An Atlas of Investigation and Management

INFLAMMATORY BOWEL DISEASE

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Abbreviations

5-ASA 5-aminosalicylic acid  
6-MP 6-mercaptopurine  
ALM adenoma-like dysplastic lesion or mass  
AS ankylosing spondylitis  
ASGE American Society of Gastrointestinal Endoscopy  
AXR abdominal X-ray  
Aza azathioprine  
BSG British Society of Gastroenterology  
CARD caspase recruitment domain  
CD Crohn’s disease  
CDT *Clostridium difficile* toxin  
CMV cytomegalovirus  
CRC colorectal cancer  
CREST (syndrome) Calcinosis, Raynaud’s syndrome, oEsophageal dysmotility, Sclerodactyly and Telangiectasia (syndrome)  
CRP C-reactive protein  
CT computed tomography  
DALM dysplasia-associated lesion/mass  
DNA deoxyribonucleic acid  
EIM extraintestinal manifestation  
EN erythema nodosum  
ERCP endoscopic retrograde cholangiopancreatography  
ESR erythrocyte sedimentation rate  
EUS endoscopic ultrasound  
FDR first degree relative  
Foxp3 forkhead box protein 3
GI gastrointestinal  
HLA human leukocyte antigen  
HSG hysterosalpingography  
IBD inflammatory bowel disease  
IBDU inflammatory bowel disease, type unclassified  
IFN-γ interferon-γ  
Il interleukin  
IPAA ileal pouch anal anastomosis (a form of RPC)  
IRGM immunity-related guanosine triphosphatase family, M  
IV intravenous  
IVF in vitro fertilization  
LBW low birth weight  
MAP Mycobacterium avium paratuberculosis  
MCP metacarpophalangeal  
MC&S microscopy, culture, and sensitivity  
MMR measles mumps and rubella vaccine  
MMX multimatrix  
MRCP magnetic resonance cholangiopancreatography  
MRI magnetic resonance imaging  
NBI narrow band imaging  
NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells  
NICE National Institute for Health and Clinical Excellence  
NOD nucleotide-binding oligomerization domain  
NSAID nonsteroidal anti-inflammatory drug  
OCTN organic cation transporter  
OGD oesophago-gastro-duodenoscopy  
PG pyoderma gangrenosum  
PSC primary sclerosing cholangitis  
RNA ribonucleic acid  
PPARγ peroxisome proliferator-activated receptor gamma  
qds (quater die sumendus) Latin: four times a day  
RPC restorative proctocolectomy (usually synonymous with IPAA)  
STAT-3 signal transducer and activator of transcription 3  
STC subtotal colectomy  
TB tuberculosis  
TGF-β transforming growth factor-β  
Th (cell) T helper (cell)  
TNF tumour necrosis factor  
TPMT thiopurine methyltransferase  
Treg regulatory T cell  
UC ulcerative colitis  
UDCA ursodeoxycholic acid  
UP ulcerative proctitis  
US ultrasonography  
VTE venous thromboembolism  
WBC white blood cell count
Part 1

DIAGNOSIS AND MANAGEMENT OF INFLAMMATORY BOWEL DISEASE

Chapter 1

Introduction: aetiology and clinical presentation

DIFFERENCES BETWEEN CROHN’S DISEASE AND ULCERATIVE COLITIS

The term inflammatory bowel disease (IBD) is generally used to describe ulcerative colitis (UC) and Crohn’s disease (CD), chronic idiopathic disorders characterized by gastrointestinal (GI) inflammation. CD can affect any part of the alimentary tract while UC affects only the large bowel. The prevalence of IBD is approximately 230 per 100,000 population in the western world, with an incidence of 15 per 100,000 per year. In 5–10% of cases there is clinical and endoscopic evidence for chronic colonic IBD but no definitive histological evidence to favour either CD or UC, and such patients are said to have indeterminate colitis, a term recently updated to inflammatory bowel disease, type unclassified (IBDU). In both conditions inflammation may occur at sites distant to the gut, so called extraintestinal manifestations. These may include arthritis, primary sclerosing cholangitis, ocular and cutaneous inflammation. The pathogenesis of IBD has not yet been fully elucidated, but it is thought to involve an abnormal, genetically predetermined response to an environmental trigger which is likely to be bacterial.

