15.11 Crohn’s disease 2925

15.11 Crohn’s disease 2925

15.11 Crohn’s disease Miles Parkes and Tim Raine ESSENTIALS Crohn’s disease is a common form of chronic inflammatory bowel disease. Typically involving one or more of the terminal ileum, colon, and perineum, it causes patchy transmural inflammation character- ized microscopically by granulomata. Common complications in- clude fibrotic strictures, fistulas, and abscesses. The initiating trigger is unknown, but an unregulated mucosal immune response to commensal bacteria drives the chronic in- flammation. Variants in several genes involved in innate immunity are strongly associated, with NOD2, interleukin-23, and autophagy pathways all implicated. Smoking also increases the risk. With a pattern of episodic flares, which are unpredictable in their timing and severity, Crohn’s disease confers significant morbidity but low mortality. Treatment of acute inflammatory disease is usually with cortico- steroids or (occasionally) therapeutic diets, the latter particularly in children. For steroid dependence, frequent relapse, or objective evi- dence of uncontrolled mucosal inflammation, immunosuppression is indicated with immunomodulator or biological therapy or a com- bination of the two. First-line immunomodulators are azathioprine or 6-mercaptopurine, with methotrexate used as second-line therapy. Antitumour necrosis factor-α (anti-TNFα) antibody therapy can induce rapid remission of resistant disease and has a key role in maintaining remission in such cases. Newer monoclonal antibodies with a role in disease management include antibodies to IL12/23 and to integrins associated with intestinal lymphocyte trafficking. Despite increased use of immunosuppressants, 70 to 80% of patients require surgery in the long term, most commonly for ileal stricturing. Timely, conservative surgery is the key, minimizing the length of small-bowel resected and using laparoscopic approaches where possible. For colonic disease requiring surgery, segmental col- ectomy or subtotal colectomy with ileorectal anastomosis are pre- ferred, but significant rectal or perianal involvement may require proctocolectomy and ileostomy. Perianal Crohn’s disease is treated medically with antibiotics, azathioprine, and anti-TNF antibody therapy, and surgically with ab- scess drainage and placement of seton sutures through fistulas where possible. Some fistulas heal with intensive medical therapy. Others may warrant attempts at surgical repair if they produce unacceptable symptoms but success rates are not high. Introduction and history Crohn’s disease is a form of chronic, relapsing inflammatory bowel disease characterized by discontinuous segments of transmural in- flammation. It can affect any part of the gastrointestinal tract but most commonly involves the terminal ileum, colon, and perineum. The eponymous term ‘Crohn’s disease’ derives from the index de- scription of chronic ileal inflammation in young people in 1932 by Crohn, Ginzburg, and Oppenheimer. However, many much earlier reports describe what would now be called Crohn’s disease. Colonic Crohn’s disease was formally differentiated from ulcerative colitis by Lockhart-Mummery and Morson in 1960, although recent gen- etic studies suggest, perhaps unsurprisingly,

that they are closely related. Aetiology Precise pathogenic mechanisms are unknown, but Crohn’s disease evidently results from a complex interplay of genetic and envir- onmental factors producing an excessive, unregulated inflamma- tory response to luminal microflora in susceptible individuals. The trigger has not been identified. Susceptibility to the initial trigger may result from a defective mu- cosal barrier: either increased intestinal permeability, allowing lu- minal antigens to access the mucosal immune system, or aberrant innate immunity, which would increase risk of microbial invasion. Evidence from genetic studies increasingly implicates the latter in Crohn’s disease, the former perhaps being more relevant in ulcera- tive colitis. There may also be a primary contribution of microbial dysbiosis. Early failure to control microbial ingress leads to activa- tion of alternative, adaptive immune pathways mediated by CD4+ T cells. In Crohn’s disease, these are predominantly Th1 and Th17 cells, secreting signature cytokines interferon (IFN)-γ/interleukin (IL)-2 and IL-17 respectively, with tumour necrosis factor (TNF)-α and IL- 23 also being critical mediators. Environmental factors The clearest environmental association is with smoking, which more than doubles the risk of developing Crohn’s disease while being protective against ulcerative colitis. The mechanism is unclear.

 Use of nonsteroidal anti-inflammatory drugs (NSAIDs) and the oral contraceptive pill are also associated, the former perhaps by increasing intestinal permeability—well recognized to precede flares of Crohn’s disease. Interestingly, 10% of healthy first-degree relatives of Crohn’s disease patients have increased intestinal perme- ability, suggesting a heritable basis. Many patients are concerned about dietary precipitants for Crohn’s disease. Excess refined sugar and lack of fibre have been noted in retrospective studies, but may reflect dietary accommoda- tion to early symptoms. Response to therapeutic diets also suggests food antigens are important but no single foodstuff is consistently associated. Microbiological determinants represent obvious potential trig- gers, and self-limiting infections such as yersinia do precede Crohn’s disease in some instances. More contentiously, specific chronic in- fections might cause the persisting inflammation. Advocates of Mycobacteria paratuberculosis, which causes the granulomatous in- testinal inflammation of Johne’s disease in cattle, highlight detection of its DNA in Crohn’s ulceration in limited, poorly controlled studies. Furthermore, recent genetic studies have highlighted substantial overlap between Crohn’s disease susceptibility genes and those for leprosy and Mendelian susceptibility to mycobacterial disease. However, epidemiological evidence shows no clustering of Crohn’s disease in livestock farmers, and antituberculous therapy is not ef- fective in unselected patients with Crohn’s disease. The contribution of mycobacteria to disease aetiology thus remains speculative. A role for commensal bacteria appears more secure, particularly in perpetuating intestinal inflammation after the initial trigger. In nearly all murine models, intestinal inflammation is markedly at- tenuated in the absence of commensal flora or upon antibiotic treat- ment. Conversely, in some models, inflammation appears to be transmissible from genetically susceptible mice to wild-type litter mate controls through cohousing and the sharing of dysbiotic flora. Clinical evidence comes from attenuation of Crohn’s disease in- flammation following diversion of the faecal stream with ileostomy. Commensal strains implicated include bacteroides and adherent invasive Escherichia coli, while others confer protection, including Faecalibacterium prausnitzii and ‘probiotic’ strains of lactobacilli and bifidobacter. Recent data have highlighted a potential role for viruses, with notable bacteriophage expansion in inflammatory bowel disease perhaps accounting for the loss of bacterial diversity that is a consistent feature. Disentangling cause–effect relationships remains a challenge. Genetic determinants Although environmental influences are clearly important, it is gen- etic studies that have made most progress over the last

