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Guide to inflammatory bowel disease



Inflammatory bowel disease (IBD)

The term 'inflammatory bowel disease' (IBD) refers to two separate conditions that both cause chronic relapsing inflammation of the intestinal tract. These conditions are ulcerative colitis (UC) and Crohn's disease (CD). Although they produce differing patterns of inflammation, there is some overlap in the clinical symptoms and the serious consequences of these conditions.

In the case of ulcerative colitis, the inflammatory process affects the colon. The inflammation is typically continuous, extending a variable distance from the rectum and is typically confined to the mucosal lining of the colon. This leads to broad areas of superficial ulceration. On rare occasions, UC may present as a more fulminant severe colitis, with more extensive inflammation and ulceration in association with systemic illness. Unlike UC, Crohn's disease may affect any portion of the gastrointestinal tract from the mouth to the anus. The disease is segmental and produces discrete, separate areas of inflammation. The inflammation in CD extends through the full thickness of the intestinal wall, leading to deep fissuring ulcers, fibrous thickening of the bowel wall and narrowing of the lumen with stricture formation. Complications may also include the formation of fistula tracts, which may extend into other segments of the intestinal tract or other organs such as the urinary bladder. The majority of patients with CD will also have anal complications, including fissures and fistulas.

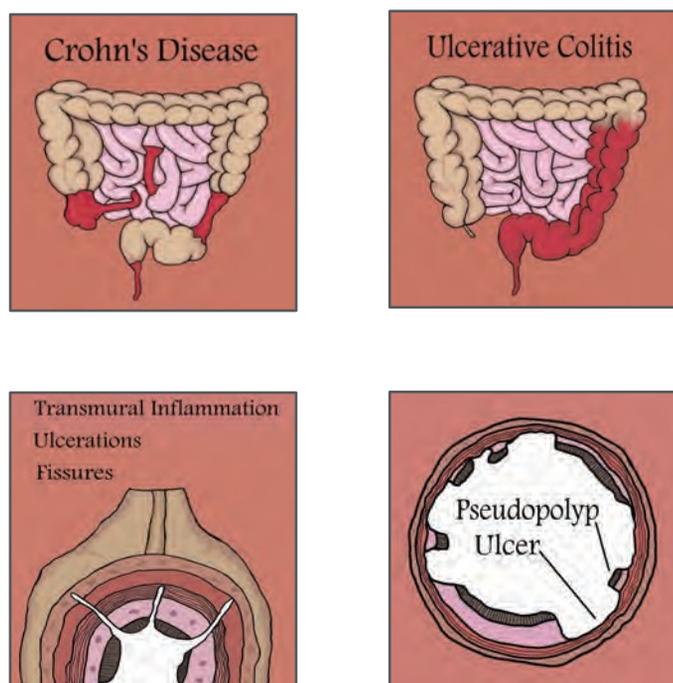


Figure 1: Patterns of disease and inflammation in Crohn's disease and ulcerative colitis.

Over many years, both UC and CD lead to pre-malignant changes (dysplasia) in the epithelial cells lining the GI tract called dysplasia. If left untreated, this will inevitably lead to cancer. The risk of cancer is greatest in UC patients whose entire colon is affected; with a 20–30 fold increased risk of cancer after 10 years. Therefore regular colonoscopies are required to monitor for this complication.

Both conditions may also be associated with extra-intestinal manifestations. In the case of Crohn's disease, approximately 25% of patients have at least one extra intestinal manifestation. These include arthritis, sacroiliitis, ankylosing spondylitis, skin lesions and liver diseases such as primary sclerosing cholangitis.

Symptoms of IBD

While there may be some overlap in the symptoms of UC and CD, the diseases typically have a slightly different presentation. UC presents as a relapsing disorder marked by episodes of bloody mucoid diarrhoea accompanied by crampy abdominal pain; the pain may persist for days, weeks or months: then subside, only to recur after an asymptomatic interval. In the worst cases, the initial disease may produce such serious bleeding and fluid loss that it may constitute an emergency. The onset of UC peaks between 20 and 25 years but the condition may arise in both younger and considerably older individuals. In the case of CD, the clinical manifestations are more variable. The disease usually begins with intermittent attacks of relatively mild diarrhoea, fever and abdominal pain, spaced by asymptomatic periods lasting from weeks to many months. In those with disease affecting the colon, overt bleeding or undetected bleeding leading to anaemia may occur. In about one-fifth of patients, the onset is more abrupt, with acute pain in the lower right quadrant, fever and diarrhoea. Most patients present with CD in the second decade of life. However, a second smaller peak occurs in adulthood. CD is more common in Western developed countries. In both conditions, the onset of symptoms may be preceded by a period of physical or emotional stress.