CD and UC may have similar symptoms, but distinguishing between the conditions is important due to differences in prognosis and management. Medical therapies are instigated to induce and maintain remission, and the efficacy of these may differ between the two conditions. Unfortunately surgical options may become necessary and the course of disease differs between UC and CD: 15–40% of those with UC will eventually come to colectomy, while between two-thirds and three-quarters of those with CD will require surgery at some time, and of these 50% will require a second operation. A colectomy for UC is generally considered to be curative; this is not the case for CD.

The main differences between CD and UC are summarized in Table 1.1. It should be noted that these are generalizations, and that more detailed explanations can be found elsewhere in the book.
# Introduction: aetiology and clinical presentation

<table>
<thead>
<tr>
<th><strong>Table 1.1 Main differences between CD and UC</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Crohn’s disease</strong></td>
</tr>
<tr>
<td><strong>Location</strong></td>
</tr>
<tr>
<td>Any part of the alimentary tract affected:</td>
</tr>
<tr>
<td>Ileocolonic</td>
</tr>
<tr>
<td>Colitis only</td>
</tr>
<tr>
<td>Terminal ileum only</td>
</tr>
<tr>
<td>Extensive small bowel</td>
</tr>
<tr>
<td>Anorectal only</td>
</tr>
<tr>
<td>Other (gastroduodenal, oral)</td>
</tr>
<tr>
<td><strong>Cases (%)</strong></td>
</tr>
<tr>
<td>45</td>
</tr>
<tr>
<td>25</td>
</tr>
<tr>
<td>20</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
</tr>
<tr>
<td>Diarrhoea +/- rectal bleeding</td>
</tr>
<tr>
<td>Weight loss</td>
</tr>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
</tr>
<tr>
<td>Perianal disease</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
</tr>
<tr>
<td>Deep, transmural inflammation</td>
</tr>
<tr>
<td>Patchy</td>
</tr>
<tr>
<td>Non-caseating granulomata characteristic</td>
</tr>
<tr>
<td>Lymphoid aggregates ++</td>
</tr>
<tr>
<td>Cryptitis and crypt abscesses +</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
</tr>
<tr>
<td>Fistula formation</td>
</tr>
<tr>
<td>Stricture disease of small bowel</td>
</tr>
<tr>
<td>Abscess formation</td>
</tr>
<tr>
<td>Vitamin B12 deficiency (ileal involvement)</td>
</tr>
<tr>
<td>Increased colonic carcinoma risk if colonic involvement; less than UC</td>
</tr>
</tbody>
</table>
AETIOLOGY

The cause of UC and CD remains unknown despite extensive research. Many hypotheses have been suggested including infectious agents such as measles virus and Mycobacterium avium paratuberculosis (MAP), environmental factors, and vascular factors. It is likely that IBD is caused by the interaction of genetic predisposition and environmental factors such as intestinal microbacteria. These interactions can probably occur at different levels, with some causing a predisposition to gut inflammation in general, some triggering UC or CD, and some determining the exact phenotype of the disease (such as disease severity and extent, and extraintestinal manifestations (1.1)).

Genetic factors

The possibility of a genetic component to the pathogenesis of IBD is suggested by the fact that the diseases are more common in certain populations such as Ashkenazi Jews, and through family studies, in which it is evident that CD, and to a lesser extent UC are more common in first degree relatives than in the general population. Twin studies have confirmed these observations, demonstrating over 50% concordance in monozygotic twins in CD, but lower levels in UC. The overall risk of a first degree relative developing IBD is between 5 and 20%, suggesting that genetic factors are important, but suggesting that environmental factors are also very important.