decade. Each child of a Crohn's disease-affected individual has a 2 to 4% risk of developing Crohn's disease, rising to approximately 30% where both parents are affected. The effect sizes for most confirmed sus- ceptibility genes are modest but they highlight critical molecular pathways predisposing to Crohn's disease. A major theme that has emerged is the importance of the early host immune response to bacterial ingress—particularly innate immunity. NOD2, the first Crohn's disease gene identified, encodes an intra- cellular receptor for bacterial muramyl dipeptide. Upon ligand binding, NOD2 activates a range of downstream partners including NF-κB (a transcription factor for several proinflammatory cytokines), caspase-1 (which releases the active, proinflammatory form of IL-1β), and mediators of autophagy (see later in this section). For NOD2 het- erozygotes, the risk of Crohn's disease is doubled compared to wild type, while homozygotes have a 17-fold increased risk. Interestingly there is significant heterogeneity, both for disease (NOD2 variants are specifically associated with ileal Crohn's disease) and ethnicity (no NOD2 coding mutations are found in Japanese patients). Other signals identified by genome-wide association scans in Crohn's disease converge on two other key immune pathways. One is the activation of naive CD4+ T cells by IL-23. Confirmed association with variants in genes for the IL-23 receptor and IL-12B (which en- codes a subunit common to IL-12 and IL-23) among other compo- nents of this pathway strongly corroborates functional experiments in mouse models, which also implicate IL-23 in chronic intestinal inflammation. Another key component is autophagy. Replicated association at two separate genes, ATG16L1 and IRGM, first highlighted autophagy—and NOD2 mutations are now known to disrupt this previously unsuspected pathway. Autophagy is the mechanism by which cells engulf, compartmentalize, and digest cytoplasmic debris and intracellular bacteria. Its disruption permits prolonged survival of several intracellular microorganisms—perhaps important for the intracellular bacteria postulated to play a role in Crohn's disease pathogenesis, including adherent invasive E. coli. The main disease-associated polymorphisms in NOD2, IL23R, and ATG16L1 are coding variants associated with hypofunction. For most genetic signals identified by genome-wide association studies in Crohn's disease, which lie in nonprotein-coding regions of the genome, aetiological understanding is at a more rudimentary stage, with presumed effects through changes in regulatory mechan- isms for gene expression. In which cells these genetic abnormalities have an effect remain unknown, but candidates include intestinal macrophages, dendritic cells, T cells, and epithelial cells. Indeed, it seems that the clinical phenotypes of Crohn's disease may represent a final common pathway of immune-mediated end-organ damage resulting from not one but several potential underlying pathologies, including failure of epithelial barrier function, innate immune de- fects resulting in susceptibility to intracellular infection, inappro- priate activation of an adaptive immune response to commensal flora, and failure of immune regulation. Pathology Crohn's disease can affect any part of the gastrointestinal tract but most commonly causes ileocaecal (40%), exclusively ileal (30%), or exclusively colonic (25%) inflammation with or without perianal in- volvement (25%). Diffuse small-bowel, upper gut, or oral Crohn's dis- ease are less frequent. Colonic disease often spares the rectum. These patterns typically remain stable in any given patient over time. Ulcers are usually present, with appearances varying from small aphthous lesions overlying lymphoid aggregates to scattered punched-out, serpiginous, longitudinal, or pleomorphic ulcers (see Fig. 15.11.2). Inflammation is patchy, giving rise to 'skip lesions', and transmural— manifest as deep ulceration and cobblestoning endoscopically, and fat wrapping on cross-sectional imaging or at surgery. The bowel wall is usually thickened, often producing luminal stenosis, and the mes- entery oedematous with regional lymph node enlargement.

15.11 Crohn’s disease 2927 Histologically, Crohn’s disease is characterized by a patchy chronic transmural inflammatory infiltrate, maximal in the submucosa and lamina propria. This consists of lymphocytes, characteristically or- ganized as lymphoid aggregates, macrophages, and plasma cells. Acutely, neutrophils infiltrate around crypts producing cryptitis. Fissuring ulcers can penetrate deeply, sometimes to the serosal sur- face to produce fistulas, and noncaseating epithelioid granulomata formed from macrophages and giant cells may be found at any level in up to 60% of cases (Fig. 15.11.1). Typically in the colon there is preservation of goblet cell numbers and crypt architecture com- pared to ulcerative colitis. Epidemiology Crohn’s disease can affect people of any age but peak incidence oc- curs in early adulthood, with a smaller peak in the seventh decade. There is a marginal predominance in women and 15% of patients have an affected relative. Crude annual incidence in Western coun- tries ranges from 2 to 20 per 100 000, with a north–south gradient (higher in the north) across Europe and North America. Incidence is highest in Ashkenazi Jews and low in Asia (0.5 per 100 000). The incidence and prevalence of Crohn’s disease appears to be rising in nearly all populations. This is especially apparent in non-Western societies, perhaps reflecting adoption of ‘Western’ lifestyles. Increased awareness and improved diagnostics have undoubtedly also contributed. Estimates of Crohn’s disease prevalence also vary significantly, in part according to ascertainment method. Population- and primary care-based surveys in the United Kingdom put the prevalence as high as 140 to 210 per 100 000, while studies in secondary/tertiary care are lower at 70 to 100 per 100 000. Either figure indicates that the burden of disease is substantial in terms of both morbidity and cost. Estimates of direct healthcare costs vary widely and are sig- nificantly impacted by country and disease severity, but recent ana- lyses suggest an average figure of £2000 to £4500/patient-year for Crohn’s disease. Clinical features The clinical presentation of Crohn’s disease varies from ‘classical’ to diagnostically challenging and nonspecific. Cardinal symptoms are the combination of abdominal pain, weight loss, and diarrhoea. With severe disease, patients may have systemic upset, with fever, tachycardia, and anaemia. More often, however, a modestly raised C-reactive protein (CRP) and vague or irritable-bowel-like symp- toms may be the only clues mandating further investigation. Many patients report remitting and relapsing symptoms for months or years before the diagnosis is made. A family history of inflammatory bowel disease and smoking history should be sought. For patients with established disease, the Harvey–Bradshaw index provides a simple assessment of activity, while the Crohn’s disease activity index requires symptom diaries plus laboratory data. In both cases, subjective elements may capture noninflammatory symptoms, leading to significant limitations. The Inflammatory Bowel Disease Questionnaire (IBDQ) is the best validated quality of life tool. Symptoms Symptoms are significantly determined by the site of intestinal inflammation and typically include lower abdominal pain, diar- rhoea, anorexia, and weight loss. Tiredness, malaise, sweats, and extraintestinal manifestations can be prominent. Abdominal pain reflects gut wall ulceration and mesenteric oe- dema, and often localizes to the right iliac fossa with ileocaecal disease. It may be constant, reflecting the presence of deep ulcer- ation, or colicky, exacerbated by eating and associated with other obstructive features such as vomiting or bloating as a consequence of luminal stricturing. Abdominal pain due to coincident gallstones or renal stones, both associated with Crohn’s disease, can cause confusion. Weight loss is common with active Crohn’s disease, particu- larly involving the small bowel, so patients should be weighed at each clinic visit. Contributory factors include food avoidance due to abdominal pain or mouth ulceration, intestinal protein loss, ca- tabolism induced by inflammation or sepsis, and malabsorption re-flecting the combination of diffuse small-bowel disease, resection, and bacterial overgrowth. Most patients experience diarrhoea. Bowel frequency correlates with inflammatory activity, particularly

in the colon, with bacterial overgrowth and ileal resection potentially contributing. Bleeding per rectum is less common than in ulcerative colitis, as is urgency— unless the rectum is involved or the anal sphincter damaged. An important point: many Crohn's disease patients consider three to four semisolid bowel evacuations per day to be 'normal' and it is the change from baseline, including nocturnal frequency, which is im- portant in assessing disease activity. Perianal symptoms will occur in around 40%. Perianal pain may indicate an abscess or fissure formation, fistula discharge is common, and anal stricture may produce constipation or tenesmus. Fig. 15.11.1 Crohn's disease affecting large bowel, showing fissuring ulceration (narrow arrow) and transmural inflammation with a 'Crohn's rosary'—lymphoid aggregates studded along the outer border of the muscularis propria (broad arrow). Courtesy of Dr Vicki Save, Addenbrooke's Hospital, Cambridge.