Causes of IBD

Numerous familial studies^{1,2} have demonstrated a genetic predisposition to IBD, with first-degree relatives exhibiting an increased prevalence. In the case of CD, relatives have a 12–15 times greater risk of contracting the disease. Conversely, 15% of IBD patients have affected first-degree relatives. These studies are supported by gene linkage studies^{3,4,5} which have shown linkage to gene loci on chromosomes 3, 5, 7, 12 and 16. However, a recent article in the journal *Nature*⁶ has reported 71 genetic associations in IBD, breaking the record for the largest number of associations for any common disease. At several of these loci, causative genes have now been identified. At present a gene called the CARD15 gene on chromosome 16 is the most understood susceptibility gene, explaining around 20% of the genetic predisposition to CD. As noted above, IBD shows considerable genetic variability. This partly explains the variability in clinical disease presentation in IBD, as differing mutations lead to differences in the nature of the IBD. As an example, the CARD15 gene mutations are associated with a small bowel disease location and a modestly earlier age of onset

The clinical variability may also relate to interactions with various external factors including diet, infections, smoking and other environmental factors. These external factors appear to interact with the intestinal immune system, which plays a critical role in the development and progression of the disease. Normally, the intestine is in a steady state of physiologic inflammation and represents a dynamic balance between factors that activate the immune system and host defences that maintain the integrity of the mucosa and down-regulate inflammation. In IBD host mucosal immunity is stimulated in response to substances in the bowel, particularly bacterial products and secreted toxins, and then fails to switch off. This leads to activation of inflammatory cells whose products cause tissue injury. Interestingly, the second half of the 20th century saw an increase in the incidence of IBD which closely mirrors the reported increase in allergic and autoimmune conditions. This has led some authors to suggest that modern living conditions may contribute to defective maturation in the normal regulation of the immune system by specific regulatory T lymphocytes. In summary, IBD results from an inappropriate response of the mucosal immune system to antigenic stimuli, including the normal enteric flora, in a genetically susceptible individual.

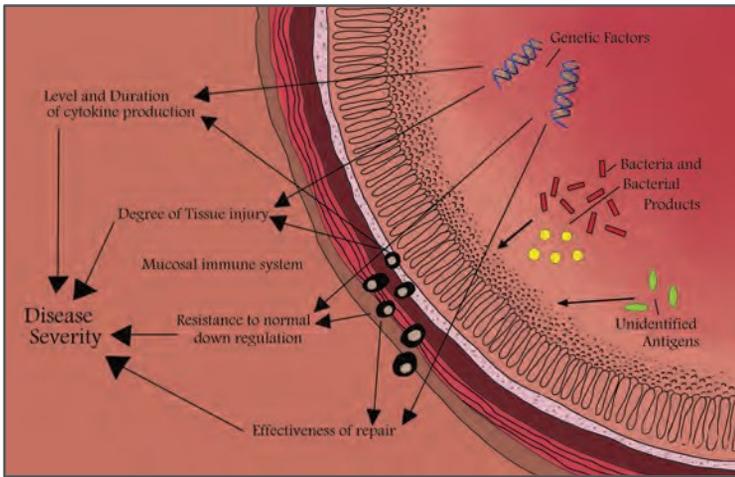


Figure 2: IBD likely results from a combination of genetic predisposition, cellular alterations and upregulated immunity.

Diagnosing IBD

There are a number of diseases that have similar presenting symptoms to IBD, including infections, coeliac disease and tumours. In addition there are conditions that produce GI symptoms but that have no identifiable cause. These fall into the category of functional disorders, of which irritable bowel syndrome (IBS) is the most common example. Until recently the only way to reliably differentiate organic disease from IBS was by performing a colonoscopy and upper GI endoscopy. During this procedure a camera is inserted into the colon, enabling the gastroenterologist to visualise the mucosal lining and take biopsies of any lesions seen. These are then processed in the pathology lab and examined under the light microscope for any abnormalities. The biopsies may be clearly diagnostic or alternatively may show nonspecific inflammation, in which case further investigations such as a stool culture may be required. In the case of CD involving parts of the small bowel not accessible to the endoscope, radiological investigation and possibly 'capsule endoscopy' may be required. The latter investigation involves swallowing a capsule that contains a small camera.