1.1 Aetiological concepts of IBD.
The advent of modern molecular biological techniques has allowed rapid progress to be made in the field of IBD genetics: genome-wide studies have identified a number of areas of the genome which appear to be linked to IBD, and within these a number of different genes have been identified which may play a role in triggering inflammation. These are largely related to control of the intestinal immune system and the way it reacts to the bacteria that normally exist in the gut. The most striking example of this is the CARD15 gene (NOD2) which is associated with ileal CD. This gene is part of the innate immune system, which recognizes components of bacterial cell walls (muramyl dipeptide) and triggers activation of the immune system through a series of nuclear transcription factors (most notably NF-κB). There are functional abnormalities in this process as a result of possessing CARD15 mutations, but how exactly this contributes to persistent inflammation is not yet clear. Other important genes are those of the HLA region, with the rare HLA-DRB1*0103 gene being associated with extensive and severe UC, colonic CD, and extraintestinal manifestations including large joint arthritis and uveitis. More recent studies have identified genes involved in the development and control of a novel group of T helper cells (T\(_{H17}\) cells) which are characterized by the production of the cytokine IL-17. This group of cells may contribute to the pathogenesis of both forms of inflammatory bowel disease. The cytokine IL-23 has an important role in triggering undifferentiated T cells to become IL-17 producing cells, and polymorphisms in the IL-23 receptor gene have been associated with both UC and CD.

1.2 Differentiation of T helper cells. T\(_{H17}\) cells are derived by stimulation of STAT-3. The cytokines TGF-β and IL-23 promote the production of these cells.
CD. Thus it is possible that changes in the genetic control of this pathway may be important in the pathogenesis of both UC and CD. The relationships of IL-23 and TH17 cells are illustrated in Figure 1.2. Other genes that have been associated with IBD are involved in autophagy – the process of engulfing and destroying host cells that are no longer useful. The list of genes associated with both UC and CD grows ever larger, and now easily numbers over 40. A list of major genetic associations found in IBD is given in Table 1.2.

The genetic studies in IBD have clearly shown that UC and CD are not caused by abnormalities in a single gene; rather it is likely that patients have to possess a critical load of predisposing genes to develop disease (i.e. multiple genes). In addition there has to be an appropriate environmental trigger, and this seems likely to be luminal bacteria in most cases.

<table>
<thead>
<tr>
<th>Gene/region</th>
<th>Chromosome</th>
<th>Association with UC/CD</th>
<th>Biological function (if known)</th>
<th>Relative risk conferred (approx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARD15</td>
<td>16</td>
<td>CD – ileal disease</td>
<td>Intracellular receptor for muramyl dipeptide – innate immune system</td>
<td>2.4–30</td>
</tr>
<tr>
<td>ATG16L1</td>
<td>2</td>
<td>CD</td>
<td>Autophagy (programmed destruction of cellular contents)</td>
<td>1.5</td>
</tr>
<tr>
<td>IL23R</td>
<td>1</td>
<td>CD &amp; UC</td>
<td>Receptor for IL-23 – helps differentiation of T cells to TH17 cells</td>
<td>0.38 (CD) 0.73 (UC) protective</td>
</tr>
<tr>
<td>IBD5</td>
<td>5</td>
<td>CD</td>
<td>?</td>
<td>2–6</td>
</tr>
<tr>
<td>IBD3</td>
<td>6</td>
<td>CD &amp; UC</td>
<td>HLA region – involved in antigen recognition and control of immune response</td>
<td></td>
</tr>
<tr>
<td>IRGM</td>
<td>CD</td>
<td></td>
<td>Autophagy</td>
<td>1.4</td>
</tr>
<tr>
<td>Csome 5p13.1</td>
<td>CD</td>
<td></td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Csome 10q21.1</td>
<td>CD</td>
<td></td>
<td>?</td>
<td></td>
</tr>
</tbody>
</table>
Environmental factors

Animal models may give an insight into the relationship between genetics and bacteria. It is possible to create models of inflammatory bowel disease by altering the genetic makeup of animals. The most well known are the HLA-B27 transgenic mouse, in which human HLA-B27 and β2-microglobulin genes are inserted, and the Il-10 knockout mouse, in which the Il-10 gene (which regulates inflammation) is deleted. In these models intestinal inflammation is not seen in animals kept in germ-free conditions, but as soon as they are reared under normal conditions the animals develop disease, demonstrating the importance of bacteria. Furthermore, different bacteria have differing abilities to cause inflammation depending on the genetic background – thus Bacteroides species and a cocktail of bacteria isolated from CD patients are able to cause colitis in the HLA-B27 transgenic rat, whereas Salmonella and E. coli species are less effective, and Helicobacter hepaticus is particularly effective at triggering inflammation in the Il-10 knockout mouse.