section 15 Gastroenterological disorders 2928 Fistulizing Crohn's disease, with or without intra-abdominal or pelvic abscess, is seen in around 40% of patients. It can be the presenting feature or evolve as a result of uncontrolled transmural inflammation. Typical fistulae include enteroenteric (often de- tected only on imaging, but may be associated with a mesenteric abscess), enterovesical (associated with pneumaturia and recurrent urinary tract infections), and rectovaginal. Perianal fistulae are more common than internal fistulae. Fertility is reduced in women with Crohn's disease, and the miscarriage rate is higher, particularly with active disease during pregnancy. Signs Many patients with active Crohn's disease appear deceptively well. A minority are anaemic or malnourished. A persisting tachycardia may point to dehydration, severe inflammation, or sepsis. The oral cavity should be inspected for ulceration and glossitis. The com- monest abnormal examination finding is right iliac fossa tenderness, often with associated fullness or a mass due to thickened and matted bowel loops. Equivalent findings may be found over any affected bowel segment. Anorectal examination may reveal various signs from violaceous fleshy or 'woody' skin tags to anal fissure, ulcer, abscess, and fistulae. Anal stenosis may be detected. Signs related to specific complications may be evident—for ex- ample, fever and tachycardia with intra-abdominal collection, dis- tension and high-pitched bowel sounds with obstruction, and so on. Extraintestinal manifestations Extraintestinal manifestations of Crohn's disease commonly affect the mouth, joints, skin, and eyes, and less commonly the liver and lungs. These are more frequent with colonic involvement and may precede intestinal symptoms. Oropharynx Aphthous ulcers are usually associated with active intestinal inflam- mation. These should be distinguished from haematinic deficiency (glossitis, angular cheilitis), oral candida, and (particularly) oropha- ryngeal Crohn's disease, which usually causes fissuring and thick- ening of the lips but can present with deep sulcal ulceration and buccal cobblestoning. There is overlap with orofacial granulomatosis where 60% have asymptomatic intestinal lesions of Crohn's disease. Both oral Crohn's disease and orofacial granulomatosis can be successfully treated with a low-benzoate, low-cinnamon diet or topical steroids. Joints Involvement is seen in 10 to 20% of Crohn's disease patients. This ranges from arthralgia to inflammatory arthritis (including anky- losing spondylitis). Inflammatory arthritis can be an asymmetric large-joint arthropathy with pain and effusions prominent during flares of inflammatory bowel disease, or a symmetrical small-joint arthropathy. Each has distinct genetic associations. Use of NSAIDs should be minimized as they increase gut permeability and can trigger a Crohn's disease flare. Skin Eczema and psoriasis often flare with active Crohn's disease, but the most common specific dermatological manifestation is erythema nodosum. Usually found at initial presentation, it settles with reso- lution of bowel inflammation and rarely recurs. Psoriasiform derma- toses have been reported with anti-TNF treatment, necessitating drug withdrawal. An important but rare complication is pyoderma gangrenosum, a neutrophilic dermatosis. This is

characterized by one or more painful, raised lesions, typically with a violaceous border. Treatment is with systemic corticosteroids or ciclosporin, or with anti-TNF therapy. Eyes Inflammation usually presents as self-limiting conjunctivitis or episcleritis, but it is important to differentiate this from more ser- ious scleritis or uveitis. Patients with Crohn's disease who develop significant eye pain, visual disturbance, or photophobia should re- ceive emergency ophthalmic assessment. Liver Persistently abnormal liver function tests, particularly if cholestatic, should prompt investigation including magnetic resonance cholangi- ography for primary sclerosing cholangitis (see Chapter 15.23.3). Differential diagnosis The differential diagnosis of Crohn's disease depends on its specific presentation. Acute ileitis in young patients closely mimics appendicitis, while chronic symptoms are often diagnosed as irritable bowel syn- drome. In older patients, colonic, particularly caecal, carcinoma must be considered. Clinicians often rely on a raised CRP or faecal calprotectin to identify patients with irritable bowel-like symptoms needing further investigation. However, strong clinical suspicion (e.g. family history of Crohn's disease) may warrant further investi- gation despite normal screening tests. Distinguishing acute inflammatory bowel disease from infection is a common challenge. Occasionally, the diagnosis of Crohn's dis- ease cannot be confirmed until the second flare. In known Crohn's disease patients, when abdominal symptoms recur, the challenge is distinguishing active inflammation from other causes. Most of the latter are discussed later (see 'Complications') but it is noteworthy that a history of inflammatory bowel disease increases susceptibility to infectious enterocolitis, and that irritable bowel syndrome is as common in individuals with Crohn's disease as in the general popu- lation. Failure to appreciate these points can cause both diagnostic confusion and inappropriate treatment choices such as overuse of corticosteroids. Yersinia enterocolitica and Mycobacteria tuberculosis can mimic Crohn's disease, sharing an ileocaecal predilection and causing acute and chronic inflammation respectively. However, the cause of most cases of acute ileitis is never determined and only a minority develop Crohn's disease. Campylobacter, shigella, and salmonella cause an acute colitis usually with fever and sometimes with a reactive arth- ritis, and Clostridium difficile is increasingly found outside conven- tional risk groups. E. coli can cause colitis, with the 0157 serotype triggering haemolytic uraemic syndrome. Rarer causes of entero- colitis include amoebae, schistosomiasis, and cytomegalovirus, emphasizing the need for careful microbiological and histopatho- logical assessment. Rectal and perianal ulceration can be caused by

 sexually transmitted infections such as gonorrhoea, syphilis, and lymphogranuloma venerium. Noninfectious mimics of Crohn's disease include drugs, ischaemia, Behçet's disease, lymphoma, small-bowel carcinoma, solitary rectal ulcer, and radiotherapy. NSAIDs can produce intestinal inflam- mation and rarely 'diaphragm' strictures, and Fleet Phospho-soda colonoscopy bowel preparation commonly causes rectal aphthoid ulceration with focal active colitis on histopathology. Nicorandil can produce oral and deep perianal ulceration, and mycophenolate mofetil occasionally causes right colonic ulceration. Ischaemic col- itis can mimic Crohn's disease with segmental involvement and soli- tary rectal ulcers can be large and pleomorphic but histopathology discriminates. Diverticulitis can mimic Crohn's disease clinically and histopathologically: colonoscopic biopsies from a diverticular segment must be labelled as such. For colonic inflammation, the major differential diagnosis for Crohn's disease is ulcerative colitis. Differentiation is possible for about 95% of cases (Table 15.11.1), leaving 5% as indeterminate or, more accurately, unclassified due to equivocal appearances. Ulcerative colitis can mimic Crohn's disease with a prominent caecal patch of inflammation well recognized in distal ulcerative colitis, or where inflammation becomes patchy on treatment. Clinical investigation Acute

