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Diagnostic dilemmas in colitis

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Many promising new approaches for medical therapy of inflammatory bowel disease are currently being explored but proven medical therapy has remained essentially unchanged for many years: corticosteroids for acute disease and 5-aminosalicylates for maintenance of remission. Some relatively minor but useful advances have occurred:

- in ulcerative colitis:
  - intravenous cyclosporin in patients with severe colitis who are responding poorly to corticosteroids[1]
  - better evidence for benefit from azathioprine in chronic remitting disease
  - demonstration of the superiority of rectal 5-aminosalicylates over rectal steroids
- in Crohn's disease:
  - clear evidence of a role for metronidazole in colonic and perianal disease[2]
  - better understanding of and evidence for the role of dietary therapy in the primary treatment of small intestinal disease
  - introduction of a delayed release formulation of corticosteroids with rapid first-pass metabolism (budesonide) to reduce the risk of steroid side effects[3].

More significant advances have been made recently in our understanding of the natural history and pathophysiology of the many different forms of colitis, and these should make a considerable impact on clinical management. This article will focus on three areas that commonly cause confusion in diagnosis and where important progress has been made:

1 Overlap between ulcerative colitis and Crohn's disease.
2 Overlap between infective colitis and idiopathic ulcerative colitis.
3 'New' syndromes of collagenous, lymphocytic (microscopic) and diversion colitis.

Overlap between ulcerative colitis and Crohn's disease

The traditional approach to the difficulties in distinguishing ulcerative colitis from Crohn's disease has been dogmatic adherence to a set of widely quoted 'typical' clinical, radiological, endoscopic and pathological criteria which 'define' the diagnoses:

- *Colonic Crohn's disease* if some or all the following are present: granulomas (found in 60–70%), inflammation deep to the muscularis mucosae, goblet cell retention in the presence of inflammation, rectal sparing, skip lesions, perianal fistulae, sinuses or skin tags.
- *Ulcerative colitis* if there is continuous disease extending proximally from the rectum, superficial inflammation with goblet cell depletion, and absence of small intestinal inflammation (apart from mild 'backwash' ileitis in total colitis).

Using such criteria, approximately 10–15% of patients with colitis are left 'unclassifiable' with some features of both conditions – and may then be told that no firm diagnosis can be made. Furthermore, although some specialists will accept the presence of granulomas in up to 4% of patients with ulcerative colitis[4], more commonly the discovery of a granuloma at routine colonoscopic biopsy in a patient with otherwise typical ulcerative colitis leads to a change in diagnosis to Crohn's disease – often

accompanied by bewilderment of the patient who becomes understandably uncertain whether the physician is competent.

The relationship between ulcerative colitis and Crohn's disease has become much clearer since recent genetic studies have shown that at least three genes simultaneously predispose to an increased risk of either disease[5]. There are many examples of families which include cases both of ulcerative colitis and of Crohn's disease, and the first-degree relatives of a patient with Crohn's disease are almost as likely to have ulcerative colitis as Crohn's disease. Recent studies of such 'mixed-disease' families have shown a strong association between smoking history and the disease phenotype[6]. Current smoking correlates positively with Crohn's disease (about two-thirds of cases are smokers) and negatively with ulcerative colitis (only about 5% of patients are current smokers).

Thus, there are genetic factors that predispose to inflammatory bowel disease, but the different disease phenotypes are probably determined largely by environmental factors[7]. Additional genetic factors are also involved with a chromosome 16 locus linkage identified specifically with Crohn's disease[8], and several HLA class II loci have influence on the extent and severity of ulcerative colitis as well as on the risk for extra-intestinal manifestations such as the sclerosing cholangitis which affects about 5% of patients with ulcerative colitis[9].

- Inflammatory bowel disease should therefore be considered as a spectrum of disease that includes ulcerative colitis, Crohn's disease, indeterminate colitis and, arguably, Behçet's disease, in which the colitis and many of the extra-intestinal manifestations may closely mimic either ulcerative colitis or Crohn's disease.
- Recognition of the typical phenotypes of ulcerative colitis and Crohn's disease nevertheless has important implications for therapy.
- The clinician needs to maintain a balance between recognition of inflammatory bowel disease as a continuous spectrum whilst at the same time recognising the important management implications of the different phenotypes.

