

# Crohn's disease

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Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract, with increasing incidence worldwide. Crohn's disease might result from a complex interplay between genetic susceptibility, environmental factors, and altered gut microbiota, leading to dysregulated innate and adaptive immune responses. The typical clinical scenario is a young patient presenting with abdominal pain, chronic diarrhoea, weight loss, and fatigue. Assessment of disease extent and of prognostic factors for complications is paramount to guide therapeutic decisions. Current strategies aim for deep and long-lasting remission, with the goal of preventing complications, such as surgery, and blocking disease progression. Central to these strategies is the introduction of early immunosuppression or combination therapy with biologicals in high-risk patients, combined with a tight and frequent control of inflammation, and adjustment of therapy on the basis of that assessment (treat to target strategy). The therapeutic armamentarium for Crohn's disease is expanding, and therefore the need to develop biomarkers that can predict response to therapies will become increasingly important for personalised medicine decisions in the near future. In this Seminar, we provide a physician-oriented overview of Crohn's disease in adults, ranging from epidemiology and cause to clinical diagnosis, natural history, patient stratification and clinical management, and ending with an overview of emerging therapies and future directions for research.

## Introduction

Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract with symptoms evolving in a relapsing and remitting manner. It is also a progressive disease that leads to bowel damage and disability. All segments of the gastrointestinal tract can be affected, the most common being the terminal ileum and colon. Inflammation is typically segmental, asymmetrical, and transmural. Most patients present with an inflammatory phenotype at diagnosis, but over time complications (strictures, fistulas, or abscesses) will develop in half of patients, often resulting in surgery.<sup>1,2</sup> Current therapeutic strategies aim for deep and prolonged remission, with the goal of preventing complications and halting the progressive course of disease.

## Epidemiology

There is no sex-specific distribution in adult Crohn's disease. The onset of the disease usually occurs in the second to fourth decade of life with a smaller peak that has been described from 50 to 60 years.<sup>3</sup> Crohn's disease has increased steadily in most regions worldwide (appendix).<sup>3</sup> Incidence and prevalence of Crohn's disease are greater in developed countries than in developing countries, and in urban areas than in rural areas.<sup>3</sup> The highest annual incidence is in Canada (20.2 per 100 000), northern Europe (10.6 per 100 000), New Zealand (16.5 per 100 000), and Australia (29.3 per 100 000). Prevalence is highest in Europe (322 per 100 000), Canada (319 per 100 000) and the USA (214 per 100 000).<sup>3</sup> Remarkably, areas of low incidence and prevalence have observed a steady increase in inflammatory bowel disease (IBD) rates, almost in parallel with their development. Asia, where some countries are undergoing fast urbanisation, is witnessing an increase in annual incidence of Crohn's disease (0.54 per 100 000).<sup>4</sup> Among populations immigrating from low-incidence to high-incidence regions, incidence

is increased in first or second generations, or if immigration occurred very early in life; these data point to a role of environment and early life exposures in the risk of developing Crohn's disease.<sup>5</sup>

## Cause and pathophysiology

Crohn's disease is believed to result from the interplay between genetic susceptibility, environmental factors, and intestinal microflora, resulting in an abnormal mucosal immune response and compromised epithelial barrier function.

## Genetics and family history

About 12% of patients have a family history of Crohn's disease.<sup>6</sup> Ashkenazi Jews have a three-to-four times higher risk of disease than in non-Jewish populations,<sup>7</sup> and African-American and Asian ancestries are associated with the lowest risk.<sup>8</sup> Genome-wide

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## Search strategy and selection criteria

We searched for relevant manuscripts using PubMed, MEDLINE, Embase, and the Cochrane library from their inception until March 1, 2016. The search combined the MeSH terms "Crohn's disease" and "inflammatory bowel disease" with the sub-headings "epidemiology", "aetiology", "physiopathology", "innate AND adaptive immunity", "genetics", "diagnosis", "endoscopy", "therapy", "surveillance", "prevention", and "complications". We searched bibliographies of included articles and consulted experts in inflammatory bowel disease to identify additional studies. We critically reviewed relevant articles published in English, and prioritised manuscripts published in the past 5 years. Regarding natural history, treatment, and prevention strategies, we gave priority to randomised, placebo-controlled trials, and meta-analyses. We also considered relevant abstracts presented at major meetings.