Table 1.3 Other theories of the aetiology of IBD

<table>
<thead>
<tr>
<th>Putative causative agent</th>
<th>Proposed mechanism</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Mycobacterium avium</em> sub. <em>paratuberculosis</em></td>
<td>Infection with this bacteria causes granulomatous inflammation similar to Johne’s disease in cattle</td>
<td>Isolation of MAP from some CD patients; may be a factor in some patients, unlikely to be a major cause in the majority</td>
</tr>
<tr>
<td>Measles, mumps and rubella vaccination</td>
<td>Combined vaccine has an effect on the overall immune system</td>
<td>Has now been largely disproved. In large population studies there is no increase in CD in subjects who have had the triple vaccination</td>
</tr>
<tr>
<td>Microparticles</td>
<td>Found in substances such as toothpastes – may excite a foreign body reaction with granulomatous inflammation</td>
<td>Little supporting evidence</td>
</tr>
<tr>
<td>Vascular inflammation</td>
<td>Inflammation of small vessels in the mesentery leading to inflammation and infarction</td>
<td>The anti-mesenteric nature of CD, and some evidence of vascular abnormalities. It is difficult to know whether these are primary or secondary</td>
</tr>
</tbody>
</table>
The challenge for investigators now is to try to unravel the complex link between the genetic background of the host and the luminal bacteria. This is particularly difficult as there are estimated to be over 400 species of intestinal bacteria, and over 40% of these are not amenable to traditional culture. New techniques such as 16S ribosomal ribonucleic acid (RNA) subunit typing may help to unpick these issues, by allowing a fuller characterization of the intestinal microbacteria. The realization of the importance of the luminal bacteria in triggering disease has also meant that much research is now being conducted into how the intestinal microbacteria may be altered to ameliorate disease, and there is currently much interest in probiotics (medications containing live bacteria to colonize the intestine) and prebiotics (foods which will favour specific bacterial species within the gut).

There have been many other theories about the pathogenesis of IBD, some of which have been highly controversial (see Table 1.3). These include an association between CD and the measles, mumps and rubella vaccine (MMR) and also MAP. It is clear that these agents do not cause the majority of CD, and epidemiological evidence has now made it clear that MMR is not associated with disease. MAP is clearly not the cause of most cases of CD, but there remains the possibility that it may be involved in a small proportion of cases.

Recommended reading


CLINICAL PRESENTATION

Introduction

Both CD and UC follow a relapsing–remitting pattern, producing ‘flares’ of variable severity and duration, and the symptoms described below are frequently intermittent and self-limiting. There is therefore an inherent delay in diagnosis, as patients tend to present with a subacute history of weeks or sometimes months, with complaints usually regarded as benign, typically of infective origin, by both themselves and treating physicians.

Symptomatology in UC typically constitutes predictable complaints related to the involvement of different parts of the colon. On the other hand, the inflammatory process in CD may involve one or more segments of bowel from the mouth to the anus, either in continuity or, much more commonly, in a segmental manner, and as such, it can produce a more variable constellation of symptoms. Recent evidence suggests, however, that there may be specific patterns in the segments of bowel involved in each individual patient, as well as in the way the disease will behave in terms of its inflammatory, strictureing, and fistulizing potential. A number of attempts have been made to classify IBD based on the site of disease and its severity.

Initially the Vienna classification was written for CD, and more recently the Montreal classification has aimed to establish clear and accurate clinical phenotypes of disease. This can be useful in clinical practice to help give a guide to long-term outcomes and natural history. The Vienna and Montreal classifications are shown in Tables 1.4–1.6. In CD the disease is classified by age at diagnosis, site of disease, and disease behaviour. In UC the disease is classified by extent and severity.

In addition, IBD can produce extraintestinal features which are either idiosyncratic due to the inflammatory response (commonly termed extraintestinal manifestations), or directly related to functional loss and malabsorption or other complications; both of these categories of symptoms will be examined separately from the luminal ones. Many of these occur at the time of first presentation and, in some cases, may be more obvious than the GI symptoms.
### Table 1.4 The Vienna and Montreal classifications of CD