Practical management implications of distinction between ulcerative colitis and Crohn's disease

Smoking

Patients with Crohn's disease who stop smoking have an approximately 40% lower risk of relapse than those who continue[10] (Fig 1). This is a greater reduction than is achievable with any form of maintenance drug therapy.

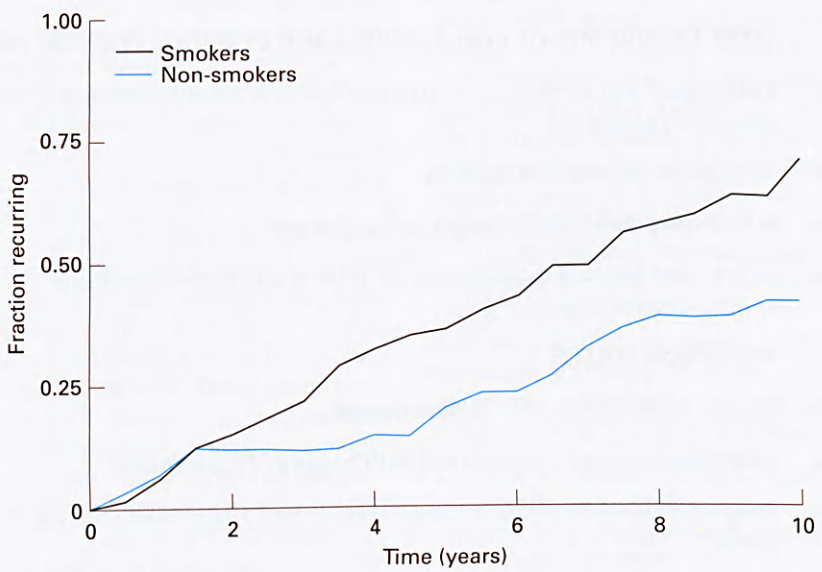
Perianal and colonic Crohn's disease

Secondary bacterial infection probably plays a major role in both perianal and colonic Crohn's disease. Oral metronidazole (400 mg three times daily in adults) is effective but may need to be continued for up to three months[11]. Longer courses of treatment are precluded by the risk of neuropathy. Controlled studies have shown no benefit from metronidazole in ulcerative colitis.

Pouch surgery

Pouch reconstruction with ileo-anal anastomosis is generally agreed to have an unacceptably high complication rate when performed in Crohn's disease, and great emphasis has been placed on the importance of excluding this disease before pouch surgery for colitis. The operation is commonly performed in two stages, with subtotal colectomy at the first operation, and proctectomy and pouch reconstruction at the second operation. This allows complete histological examination of the resected colon before a final decision is made regarding pouch reconstruction. In the cases (ca 15%) where the diagnosis is still in doubt after this histological examination, 'indeterminate' colitis, the morbidity associated with

Figure 1. Effect of stopping smoking on relapse in Crohn's disease (Adapted from Ref 10 by permission of *Gastroenterology*).



pouch reconstruction is no greater than in 'typical' ulcerative colitis[4].

Segmental colonic resection

If colectomy is required in ulcerative colitis, total colectomy is always indicated. Preservation of the rectum and ileo-rectal anastomosis is occasionally a reasonable option if there is an unusual degree of rectal sparing, but left hemicolectomy is universally disastrous with rapid recurrence of disease in the remaining colon. In 'typical' Crohn's disease, however, the disease is segmental and associated with rectal sparing. Segmental resection of the diseased colon can then be performed with good results[12].

Dietary therapy and diversion of the faecal stream

Diversion of the faecal stream by defunctioning ileostomy or intravenous feeding and bowel rest has proved effective in Crohn's disease but not in ulcerative colitis. Enteral feeding is as effective as intravenous feeding. Early studies used amino acid-based feeds (eg EO28), but later studies have shown equally good results with some, but not all, whole protein feeds. There is circumstantial evidence that a low fat content of the feed may be important[13]; further studies are needed to confirm or refute this. The therapeutic response to enteral feeding and bowel 'rest' in Crohn's disease is similar to that achievable with corticosteroids but at much greater cost and inconvenience. It should nevertheless be considered as first-line therapy in patients who have extensive small bowel disease, multiple previous resections or sepsis, and in children with short stature.

