptible mucosa, faecal stasis, and bacterial flora merit further investigation. Metronidazole is an effective first line treatment. In pregnant patients with ileal pouch-anal anastomosis, delivery by caesarean section should be considered as sphincter damage may be detrimental to pouch function. Though fertility is not reduced in ulcerative colitis in itself, postoperative fertility may be reduced after ileal pouch-anal anastomosis in women of childbearing age.⁴²

Malignancy complicating ulcerative colitis

Disease duration of more than eight years and disease extent proximal to the sigmoid colon are the two major determinants of increased risk of colorectal cancer in ulcerative colitis (box 3). Coexistent primary sclerosing cholangitis also increases the risk.⁴³ Screening for dysplasia by colonoscopy at regular intervals (1-2 years) remains the only feasible method for surveillance (fig 3). End points such as surgery must be understood by the patient before entering a surveillance programme. The limitations of colonoscopy as well as alternative options (colectomy after 10 years of extensive disease) need to be discussed in detail. Detection of dysplasia is an imperfect science and other reliable markers of a premalignant stage are needed. p53 mutations,⁴⁴ Ki-ras,⁴⁵ Ki-67, and sialosyl-Tn are among some of the candidates being evaluated.

Sclerosing cholangitis in ulcerative colitis

Primary sclerosing cholangitis is the commonest form of chronic liver disease associated with ulcerative colitis and may be present in 2-7% of patients depending on how diligently it is sought.⁴⁶ Primary sclerosing cholangitis associated with ulcerative colitis is twofold more common in men than women. The ulcerative colitis affects the entire colon in 90% of patients but symptoms are often mild. Endoscopic retrograde cholangiography is the best method of confirming the diagnosis, but magnetic resonance cholangiography is likely to become the non-invasive diagnostic method of choice. Perinuclear antineutrophil cytoplasmic antibodies may be detectable in serum.⁴⁷ Medical treatment

Box 3: Risk factors for malignancy in ulcerative colitis

- Longstanding disease of more than 8 years
- Extensive colitis
- Sclerosing cholangitis
- Family history of colon cancer
- Expression of sialosyl-Tn antigen in mucosal biopsies
- ? Onset in childhood and adolescence

with agents such as corticosteroids, colchicine, penicillamine, and ursodeoxycholic acid has not been shown to retard progression of liver disease.⁴⁸ Endoscopic treatment may be beneficial in selected patients with dominant extrahepatic biliary strictures.⁴⁹ Progressive cholestatic jaundice with liver failure and development of cholangiocarcinoma are the two fatal consequences of primary sclerosing cholangitis. Orthotopic liver transplantation is the only treatment available to patients with advanced liver disease.⁵⁰ It is important to continue surveillance colonoscopy after liver transplantation to detect colonic dysplasia.⁵¹

Conclusion

The diagnosis and management of ulcerative colitis remain a challenge to clinicians. Rigorous epidemiological study of the negative relations between ulcerative colitis, smoking habit, and appendectomy may yield further clues to the cause of this condition. Most patients can be managed wholly as outpatients. Symptomatic relapses are the rule, however, and so maintenance treatment with oral 5-aminosalicylic acid preparations is important to keep these to a minimum. Most have distal disease that is amenable to topical application of 5-aminosalicylic acid or corticosteroid preparations, and many patients will begin self treatment with these at the first signs of a flare up. The overall prognosis in ulcerative colitis is good, and with the exception of the first year of diagnosis when the risk of colectomy is statistically highest there is no significant excess in mortality.

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