<table>
<thead>
<tr>
<th>Vienna and Montreal classifications</th>
<th>Vienna</th>
<th>Montreal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Crohn's disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>A1 below 40 y</td>
<td>A1 below 16 y</td>
</tr>
<tr>
<td></td>
<td>A2 above 40 y</td>
<td>A2 between 17 and 40 y</td>
</tr>
<tr>
<td></td>
<td>A3 above 40 y</td>
<td>A3 above 40 y</td>
</tr>
<tr>
<td>Location</td>
<td>L1 ileal</td>
<td>L1 ileal</td>
</tr>
<tr>
<td></td>
<td>L2 colonic</td>
<td>L2 colonic</td>
</tr>
<tr>
<td></td>
<td>L3 ileocolonic</td>
<td>L3 ileocolonic</td>
</tr>
<tr>
<td></td>
<td>L4 upper</td>
<td>L4 isolated upper disease*</td>
</tr>
<tr>
<td>Behaviour</td>
<td>B1 non-stricturing, non-penetrating</td>
<td>B1 non-stricturing, non-penetrating</td>
</tr>
<tr>
<td></td>
<td>B2 stricturing</td>
<td>B2 stricturing</td>
</tr>
<tr>
<td></td>
<td>B3 penetrating</td>
<td>B3 penetrating</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p perianal disease modifier**</td>
</tr>
</tbody>
</table>

*L4 is a modifier that can be added to L1–L3 when concomitant upper gastrointestinal disease is present

** ‘p’ is added to B1–B3 when concomitant perianal disease is present

Adapted from Satsangi J, *et al.* Gut 2006;55:749–53
### Table 1.5 The Montreal Classification of UC – disease extent

<table>
<thead>
<tr>
<th>Disease extent</th>
<th>Anatomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extent E1 ulcerative proctitis</td>
<td>Involvement limited to the rectum, i.e. proximal extent of inflammation is distal to the rectosigmoid junction</td>
</tr>
<tr>
<td>Extent E2 left-sided UC (distal UC)</td>
<td>Involvement limited to the proportion of the colorectum distal to the splenic flexure</td>
</tr>
<tr>
<td>Extent E3 extensive UC</td>
<td>Involvement extends proximal to the splenic flexure</td>
</tr>
</tbody>
</table>

Adapted from Satsangi J, et al. Gut 2006;55:749–53

### Table 1.6 The Montreal Classification of UC – disease severity

<table>
<thead>
<tr>
<th>Disease severity</th>
<th>Anatomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity S0 clinical remission</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Severity S1 mild UC</td>
<td>Passage of 4 or fewer stools/day (with or without blood), absence of any systemic illness, and normal inflammatory markers</td>
</tr>
<tr>
<td>Severity S2 moderate UC</td>
<td>Passage of more than 4 stools per day but with minimal signs of systemic toxicity</td>
</tr>
<tr>
<td>Severity S3 severe UC</td>
<td>Passage of at least 6 bloody stools daily, pulse rate of at least 90 beats per minute, temperature of at least 37.5°C, haemoglobin of less than 10.5 g/100 ml, and ESR of at least 30 mm/hr</td>
</tr>
</tbody>
</table>

ESR: erythrocyte sedimentation rate

Adapted from Satsangi J, et al. Gut 2006;55:749–53
**Luminal symptoms of CD**

**Small bowel (1.3)**

CD involves the small bowel in about 50% of cases. The symptomatology produced by small bowel CD can be accounted for either directly due to inflammation of the intestinal mucosa, or indirectly in terms of the manifestations of various degrees of functional loss; it mainly includes diarrhoea, abdominal pain, and weight loss. Diarrhoea is the cardinal feature of small bowel CD, and it typically persists during the night leading to sleep disturbance of variable severity. When the terminal ileum is involved to such a degree that fat and bile salt malabsorption occur, patients describe steatorrhoeic stool, which is pale in colour, stains the pan, and is difficult to flush. Other proposed mechanisms accounting for the diarrhoea in jejuno-ileitis are bacterial overgrowth, particularly proximal to stenosed segments, and a reduced capacity of the inflamed mucosa to absorb water, which is more significant pathophysiologically in large bowel CD. Abdominal pain may be due to the inflamed segments or due to the effects of bowel wall oedema and subsequently stricturing. When strictures are responsible for the abdominal pain it usually occurs within 1 or 2 hours after food, and it is more prominent following consumption of high-fibre diets. Depending on severity, strictures can be associated with various degrees of post-prandial abdominal distention and vomiting. Weight loss, which is typically modest, is also multifactorial, and it can be accounted for by the catabolic state of the inflammatory response, the malabsorption, and the food avoidance resulting from the post-prandial exacerbation of symptoms.