Cancer surveillance

In patients with extensive ulcerative colitis the relative risk for development of colorectal cancer is increased approximately eleven-fold. There has been considerable controversy recently over the cost-benefit of colonoscopy screening in long-standing ulcerative colitis[14]. Even in well-administered screening programmes, up to 50% of cancers have been diagnosed in between screening visits and the indications for colectomy in dysplasia remain contentious. It is now known that the increased risk for colon cancer is equally high in extensive colonic Crohn's disease. Logically, therefore, screening should be offered for both conditions or neither. It does not, however, seem appropriate to consider stopping screening for a high risk group of patients at a time when there is increasing support for endoscopic screening of asymptomatic subjects. Most centres offer annual colonoscopy to patients with colitis of at least 10 years' duration that extends proximal to the splenic flexure. Proctitis and distal colitis are associated with little or no increased risk for cancer. Colon cancer risk is age-related even in colitis, so the yield will be extremely low if surveillance is applied to patients under 35 years.

Key Points

OVERLAP BETWEEN ULCERATIVE COLITIS (UC) AND CROHN'S DISEASE

- Despite the overlap there are important differences in treatment:
- Metronidazole is effective in colonic Crohn's but not UC
- Enteral feeding reduces disease activity in Crohn's but not UC
- Smoking correlates negatively with UC but positively with Crohn's, which is more likely to relapse in smokers
- Segmental colectomy is useful in Crohn's but not UC

OVERLAP BETWEEN INFECTIVE COLITIS AND ULCERATIVE COLITIS

- Carefully exclude infection in relapse of inflammatory bowel disease
- Consider inflammatory bowel disease in 'prolonged infective colitis' and treat with corticosteroids and a fluoroquinolone.

'NEW' SYNDROMES OF COLLAGENOUS AND LYMPHOCYTIC COLITIS

- Both cause watery diarrhoea, mucosa 'normal' on colonoscopy - diagnose by biopsy
- Both more common in women
- A few cases due to NSAIDs or coeliac disease
- Often have bile salt malabsorption; treat with cholestyramine if sulphasalazine fails

DIVERSION COLITIS

- Occurs when distal colon defunctioned
- Resembles mild UC, sometimes with lymphoid hyperplasia
- Responds to enemas containing butyrate and other short chain fatty acids

Explanation for patients

Patients, particularly those with mixed features of ulcerative colitis and Crohn's disease, should be told that ulcerative colitis and Crohn's disease represent a spectrum of inflammatory bowel disease. Overdogmatic application of diagnostic labels in the absence of secure diagnostic criteria should be avoided.

Overlap between infective colitis and idiopathic ulcerative colitis

Infective colitis due to organisms such as *Campylobacter jejuni* and *Salmonella* spp can closely mimic ulcerative colitis, with bloody diarrhoea, mucosal ulceration and even toxic megacolon. Rectal mucosal histology may help to distinguish the two. Crypt branching, basal plasmacytosis and Paneth cell metaplasia all suggest inflammatory bowel disease, but none of these features has a sensitivity or specificity better than about 70%. Vomiting on the first day of illness and sudden onset of profuse diarrhoea suggest infective colitis, but attacks of ulcerative colitis may have an abrupt onset in about 50% of cases and infective colitis may have an insidious onset in 10%[15]. Furthermore, relapse or first attacks of ulcerative colitis may be precipitated by infection. One study showed that 21% of patients with inflammatory bowel disease had positive microbiology at initial presentation; this is quite likely to be an underestimate[16]. The positive culture rate in cases of suspected infective colitis more than doubled in one study in which mucosal biopsies were cultured in addition to stool culture[17].