enterocolitis With any significant acute enterocolitis, excluding infection is critical. Three stool samples should be sent for microscopy, cul- ture, and C. difficile toxin assay. Serological tests for yersinia and polymerase chain reaction for cytomegalovirus should also be re- quested where appropriate. Routine laboratory tests For chronic symptoms, a few baseline tests provide important diag- nostic indicators. Faecal calprotectin is highly sensitive for intestinal inflammation. On blood tests an even modestly elevated CRP or ESR is consistent with active Crohn's disease, sometimes accom- panied by elevated platelet and neutrophil counts and a low serum albumin. The latter reflects cytokine-mediated downregulation of hepatic synthesis and intestinal protein loss. Anaemia is common, and multifactorial in origin; ferritin, vitamin B12, and folate should be checked. Liver and renal function tests and coeliac serology are advisable. Anti-Saccharomyces cerevisiae antibody assays are posi- tive in 50 to 75% of established cases but add little to diagnosis and are not widely used. Where baseline tests indicate possible Crohn's disease, the choice of the next investigation depends on the clinical context. Endoscopy Endoscopic examination remains the benchmark for mucosal visualization. Ileocolonoscopy with biopsies is highly sensitive for Crohn's disease presenting with diarrhoea. Appearances vary, but Crohn's disease hallmarks are segmental inflammation with pleomorphic ulceration and cobblestoning, most commonly ileocaecal (Fig. 15.11.2). Endoscopists should biopsy the rectum and intervening normal colon where inflammation is patchy to aid histopathological interpretation, and since histological findings in Crohn's are often nonspecific, it is important that histology is inter- preted in the clinical context. The small bowel can be imaged using wireless capsule endoscopy and accessed by balloon enteroscopy, the latter usually being used to obtain biopsies where there is diag- nostic doubt or occasionally to dilate short strictures. Radiological imaging A range of imaging modalities are available to support the evalu- ation of Crohn's disease. Plain abdominal radiography helps as- sessment of severe diarrhoea or possible obstruction, although increasingly CT is the investigation of choice for the latter. The use of conventional CT or CT enterography provides good def- inition of mucosal disease, as well as demonstrating extraluminal features such as fat wrapping and collections (Fig. 15.11.3). MRI enterography is increasingly available and provides similar infor- mation without exposure to ionizing radiation, as well as detecting subtle submucosal disease and affording precise definition of fistula Table 15.11.1 Features distinguishing Crohn's disease from ulcerative colitis Crohn's disease Ulcerative colitis Clinical features Bloody diarrhoea Uncommon Common Perianal disease Common Uncommon Abdominal mass Common Rare Endoscopy/radiology Rectal inflammation Uncommon Defining feature Distribution Patchy Continuous Ulceration Pleomorphic, deep Superficial, fine Strictures/fistulas Characteristic Rare Histology Depth Transmural Superficial Infiltrate Lymphocytes, macrophages, plasma cells Neutrophils, plasma cells, eosinophils Granulomas Characteristic Confined to ruptured crypts
Fig. 15.11.2 Colonoscopic appearance of linear and pleomorphic ulceration of Crohn's disease.

 anatomy (Fig. 15.11.4). Small-bowel ultrasonography is a highly operator-dependent technique which can allow for sensitive, low- cost detection of small-bowel disease (Fig. 15.11.5). Fistula anatomy should be defined using a combination of imaging (typically MRI) and, for perianal disease, examination under anaes- thesia. Perianal fistulae are classified by their complexity (simple, single track vs complex branching or multiple tracks) and their rela- tionship to the internal and external anal sphincters. Criteria for diagnosis No single feature is sufficient or necessary to diagnose Crohn's dis- ease. Instead, diagnosis is based on cumulative clinical, laboratory, (a) (b) Fig. 15.11.3 Crohn's disease with acute inflammation. CT enterography showing mural stratification of multiple segments of distal ileum.

There is intense mucosal hyperenhancement (arrow in (b)) and enlargement and engorgement of the vasa recta (arrow in (a)), producing the ‘comb sign.’ An enhancing polypoid postinflammatory polyp is seen projecting into the distal ileal lumen (arrowhead). From Levy AD, Mortele KJ, Yeh BM (eds) (2015). Gastrointestinal imaging. By permission of Oxford University Press. (a) (b) (c)
Fig. 15.11.4 Crohn’s disease with active inflammation and stricturing. Magnetic resonance enterography shows marked mural thickening of a long segment of distal ileum. On MRI, mural thickening in active inflammation is of low signal intensity on T2 half-Fourier-acquisition single-shot turbo spin-echo (HASTE) (arrow in (a)); intermediate signal intensity on true fast imaging with steady-state precession (TrueFISP) (b); and shows mural stratification with marked mucosal enhancement on the intravenous gadolinium-enhanced volume interpolated breath-hold examination (VIBE) image (arrow in (c)). Short strictures are present in the inflamed segment, and there is adjacent fibrofatty proliferation (asterisk). From Levy AD, Mortele KJ, Yeh BM (eds) (2015). Gastrointestinal imaging. By permission of Oxford University Press.

15.11 Crohn’s disease 2931 radiological, endoscopic, and histopathological evidence. This is usually straightforward, but the multidisciplinary team should carefully review the evidence when there is uncertainty. Management Management of Crohn’s disease must be tailored to the individual. Patients need a consistent medical approach underpinned by in- formation and support, for example, from specialist nurses and national patient organizations (see ‘Useful websites’). Nutritional deficits must be corrected, with medical therapy for active disease and timely surgery for refractory inflammation or complications. Treatment should be escalated according to disease severity and clinical progress. The ultimate goals of therapy are debated, and per- spectives may differ between physicians and patients. Although the long-term avoidance of complications and maintenance of quality of life might be desired, very few clinical trials target these outcomes. Much recent emphasis has been placed on endoscopic evidence of mucosal healing as a treatment goal. This may indeed reduce the risk of complications, but at a cost to the patient and healthcare economy of a greatly increased need for immunosuppression. There remains a discordance in some patients between clinical symptoms and endo- scopic activity, which may complicate management decisions. The site of disease affects treatment choice, as does the patient’s previous experience and views regarding tolerability and risks versus benefits. Prospectively evaluated prognostic biomarkers are emerging but have yet to be adopted. Clinically, and based on some retrospective data, Crohn’s disease often behaves more aggressively in those with an early age of onset, diffuse disease or deep ulceration, marked peri- anal involvement, early requirement for steroids, and prominent extraintestinal manifestations. In such patients, and those with recur- rent relapse, maintenance immunosuppressive or biological therapy must be considered early. The clinician must synthesize all these strands in formulating an appropriate, individualized treatment plan. Smoking All Crohn’s disease patients who smoke should be advised to stop. This halves the risk of relapse, but even with focused interventions delivered in the context of a dedicated Crohn’s service, sustained ces- sation rates at 1 year are only around 30%. Diet and nutrition Dietetic assessment and advice is important, particularly in patients who have lost weight. Enteral supplements may be required, and specific deficiencies corrected. Parenteral nutrition is reserved for those with intestinal failure due to obstruction, high-output fistula, or short-bowel syndrome. For Crohn’s disease affecting the upper gastrointestinal tract and small bowel, therapeutic diets can—by poorly understood ef- fects on mucosal immunity and gut flora—suppress inflammation. Although meta-analyses have suggested that such diets are less ef- fective than corticosteroids on an intention-to-treat basis, it appears that dietary therapy can perform well,