While endoscopic assessment and microscopic examination of biopsies represents the gold standard in diagnosing IBD, endoscopy is associated with unpleasant bowel preparation, some discomfort and a small risk of complications. In the primary care setting, in a majority of patients with non-acute abdominal complaints, no organic pathology will be found with endoscopy. Ideally, these patients should initially be assessed by a non-invasive test that identifies those patients who require a subsequent colonoscopy. Blood tests for systemic markers of inflammation, such as CRP and ESR, may indicate an inflammatory process. However, the tests are not specific for intestinal inflammatory disease and tend to correlate poorly with symptoms and disease activity. Attention has therefore turned to investigation of faeces to look for markers of inflammation. Of the various faecal markers available, faecal calprotectin has been the most widely adopted test.

Calprotectin is a cell protein derived predominantly from neutrophils, one of the types of white blood cells responsible for inflammation. Calprotectin is found in various body fluids in proportion to the degree of inflammation and has antibacterial and antifungal properties.

A recent meta-analysis reported the pooled sensitivity and pooled specificity of calprotectin in detecting inflammatory bowel disease in adults was 93% and 96% respectively. Studies assessing faecal calprotectin levels in IBD patients have found sensitivities and specificities from 90 to 95% for the identification of organic disease⁷. Calprotectin is particularly suitable for analysis as its level is relatively uniform within the stool; therefore, a small sample is representative. In addition it is not degraded rapidly, with no change after storage at room temperature for up to 7 days. One recent review of the literature suggests that screening with faecal calprotectin could significantly reduce the number of adults requiring endoscopy.



Figure 3: Endoscopic appearance of ulcerative colitis.

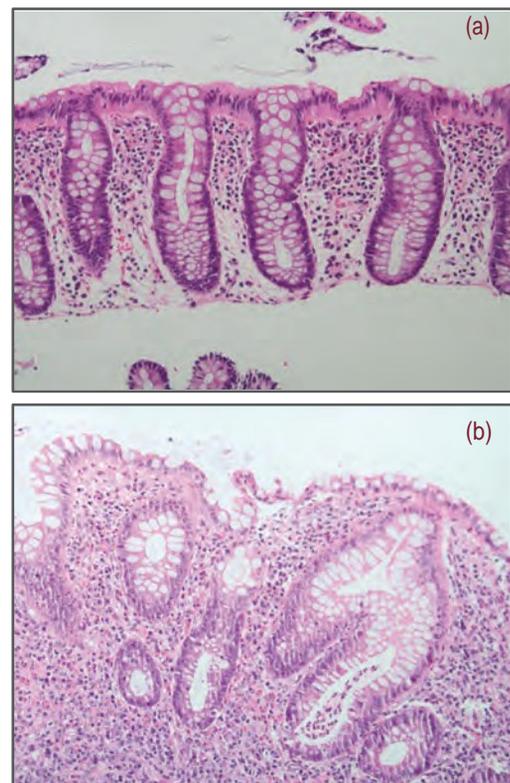


Figure 4: (a) Normal colonic mucosa showing regular crypt architecture and no acute inflammation; (b) colonic biopsy showing ulcerative colitis. There is architectural distortion with crypt branching, an increase in inflammatory cells within the mucosa and a collection of neutrophils within a crypt.

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Faecal calprotectin in clinical use

Faecal calprotectin can be useful in the following situations:

- Differentiation of irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD), or other organic GI disorder
- Assessment of disease activity in IBD
- Monitoring of response to treatment in IBD

While faecal calprotectin is indicative of organic disease, it cannot differentiate the type of disease. In addition to IBD, increased faecal calprotectin concentrations have been reported in bacterial gastroenteritis, colorectal cancer and diverticular disease. Therefore, patients with markedly elevated calprotectin levels will require further investigation, including endoscopy. Patients may also have variable calprotectin concentrations. Therefore, patients with slightly raised calprotectin levels who present to the GP for the first time may require a repeat sample 1–2 weeks later. The regular use of non-steroidal anti-inflammatory drugs (NSAIDs) may also cause inflammation of the intestine and it has been recommended that patients stop NSAIDs use several weeks before measuring faecal calprotectin. Below is one suggested clinical algorithm for the use of faecal calprotectin measurements in the differential diagnosis of irritable bowel syndrome and inflammatory bowel disease.