- All cases of suspected colitis, even relapse of known ulcerative colitis, should have stool culture for pathogens (and microscopy of 'warm-transported' stool for pathogenic amoebae if recently in an endemic area).
- Culture of mucosal biopsy greatly increases the yield of pathogens.
- Where doubt remains, corticosteroid therapy should be used as indicated for ulcerative colitis (it seems remarkably safe even in infective colitis), but should be given in combination with a fluoroquinolone antibiotic such as ciprofloxacin 500 mg twice daily.

'New' syndromes of collagenous, lymphocytic and diversion colitis

Collagenous and lymphocytic colitis

Collagenous colitis was first described in 1976, and lymphocytic colitis, originally named microscopic colitis, was identified four years later[18]. Both conditions present predominantly in women, with fluctuating chronic watery diarrhoea believed to be due to reduced colonic absorption and/or increased secretion, and both run a benign clinical course. Cramping abdominal pains may occur and there may be periods of spontaneous remission. Blood tests, including markers of inflammation, barium enema and colonoscopy are all normal. Stool microscopy for blood and polymorphs is negative, thus excluding inflammatory bowel disease, and pathogens are absent. In both conditions, the diagnosis is based on colonic histology (collagenous colitis may be missed on rectal biopsy alone). Intraepithelial lymphocyte infiltration is invariable in lymphocytic colitis (Fig 2); it is frequently present in collagenous colitis, which is defined by the presence of a patchy subepithelial collagen layer greater than 10 μm wide (normally about 3 μm) (Fig 3).

An immune aetiology has been proposed for both conditions; this is supported by associations with other immune disorders such as coeliac disease, seronegative arthritis and Raynaud's disease. There have been reports of histological progression from lymphocytic colitis to collagenous colitis, suggesting that the two conditions represent one disease process[19]. However, collagenous colitis has been associated with long-term use of non-steroidal anti-inflammatory drugs, whereas lymphocytic colitis has no known association with drugs but, unlike collagenous colitis, is associated with an increased frequency of HLA A1 and decreased HLA A3[20]. There is little evidence for any association between either condition and inflammatory bowel disease but a minority of patients with lymphocytic colitis have been found to have coeliac disease.

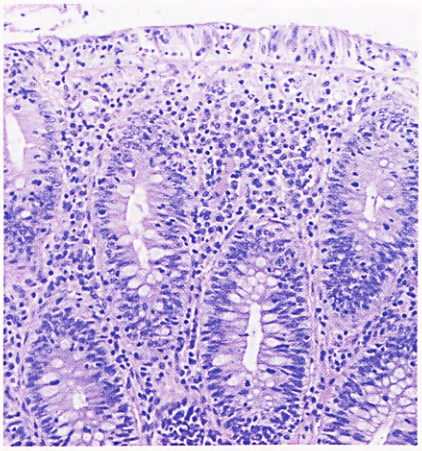


Figure 2. Lymphocytic colitis: the mucosa shows normal architecture with diffuse lymphoplasmacytic infiltrate down to the muscularis mucosae and increased intraepithelial lymphocytes infiltrating the crypt epithelium.

Medical treatment has proved only moderately effective. Antidiarrhoeal agents are usually ineffective. Sulphasalazine and cholestyramine have given good results in some uncontrolled studies. Prednisolone may also help, but diarrhoea recurs when treatment is stopped and it should be used only in short courses for acute attacks. The diagnoses of collagenous colitis and lymphocytic colitis need to be considered in patients with persistent watery diarrhoea and many cases are probably missed at present. In patients with lymphocytic or collagenous colitis:

- Non-steroidal drug therapy should be stopped.
- Serum anti-endomysial antibody should be checked to exclude coeliac disease.