**Large bowel (1.4)**

Large bowel CD occurs either in isolation or in combination with terminal ileal disease, when the caecum and ascending colon are preferentially involved. Diarrhoea is again a prominent feature and may be attributed to the reduced capacity of the inflamed mucosa to resorb water as well as to alterations in transit times. Excessive inflammation results in variable amounts of rectal bleeding associated with the diarrhoea, which is more pronounced when distal segments are involved. In addition, patients with rectal inflammation frequently present with urgency and incontinence as the capacity of the inflamed rectum is reduced. This is often a debilitating symptom severely affecting quality of life. Furthermore, with more distal involvement patients frequently describe a mucoid appearance of the stool, or even the sole passage of blood and/or mucus independent of the diarrhoea.

Pain produced by large bowel inflammation is usually crampy in character, preceding and relieved by defecation. As the inflammation in CD is typically transmural, serosal wall abscesses may form, resulting in more severe and persisting pain, localized peritonitis, and a septic state.

**Fistulae and perianal involvement**

Fistula formation is one of the most distressing complications in CD, occurring in approximately one-third of patients. In fistulizing forms of the condition, fistulae may form between segments of the bowel, presenting with high-output diarrhoea and pain, in addition to the effects of the usually profound electrolyte depletion. Occasionally fistulae may form between the small intestine and the bladder or the female reproductive organs, producing the corresponding local symptoms of recurrent urinary tract infection, pneumaturia or faecuria, as well as abnormal vaginal discharges.

Perianal involvement has a varying reported prevalence according to the distribution of the luminal pathology, ranging from >90% of patients with Crohn’s colitis with rectal involvement to 12% of patients with isolated small bowel disease. Common findings include skin tags and haemorrhoids, anal fissures which are frequently painless, perianal fistulae and abscesses, anal canal stenosis and, rarely, anal cancer. They contribute significantly to morbidity, and together with fistulae described above they constitute the most persistent manifestations of CD, commonly requiring protracted medical and surgical management.

**Oesophagus–stomach**

The upper GI tract is the least commonly involved segment. When the oesophagus is involved, odynophagia and dysphagia are the cardinal symptoms. In cases of gastric involvement, patients complain of nausea, vomiting, and epigastric pain.
Introduction: aetiology and clinical presentation

1.3 Symptoms of small bowel CD.

**Symptoms**
- Diarrhoea
- Abdominal pain
- Weight loss
- Symptoms of malabsorption

1.4 Symptoms of large bowel (ileocolonic) CD.

**A combination of**
- Diarrhoea
- Abdominal pain
- Weight loss
- Symptoms of malabsorption
- Rectal bleeding
- Urgency
  (according to degree of large bowel involvement)
Luminal symptoms of UC

**Proctitis (1.5)**
Patients with proctitis usually complain of the passage of fresh blood, or blood-stained mucus, which is either mixed with stool or streaked onto its surface. Tenesmus and urgency are also prominent features, with episodes of incontinence being not uncommon. In addition, many patients may actually complain of constipation, frequently confirmed on imaging, which has been attributed to slower whole colon transit times in the presence of distal constipation.

**Left-sided and extensive disease (1.6)**
As the disease extends beyond the rectosigmoid, episodes of bloody diarrhoea, frequently containing pus, are the predominant feature. As in CD, multiple nocturnal episodes of diarrhoea frequently lead to sleep disturbance. Abdominal pain of variable severity is also a feature of more extensive colitis, both in the form of lower abdominal discomfort as well as central abdominal cramping.
Extraintestinal manifestations

The life-time risk for the development of extraintestinal manifestations (EIMs) in both UC and CD is around 25–30%, and they occasionally precede or predominate over the GI symptoms. Thus, in patients presenting with features of possible EIMs of a GI condition, a careful GI history should be obtained at the onset, in an attempt to establish if IBD is a likely underlying diagnosis.