leading to disease remission in 40 to 80% of those able to tolerate the feeds. Amino acid ('elemental'), peptide, and protein-based liquid feeds are equally effective, being nutritionally replete and used exclusive of all other foods for 2 to 4 weeks. Advantages of therapeutic diets include rapid nutritional res- titution and avoidance of corticosteroids—limiting their adverse impact on growth (in children), osteoporosis, and superadded sepsis. Limitations mainly relate to palatability and frequency of early relapse. Specialist dietetic supervision, offering choice of fla- vour or preparation, and building gradually towards calculated nutritional requirements greatly increases adherence. Nasogastric or gastrostomy tube feeding are occasionally required. Successful transition to eating should start with a basic low-fat, low-fibre ex- clusion diet with phased reintroduction of normal foods over sev- eral weeks to identify specific dietary intolerances. This approach also deals with any superadded food intolerances that may con- tribute to symptoms, and can in itself produce prolonged remis- sion, although addition of immunomodulatory therapy is often required. Patients with a stricture should have a low-residue diet to avoid bolus obstruction (avoiding sweetcorn, apple skins, etc.); and lactose intolerance is common in Crohn's disease, requiring a lactose-free diet with calcium supplementation. Oral Crohn's disease often re- sponds to a low-benzoate, low-cinnamon diet. (a) (b) Fig. 15.11.5 Crohn's disease with active inflammation in the ileum. Ultrasonography shows marked thickening and ulceration of an ileal segment (arrows in (a)). The normal sonographic layers of the bowel wall are preserved. On colour Doppler, there is hyperaemia of the segment. From Levy AD, Mortele KJ, Yeh BM (eds) (2015). Gastrointestinal imaging. By permission of Oxford University Press.

section 15 Gastroenterological disorders 2932 Medical therapies 5-Aminosalicylates Mesalazine lacks efficacy in Crohn's disease. Of six methodologic- ally rigorous trials, some indicated modest benefit, but this was not significant on meta-analysis. There is a strong case for dropping mesalazine from the treatment algorithm of mild to moderately ac- tive Crohn's disease. Mesalazine should also be abandoned as maintenance therapy following medically induced remission because of its demonstrated lack of efficacy, potential nephrotoxicity, and high cumulative cost. After many years on treatment, many patients may be resistant to the idea of stopping (indeed, may report symptom recurrence). A prag- matic approach is to try a slow wean. After surgical resection, maintenance mesalazine may confer some benefit, although the effect size is small (number needed to treat (NNT) = 11 to prevent one relapse at 12 months) and appears restricted to exclusively small-bowel disease. Given the cost and in- convenience it should be reserved for selected cases, and only after more effective measures such smoking cessation. Antibiotics Antibiotics can successfully treat perianal abscesses, discharging fis- tulas, and small-bowel bacterial overgrowth complicating Crohn's disease. Metronidazole with or without ciprofloxacin is best and may be required for several weeks. Some clinicians recommend antibiotics for active Crohn's colitis but supporting trials evidence is modest. A randomized controlled trial of antimycobacterial therapy for Crohn's disease showed no benefit over placebo. Corticosteroids For most gastroenterologists, corticosteroids constitute the thera- peutic mainstay for induction of remission active Crohn's disease. They induce symptomatic remission or satisfactory clinical response in 80% of patients with active disease. Typically given as a course of oral treatment reducing over 6 to 8 weeks, the conventional starting dose is prednisolone 40 mg/day. Smaller starting doses appear less effective. Severe disease mandates hospital admission for intra- venous therapy with hydrocortisone (100 mg four times daily) or methyl prednisone (40 mg twice daily). Corticosteroid side effects can be mitigated by using oral budesonide, formulated for ileocaecal release. High first-pass hep- atic metabolism ensures low systemic availability. Budesonide's ef-

ficacy approaches that of prednisolone. Where the latter is required (e.g. for more severe and extensive disease), calcium and vitamin D with or without oral bisphosphonate should be coprescribed to limit osteoporosis. Long-term corticosteroid therapy is ineffective and should be avoided in Crohn's disease. For the 35 to 40% of patients relapsing frequently off steroids (e.g. at least two relapses a year) or unable to wean without relapse, immunosuppressive or biological therapies are mandated. Immunosuppressants Azathioprine and 6-mercaptopurine are the most commonly used immunosuppressants, with methotrexate second line and alterna- tives such as tacrolimus and thalidomide used rarely. Where re- mission is maintained, the vogue is towards increased duration of therapy—driven by evidence of an increased risk of relapse on stop- ping even after many years in remission. Azathioprine and 6-mercaptopurine The thiopurines azathioprine (2–2.5 mg/kg) and 6-mercaptopurine (1.5 mg/kg) are steroid sparing and effective in maintaining remis- sion in Crohn's disease (NNT = 3). They inhibit purine synthesis via 6-thioguanine triphosphate to prevent leucocyte proliferation and take up to 16 weeks to work; hence, they should be used along- side a more rapid strategy for induction of remission. Those with aggressive disease, severe perianal disease, or steroid dependence, or patients requiring two or more courses of corticosteroids per year are most likely to require azathioprine to maintain remission, though recent trials do not suggest a benefit of protocolized early introduction in these higher-risk patients compared to treatment based upon clinical need alone. Immunomodulator therapy should continue for at least 4 years when effective and well tolerated—and often longer. Some 20 to 30% of patients will be intolerant of thiopurines due to myalgias, nausea, rash, mild hepatitis, or cytopenias, and occasion- ally pancreatitis (2%). Risk of lymphoma is increased by a factor of 4, but remains rare particularly in young age groups. Patients should be warned of possible profound neutropenia and need regular monitoring of blood count and liver function, particularly following commencement or dose increase. Minor elevations of liver enzymes, lymphopenia, and macrocytosis are not significant. Variation in the thiopurine methyltransferase (TPMT) gene af- fects efficacy and safety of thiopurines. About 1 in 300 Europeans have negligible enzyme activity and risk severe neutropenia— preventable by measuring TPMT activity or genotype before starting therapy, although subsequent blood test monitoring is still required. TPMT heterozygotes are predisposed to thiopurine side effects including leucopenia, and usually respond to 50% of standard dose. Polymorphisms in the NUDT15 gene are also strongly associated with leukopenia. Where toxicity develops, switching from one thiopurine to the other often helps, despite their chemical similarity. For patients seemingly unresponsive or intolerant, doses can be increased to the limit of the dosing range or tolerability for 16 weeks before trying alternatives. Monitoring of thiopurine metabolites 6TGN (the active moiety) and 6MMP (a by-product which can in- duce hepatotoxicity) can help to optimize therapy—for example, checking compliance, increasing doses where 6TGN levels fall below the target range, or adding allopurinol and reducing ini- tial thiopurine doses by 75% in individuals who are preferential 'shunters' toward 6MMP (often indicated by abnormal liver func- tion tests on thiopurine therapy). Methotrexate Methotrexate is also effective for inducing and maintaining steroid- free remission in Crohn's disease. The index randomized controlled trial used an induction dose of 25 mg/week and 15 mg/week main- tenance given intramuscularly. Many centres now use subcutaneous or oral methotrexate at these doses—supported by retrospective evi- dence of efficacy. Nausea is common but reduced by prescribing a weekly dose of folic acid the day after the methotrexate. Blood test monitoring is again advised. Methotrexate is teratogenic and should be avoided in women of child-bearing potential.