In addition to the diagnostic setting, recent studies have highlighted the usefulness of faecal calprotectin in monitoring the response of patients with IBD to treatment, the aim of which is the suppression of the inflammatory response. Even in cases of successful symptomatic treatment, subclinical inflammation may persist, contributing to the risk of relapse. Studies have demonstrated that high faecal calprotectin identifies those patients with IBD in clinical remission who are at risk of early relapse because of persistent mild inflammation. The predictive value appears to be stronger for ulcerative colitis (UC) than for Crohn's disease (CD).

Critically, there are a number of clinical settings where immediate colonoscopy/endoscopy is indicated and faecal calprotectin testing is inappropriate. These have been referred to as 'red flag' indicators and include age over 50 years, a positive family history of bowel cancer, unexplained weight loss, rectal bleeding, a prolonged change in bowel habit in an older patient, anaemia and a palpable abdominal or rectal mass. Should any of these indicators be present, an immediate referral to a gastroenterologist is required. However, in cases where 'red flag' indicators are not present, a faecal calprotectin measurement has the potential for clinicians to assess the need for further investigation and prevent unnecessary invasive testing.

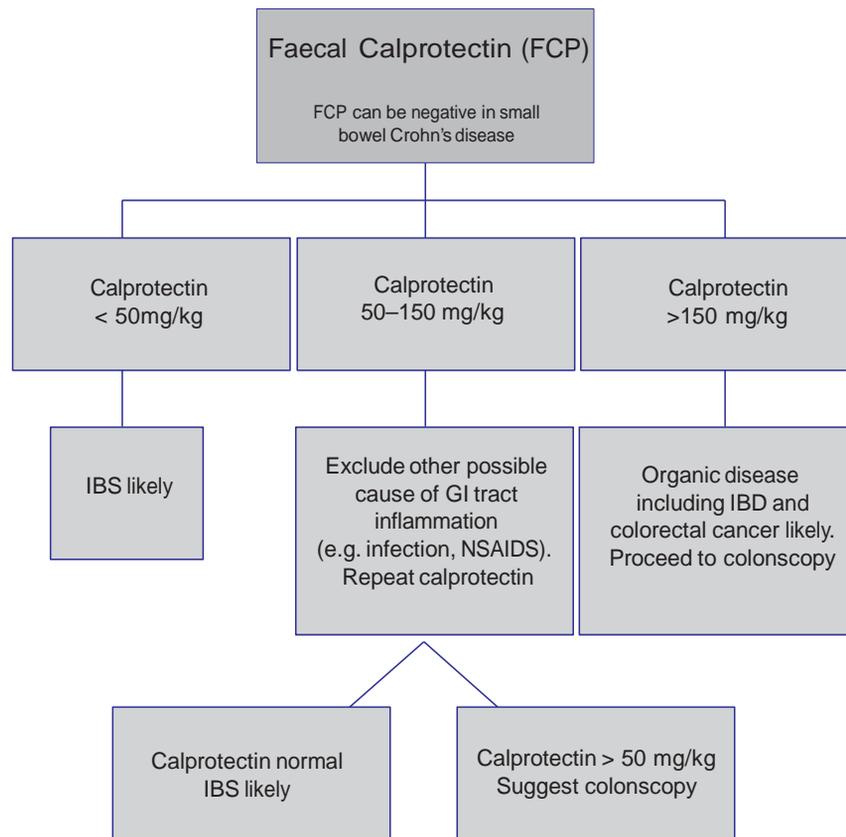


Figure 5: An algorithm for the use of faecal calprotectin measurements in the differential diagnosis of irritable bowel syndrome and inflammatory bowel disease⁸.

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This test is non rebatable, there will be an out of pocket cost of \$85.00 Correct at time of printing May 2015