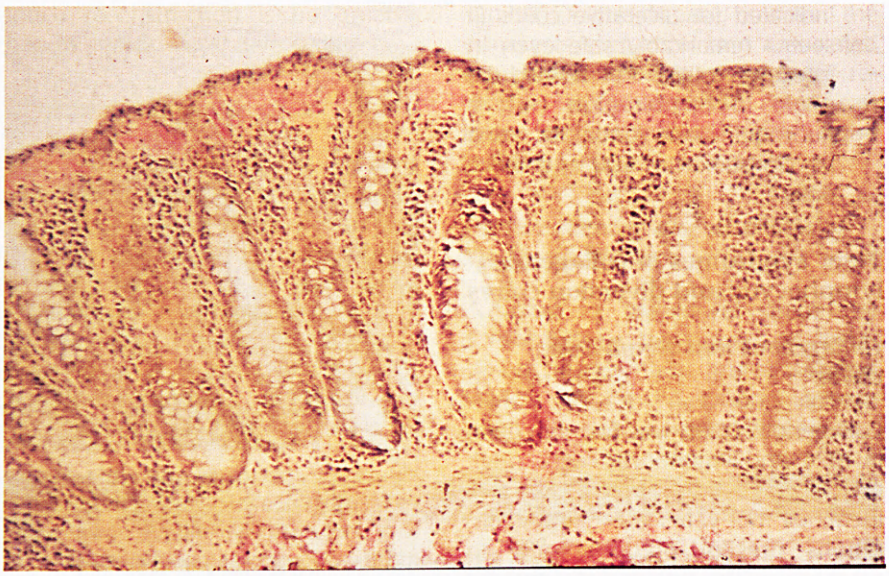


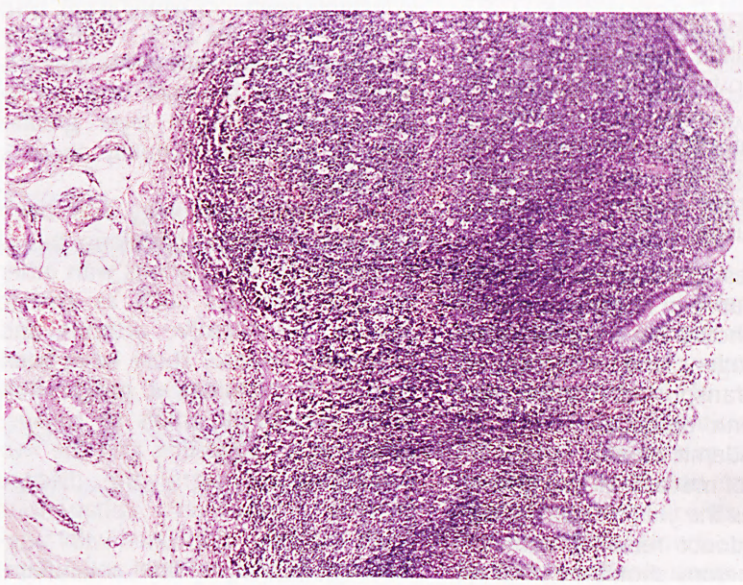
Figure 3. Histological appearance of collagenous colitis (note the subepithelial pink-staining collagen band).

- Alternative causes of diarrhoea should be excluded (eg hypolactasia, high sorbitol intake, laxatives).
- If specific therapy is still required, oral sulphasalazine 1 g twice daily should be tried first; if that fails, cholestyramine 1–2 g twice daily before meals. A last resort is corticosteroids, which may need to be in quite high dose (oral prednisolone 40 mg once daily), but used in short duration for episodes of particularly severe diarrhoea.

Diversion colitis

Diversion colitis is a mild colitis that quite commonly affects a colon that has been defunctioned by a more proximal colostomy. Histologically, it mimics ulcerative colitis with superficial inflammation and crypt abscess formation, but usually with only mild disturbance of crypt architecture and little goblet cell depletion. Follicular lymphoid hyperplasia may be prominent (Fig 4). The preferred energy source used by the normal colonic epithelium is butyrate, a short-chain fatty acid produced by bacterial digestion of dietary fibre and deficient in the defunctioned colon. Treatment with enemas of short-chain fatty acids is usually effective (60 mmol/l acetate, 30 mmol/l propionate, 40 mmol/l butyrate), but 5-aminosalicylic acid enemas are an effective alternative. The colitis resolves when continuity of the colon is restored[21].

Figure 4. Diversion proctitis: the lamina propria contains a diffuse lymphoplasmacytic infiltrate with prominent lymphoid follicular hyperplasia, seen on endoscopy as mucosal nodularity.



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