15.11 Crohn’s disease 2933 Other immunosuppressants Randomized trial evidence is lacking for other immunosuppres- sants. From available data, tacrolimus appears promising for refrac- tory inflammatory disease and closing fistulas, and thalidomide may have a short-term role but is limited by toxicity. Oral ciclosporin is not effective. Biological therapies Anti-TNF therapies The treatment of moderate or severe Crohn’s disease has been revolutionized by the demonstration that monoclonal antibodies targeting TNFα are clinically effective for both acute presenta- tions and long-term maintenance. Infliximab, a chimeric human/ mouse monoclonal antibody, was demonstrated in the landmark ACCENT 1 study to induce symptomatic improvement in 60% of patients with active luminal Crohn’s disease. Subsequent data dem- onstrated benefit in closing fistulas, healing ulcerated mucosa, and maintaining steroid-free remission in 30 to 50% of patients re- sponding to initial induction and then given 8-weekly infusions of infliximab. Improved quality of life and reduced hospitalization sig- nificantly offset treatment costs. Subsequent studies with alternative anti-TNF antibody therapies such as adalimumab and certolizumab appear similarly effective, though only infliximab has been licensed for fistulizing disease. The benefits of anti-TNF therapy have been extended to increasing numbers of patients, particularly since expiry of original patents and the associated introduction of 'biosimilars', with corresponding reductions in drug costs. Anti-TNF therapies are generally well tolerated and long-term postmarketing registry data supports their use in a wide range of pa- tient populations. Major side effects include increased susceptibility to infection (sepsis must be controlled before treatment), reactiva- tion of tuberculosis (mandating screening), infusion reactions, and a possible slight increase in risk of lymphoma. Biologicals that affect lymphocyte trafficking More recently, monoclonal antibodies have been developed that target the surface receptors that direct lymphocyte trafficking to the gastrointestinal mucosa. The first of these, natalizumab, which tar- geted integrin α4, proved effective for Crohn’s disease, but it is now rarely used as associated inhibition of lymphocyte trafficking to the central nervous system leads to reactivation of JC virus and develop- ment of progressive multifocal leucoencephalopathy. Vedolizumab, which binds to the α4β7 heterodimer, inhibits lymphocyte trafficking more selectively to the gastrointestinal tract and has not been associated with development of progressive multifocal leucoencephalopathy. In the large-scale GEMINI 2 and GEMINI 3 trials, vedolizumab showed significant benefits over pla- cebo in the maintenance of remission. It may also have a role in in- duction of remission, but the benefits in this regard are modest and it appears to be slow to take effect. Vedolizumab should thus be con- sidered a second-line biological therapy in Crohn’s disease—a useful treatment option for patients who have failed anti-TNF therapy or in those who wish to maintain remission using an agent that avoids targeting systemic immunity. Ustekinumab Ustekinumab is a monoclonal antibody targeting the p40 subunit common to IL-12 and IL-23. It has demonstrated efficacy in luminal Crohn's disease in both patients who have failed anti-TNF therapy and in those naive to anti-TNF therapy, and is licensed in both pa- tient groups. Data from other inflammatory disorders suggests a lower risk of infection than observed in patients on anti-TNF therapy. Biologicals in combination with other immunosuppressants A key question with all biological therapies is whether or not com- bination with other immunosuppressants provides a clinical benefit that can outweigh the increased side-effect profile. For infliximab, use in combination with azathioprine has been shown in the SONIC trial to be more effective at maintaining remission than either therapy alone. Furthermore concomitant thiopurine therapy is known to re- duce immunogenicity (anti-drug antibody formation) and hence reduce secondary loss of response to anti-TNF therapy—which is a particular problem with infliximab. In contrast, the combination of infliximab with methotrexate at induction did not provide signifi- cant clinical benefit at 1 year in the COMMIT trial. Interestingly, in COMMIT

rates of anti-infliximab antibody development were lower in those receiving methotrexate, which might suggest the po- tential for clinical benefits beyond the 1-year follow-up of the study. The advantages of combinations of adalimumab with immuno- suppression are less clear cut and not born out by randomized clin- ical trials, although immunogenicity remains a problem for certain patient groups, including those with the HLA allele DQA1*05. Long term efficacy data for both vedolizumab and ustekinumab suggest that patients who achieve remission on either drug are likely to stay in remission on drug over a number of years. This may be related to low rates of immunogenicity observed with both agents. Trial data for these drugs in combination with immunosuppressants are limited to post-hoc analyses which do not suggest an observable benefit to com- bination therapy. Additional controversy comes with measuring and interpreting serum drug levels and levels of antidrug antibodies. These are par- ticularly helpful in individuals with secondary loss of response to anti-TNF therapy, where low drug levels and high antibody levels suggest the need to switch to an alternative anti-TNF therapy, while high drug levels might suggest switching to a different drug class. It seems likely that such therapeutic drug monitoring will become rou- tine practice for both biological and immunomodulator therapies, helping to optimize and personalize these therapies. Duration of treatment An additional question for all maintenance therapies, but particu- larly pressing for biologicals given their higher cost, is how long to continue treatment for, and with what agent or combination of agents. Trials of drug cessation suggest approximately 50% risk of flare upon withdrawal of any maintenance therapy by two years, al- though as a general theme the risk appears lowest in those without clinical, biochemical, endoscopic or histological evidence of ongoing disease activity (so-called deep remission). Response appears to be recaptured in nearly all cases when the drug is restarted. Other therapies Several novel therapies are currently being evaluated. These include oral and subcutaneous anti-integrin agents and oral inhibitors of the Janus kinase family, involved in downstream signalling for several cytokines. Oral agents targeting lymphocyte trafficking through modulation of the sphingolipid receptor S1PR are also in late phase clinical trials.