Cutaneous manifestations

Up to 10% of patients with IBD describe cutaneous symptoms, most commonly erythema nodosum, pyoderma gangrenosum, and oral manifestations. Erythema nodosum is characterized by sudden-onset painful bilateral nodules of average diameter around 2 cm. They commonly occur on the shins but have also been described on the calves, face, and trunk. It is more common in UC, and it usually mirrors the activity of the luminal disease. Pyoderma gangrenosum has been described in 0.5–20% and 1–10% of patients with CD and UC, respectively. Pain typically precedes the development of pustules and the rapid formation of a necrotic ulcer with bluish borders. Like erythema nodosum, the overwhelming majority occurs on the lower legs. Oral manifestations of IBD include aphthous ulceration, which occur in about 10% of patients, and may constitute the presenting complaint. Painful mucosal cobblestoning and pyostomatitis vegetans have also been described.

Musculoskeletal manifestations

Central arthropathies related to IBD include a range of syndromes. Asymptomatic sacraliitis detected by radiological evidence only has an estimated prevalence of up to 50%. At the other end of the spectrum, full-blown ankylosing spondylitis occurs in approximately 5% of patients. Inflammatory back pain characteristically is low back pain at night or at rest, and improving with movement, and occurs in up to 30% of patients with CD. It typically radiates to the buttocks, is associated with morning stiffness for more than 30 minutes, and responds well to nonsteroidal anti-inflammatory medication. It is often a challenge to distinguish this pain from mechanical low back pain, which is very common.

Peripheral arthropathies occur in 5–20% of patients with IBD and they are subcategorized into Type I (pauciarticular, large joints, fewer than 5 joints involved with evidence of swelling and effusion, mainly asymmetrical) and Type II (polyarticular, with 5 or more joints involved with evidence of swelling and effusion, mainly symmetrical). Both types occur significantly more commonly in women. In 25–30% of large joint arthritis (Type I), the arthritis is one of the presenting features of the IBD. Clinically, it is identical to a post-enteric infection reactive arthritis. Thus, in patients who present with large joint arthritis in combination with intestinal symptoms, a rectal biopsy looking for signs of chronic inflammation is often helpful. If the GI symptoms persist, then a colonoscopy is mandatory.

Ocular manifestations

Ocular manifestations of IBD occur in less than 10% of patients but contribute significantly to overall morbidity in those affected. Episcleritis is the commonest complication and typically flares during increases in IBD activity, and it should be suspected in patients presenting with acute unilateral or bilateral redness, irritation, and burning. When photophobia and reduction of visual acuity are superimposed on the above symptoms, then scleritis or uveitis should be suspected, prompting an urgent ophthalmological referral.

Hepato-biliary manifestations

Primary sclerosing cholangitis is the main hepato-biliary manifestation of IBD, with a prevalence of up to 3% of cases. Although usually detected in the asymptomatic phase, patients may present with symptoms of biliary stasis, such as jaundice and pruritus, and, in late cases, biliary sepsis may ensue.
Symptoms related to complications

**Manifestations of malabsorption**
CD affecting the small bowel can result in malabsorption and nutritional deficiencies, which produce a wide symptomatology (outlined in Table 1.7).

**Thromboembolic events**
IBD has been increasingly recognized as an independent risk factor for the development of venous thromboembolism (VTE). A high clinical suspicion should therefore be maintained both for symptoms at common sites such as leg swelling, pleuritic chest pain, and shortness of breath as well as at rarer locations, e.g. arm swelling in axillary/subclavian thromboses and neurological symptoms in cerebral venous sinus thromboses.

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Symptoms of deficiency/excess</th>
</tr>
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<tbody>
<tr>
<td>Albumin</td>
<td>Generalized dependent oedema, cardiac failure, altered handling of several drugs</td>
</tr>
<tr>
<td>Calcium</td>
<td>Neuromuscular: perioral and peripheral tingling, cramps/tetany, bronchospasm Neurological: irritability, depression, behavioural changes, seizures Cardiac: shortness of breath, congestive cardiac failure Cutaneous: coarse hair, brittle nails, psoriasis, dry skin</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Weakness, muscle cramping, palpitations</td>
</tr>
<tr>
<td>Oxalate</td>
<td>Renal colic, gross haematuria</td>
</tr>
<tr>
<td>Niacin</td>
<td>Pellagra-like symptoms</td>
</tr>
<tr>
<td>B12</td>
<td>Symptoms of anaemia, peripheral neuropathy</td>
</tr>
</tbody>
</table>

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