section 15 Gastroenterological disorders 2934 Surgery The increased use of immunosuppression since the 1980s has cor- related with a reduced incidence of surgery, but nonetheless this is still required in up to 70 to 80% of patients with Crohn’s disease in the long term. The two main indications are refractory inflam- mation and complications of disease (the latter are discussed in the following section). Close collaboration between experienced supervising physicians and surgeons, and open discussion with the patient regarding treatment options, facilitates joined-up clinical management. Surgery for refractory Crohn’s disease should be timely and conservative. In most cases laparoscopic approaches are used. Timeliness means patients not enduring medical therapies when it is clear they are not working, nor being propelled toward surgery before it is warranted (e.g. for radiologically severe but minimally symptomatic strictures). Patients should be involved in discussions regarding long-term efficacy and safety of second-line medical ther- apies versus the risks, benefits, and expected outcomes of surgery. Conservative surgery minimizes risk of long-term harm, particu- larly short-bowel syndrome. Thus strictureplasties (incising longitu- dinally and suturing vertically) effectively open short strictures and are favoured over small-bowel resections where possible, while for resections only macroscopically involved bowel is removed. For co- lonic disease, panproctocolectomy carries the lowest risk of relapse but at the cost of permanent ileostomy. Segmental colectomy or sub- total colectomy with ileorectal anastomosis are usually preferred where possible. Surgery for perianal sepsis and fistulas usually in- volves drainage and placement of seton sutures, together with med- ical management, rather than more

aggressive interventions which carry a high risk of nonhealing wounds or faecal incontinence. Optimization for surgery includes dietitian-supervised correction of any malnutrition. Oral supplements are preferred but parenteral nutrition may be required. Corticosteroids should be minimized to limit adverse impact on wound healing—but evidence indicates that thiopurine therapy can safely be continued during the periopera- tive period. For anti-TNF therapies the data are more varied, with a major, recent meta-analysis suggesting a slight excess of septic complications perioperatively. For severe coloanal Crohn's disease, a defunctioning ileostomy should be considered. Technically straight- forward, diverting the faecal stream usually settles coloanal inflam- mation, relieving symptoms and permitting subsequent elective panproctocolectomy on a clinically fit patient. Whether some pa- tients might avoid colectomy and be maintained in remission on stoma reversal if started on thiopurine or biological therapy is un- clear, but recent analyses suggest that this is unlikely for most. Approximately one-half of patients requiring surgery for small- bowel Crohn's disease require a repeat operation within 10 years, es- pecially smokers. Postoperative treatment with metronidazole and/ or azathioprine has been shown to be associated with a lower risk of disease recurrence. The use of postoperative anti-TNF therapy in high-risk patients in the PREVENT study was associated with better endoscopic outcomes, but not with a detectable clinical benefit. In the POCER study, the use of endoscopic assessment at 6 months to guide treatment escalation/de-escalation was associated with im- proved clinical outcomes and reflects a sound evidence-based ap- proach. Serial faecal calprotectin measurement offers a less invasive alternative to colonoscopy with a sensitivity for endoscopic recur- rence of around 90%. Pregnancy Most Crohn's disease therapies, with the exceptions of methotrexate and thalidomide, are safe in pregnancy, but risks and benefits should be carefully discussed with patients. Acute flares should be treated with corticosteroids or dietary therapy (elemental or polymeric), and maintenance treatment with azathioprine and/or anti-TNF therapy (the latter until the third trimester) should usually be continued. Complications and their management The complications of Crohn's disease confer significant morbidity and some mortality. Acute complications Intestinal Intestinal obstruction manifesting as colicky pain, vomiting, disten- sion, and absolute constipation presents acutely or subacutely and is due variably to food bolus, active inflammation (with mural oe- dema), adhesions, and fibrotic stenosis. Strictures usually affect the terminal ileum but can occur anywhere from oesophagus to anal canal. Inflammatory markers and abdominal CT or MRI consti- tute key investigations. Episodes usually resolve with conservative management: nil by mouth, intravenous fluids, corticosteroids, and nasogastric tube for pronounced vomiting. Recurrent episodes re- fractory to a low-residue diet (exclusion of mushrooms, sweetcorn, vegetable skins, etc.) and increased immunosuppression (if evidence of inflammation) require endoscopic dilatation or surgical resec- tion/strictureplasty. Intestinal perforation, caused by deep fissuring ulcers character- istic of Crohn's disease, presents acutely as peritonitis, but symptoms may be considerably masked by corticosteroid therapy. Following diagnostic confirmation, usually on CT, urgent surgical resection is mandated. Fortunately, free perforation is rare as fibrotic serosal re- action and fat wrapping contain most leaks. Toxic megacolon is rare in Crohn's disease, but those with acute se- vere colitis and systemic upset (fever, tachycardia, etc.) require close monitoring and serial abdominal radiographs. Where transverse colonic diameter is more than 6 cm at presentation and this persists despite 24 to 48 h of maximal medical therapy, or develops during such treatment, colectomy is mandated to prevent perforation. Severe bleeding is rare. After resuscitation, therapeutic options in- clude endoscopic haemostasis (adrenaline injection and clipping), angiographic occlusion, or surgical resection. Other medical Venous thromboembolism is common and potentially life- threatening, requiring

vigilance and low molecular weight heparin during all hospital admissions. Subacute/chronic complications Perianal fistulae Asymptomatic simple fistulae may not require specific treat- ment. Treating symptomatic perianal fistulae requires a joint medical and surgical approach. Medical management involves control of infection with antibiotics and control of disease with immunomodulators and/or biological therapy. Surgical

15.11 Crohn’s disease 2935 approaches primarily include drainage of abscesses and keeping the fistula track open with noncutting setons. More definitive management may be attempted, for example, with instillation of fibrin glue, use of collagen plugs, or reconstructive approaches, but these are successful in less than 50% of cases. Emerging data using mesenchymal stem cells injected into the fistula tract have shown promise for improved healing rates, with one such therapy now li- censed. In severe disease, a defunctioning stoma may be required. Surgical complications Intra-abdominal or pelvic abscesses can result from localized per- foration or internal fistulation. Symptoms include abdominal pain and marked weight loss, but can be surprisingly nonspecific and frequently mistaken for active luminal inflammation. Markedly elevated inflammatory markers indicate sepsis and mandate ab- dominal CT. Treatment options, decided by multidisciplinary review and depending on the patient’s clinical status, include antibiotics (metronidazole and ciprofloxacin) with radiological drainage and elemental diet or corticosteroids to suppress Crohn’s inflammation. Surgical drainage/resection is usually best deferred while sepsis is thus controlled. Parenteral nutrition and intensive care may be required in severe cases. Symptomatic anal strictures should be dilated under anaesthetic, with benefit prolonged by using a dilator at home. Gallstones and renal stones are common, and symptoms may be confused with active Crohn’s disease. Conventional management is indicated. The risk of colon cancer is increased in Crohn’s disease affecting the colon. As with ulcerative colitis, risk correlates with disease ex- tent, activity, and duration. In one study, neoplasia was detected in 16% of patients over 20 years. Regular surveillance colonoscopy is warranted after 10 years’ extensive Crohn’s colitis, with biopsy series including any mucosal irregularities. The risk of small-bowel car- cinoma increases 40-fold compared to the general population, usu- ally within chronic strictures, but remains very rare. Medical and nutritional complications Short-bowel syndrome following extensive resection is likely if there is less than 120 cm of small bowel ending in an ileostomy or 80 cm with colon in situ (colonic bacteria ‘scavenge’ calories by fermenta- tion, producing volatile fatty acids which are absorbed). Other patterns of malabsorption in Crohn’s disease include (1) vitamin B12 deficiency—following ileal resection, levels should be monitored yearly and replaced parenterally where deficient; (2) iron deficiency—oral iron preparations are frequently poorly tolerated or ineffective, hence intravenous iron sucrose/iron dex- tran is often required; and (3) zinc, magnesium, and selenium defi- ciencies should be sought and treated. Ileal resection prevents resorption of bile acids in the entero- hepatic circulation. In the colon they can stimulate marked watery (choleretic) diarrhoea, which can be treated with colestyramine. Bacterial overgrowth of the small bowel results from stasis pro- duced by scarring and stricturing. Symptoms include diarrhoea, nausea, bloating, and flatulence. Treatment is with antibiotics (e.g. metronidazole, doxycycline, co-amoxiclav); prolonged or rotating courses are often required. Osteoporosis occurs in approximately 12% of Crohn’s disease pa- tients, with increased fracture risk. Corticosteroid therapy, low body mass, poor dietary intake of calcium, smoking, hypogonadism, and uncontrolled inflammation all contribute. Regular bone densi- tometry is indicated, with calcium/vitamin D supplements and bisphosphonates given as required. Growth failure is a major risk in adolescents, particularly with dis- ease activity around puberty. Height and weight must be monitored on growth charts. Acute

relapse should be managed with dietary therapy (elemental/polymeric) where possible. The priority is rapid induction of remission to restore growth, and infliximab or surgery may be required to achieve this. Long-term corticosteroids must be avoided: azathioprine or infliximab are frequently used to maintain remission. Prognosis To a patient newly diagnosed with Crohn's disease, the lack of a cure and uncertain future is understandably concerning. However, an aggressive or refractory course is unusual, and although morbidity during flares is substantial these are mostly short-lived and usu- ally interspersed with long periods of remission with near-normal quality of life. Although reliable prognostic markers are currently lacking, population-based data from Denmark indicate 55% of patients to be in remission and 15% with mild disease only 1 year after diagnosis. Some 10 to 30% of patients relapse each year, less if immunomodulatory drugs are used. Up to 80% of Crohn's disease patients require surgery in the long term. For ileal/small-bowel Crohn's disease, surgery is required on average 8 years after diagnosis. Some 30 to 40% of patients experi- ence symptomatic relapse by 5 years postoperatively, with 30% re- quiring further surgery within 10 years. Smoking more than doubles this risk. Surgery is required less frequently for exclusively colonic disease. Risk of relapse following panproctocolectomy is low in such individuals. Large population-based studies have suggested slightly higher mortality rates in patients with Crohn's disease. Cause-specific mortality includes an excess of colorectal cancer, but also ex- cess cardiovascular mortality, as well as acute complications including sepsis, pulmonary embolism, bowel perforation, and postoperative complications. Areas of controversy Key research priorities include identifying the precise role of specific microorganisms and the commensal gut flora in triggering and sus- taining the intestinal inflammation of Crohn's disease. For patients requiring treatment escalation, we need data on optimal sequences of therapy with anti-TNF agents, vedolizumab or ustekinumab that produce the best overall results and best cost-effectiveness. For - patients in remission, it will be important to understand better how long to continue with a given therapy, or combination of therapies, and to develop better risk models for considering drug-specific long-term risks and benefits. Likewise, more data are needed on optimal treatment algorithms, in particular the incorporation of therapeutic drug monitoring and endoscopic and biomarker moni- toring, and whether these result in improved clinical outcomes and are cost-effective?

section 15 Gastroenterological disorders 2936 Likely future developments In the near future, we expect to see the increased understanding of biomarkers that may be used to stratify patients. In particular, the use of genetic data and biomarkers at diagnosis and throughout treat- ment will help identify patients destined to run an aggressive disease course, with such patients targeted for more aggressive therapy. At the same time, progress in knowledge regarding pathogenic mech- anisms will feed development of new therapies, alongside progress in characterizing environmental triggers. Patients will continue to gain better access to biological and other novel immunotherapies. Increasing complexity of patient manage- ment will be supported with increasing use of specialist nurses and patient self-management. FURTHER READING Ananthakrishnan AN (2015). Epidemiology and risk factors for IBD. Nat Rev Gastroenterol Hepatol, 12, 205–17. Biedermann L, et al. (2012). Pregnancy and breastfeeding in inflam- matory bowel disease. Digestion, 86 Suppl 1, 45–54. Colombel JF, et al. (2004). The safety profile of infliximab in patients with Crohn's disease: the Mayo clinic experience in 500 patients. Gastroenterology, 126, 19–31. Colombel JF, et al. (2010). Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med, 362, 1383–95. Cosnes J, et al. (2001). Smoking cessation and the course of Crohn's disease: an intervention study. Gastroenterology, 120, 1093–9. Cosnes J, et al. (2005). Impact of the increasing use of immunosup- pressants in Crohn's disease on the need for intestinal surgery. Gut, 54,

237–41. Dignass A, et al. (2010). The second European evidence-based con- sensus on the diagnosis and management of Crohn’s disease: cur- rent management. J Crohn’s Colitis, 4, 28–62. Hanauer SB, et al. (2002). Maintenance infliximab for Crohn’s dis- ease: the ACCENT I randomised trial. Lancet, 359, 1541–9. Irving P (ed) et al. (2011). Clinical dilemmas in inflammatory bowel disease: new challenges, 2nd edition. Wiley-Blackwell, Chichester. Jostins L, et al. (2012). Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature, 491, 119–24. Kostic AD, et al. (2014). The microbiome in inflammatory bowel dis- ease: current status and the future ahead. Gastroenterology, 146, 1489–99. Lamb CA, et al. (2019). British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut, Sep 27. pii: gutjnl-2019-318484. Prefontaine E, et al. (2009). Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn’s disease. Cochrane Database Syst Rev, 1, CD000067. Sandborn WJ, et al. (2013). Vedolizumab as induction and mainten- ance therapy for Crohn’s disease. N Engl J Med, 369, 711–21. Sandborn WJ, Feagan BG, Lichtenstein GR (2007). Medical manage- ment of mild to moderate Crohn’s disease: evidence-based treat- ment algorithms for induction and maintenance of remission. Sandborn W, et al. (2012). Ustekinumab induction and maintenance therapy in refractory Crohn’s disease. N Engl J Med, 367, 1519–28. Useful websites Crohn’s and Colitis Foundation of America: http://www.ccfa.org Crohn’s and Colitis UK: http://www.crohnsandcolitis.org.uk International IBD Genetics Consortium: http://www.ibdgenetics.org/

Revision #1
Created 2026-01-22 16:38:33 UTC by Omar Ayman
Updated 2026-01-22 16:38:33 UTC by Omar Ayman