See Online for appendix

association studies have identified more than 200 alleles associated with IBD, of which 37 are specific for Crohn's disease.<sup>9,10</sup> The discovery of genes associated with bacterial sensing and innate immunity, and related to Th17-cell function (*NOD2*, *ATG16L1*, *LRRK2*, *IRGM*, *IL23R*, *HLA*, *STAT3*, *JAK2*, and Th17 pathways)<sup>9,11</sup> and an altered mucus layer (*MUC2*),<sup>9,11</sup> brought major insights into disease pathogenesis. These findings pointed to altered bacterial handling as a key factor and led to the discovery of new therapeutic targets. Only 13·1% of disease heritability is explained by genetic variation, highlighting the importance of epigenetic and other non-genetic environmental factors.<sup>8</sup> Despite all advances, genetics alone has failed to explain disease variance and phenotypes,<sup>12</sup> and therefore, genetic assessment is not used in clinical practice.

#### Environmental factors

As low-risk countries such as Japan, China, and India adopt a western lifestyle, the incidence of Crohn's disease has increased sharply.<sup>7</sup> Factors such as breastfeeding, living on farms, and childhood contact with animals have only inconsistently been identified as being protective for Crohn's disease.<sup>7</sup> Being born by caesarean section does not seem to increase the risk of IBD.<sup>13</sup> Cigarette smoking is the best studied environmental factor; it is associated with a two-times increase in risk for Crohn's disease (odds ratio [OR] 1·76; 95% CI 1·40–2·22).<sup>14</sup> Antibiotic exposure in childhood increases the risk of Crohn's disease (OR 1·74; 95% CI 1·35–2·23).<sup>15</sup> Other medications potentially associated with increased risk include oral contraceptives,<sup>16</sup> aspirin, and non-steroidal anti-inflammatory drugs,<sup>17</sup> whereas statins have been linked with a decreased risk, especially in older people.<sup>18</sup> A reduction in dietary fibre and an increase in saturated fat intake have also been associated with increased risk.<sup>19</sup> A role has also been proposed for micronutrients (zinc and iron) and vitamin D.<sup>7</sup> Causative association remains to be proven for many environmental factors. Furthermore, environmental factors have not been unanimously identified across populations. Asia and Africa, despite having high rates of smoking, present a very low incidence of Crohn's disease.<sup>20</sup> Conversely, northern European countries present a very high incidence of Crohn's disease despite low smoking rates.<sup>21</sup>

#### Microbiota

Dysbiosis in patients with Crohn's disease includes a decrease in Bacteroides and Firmicutes bacteria (specifically those from the *Clostridium* clusters XIVa and IV) and an increase in Gammaproteobacteria and Actinobacteria.<sup>22</sup> Approximately a third of patients with Crohn's disease have an increased abundance of mucosa-associated adherent-invasive *Escherichia coli*.<sup>23,24</sup> These strains cross the mucosal barrier, adhere to and invade intestinal epithelial cells, and survive and replicate within macrophages, provoking the secretion of high amounts

of TNF $\alpha$ .<sup>23,24</sup> *Faecalibacterium prausnitzii*, a commensal bacterium with anti-inflammatory properties, is reduced in Crohn's disease.<sup>25,26</sup> Patients with IBD also harbour an expansion of caudovirales viruses in their stool<sup>27</sup> and fungal dysbiosis.<sup>28</sup> Although this change in microbiota in Crohn's disease is a highly active research area, thus far findings have not yet translated into practice, because most strategies manipulating microbiota (probiotics or antibiotics) have failed.

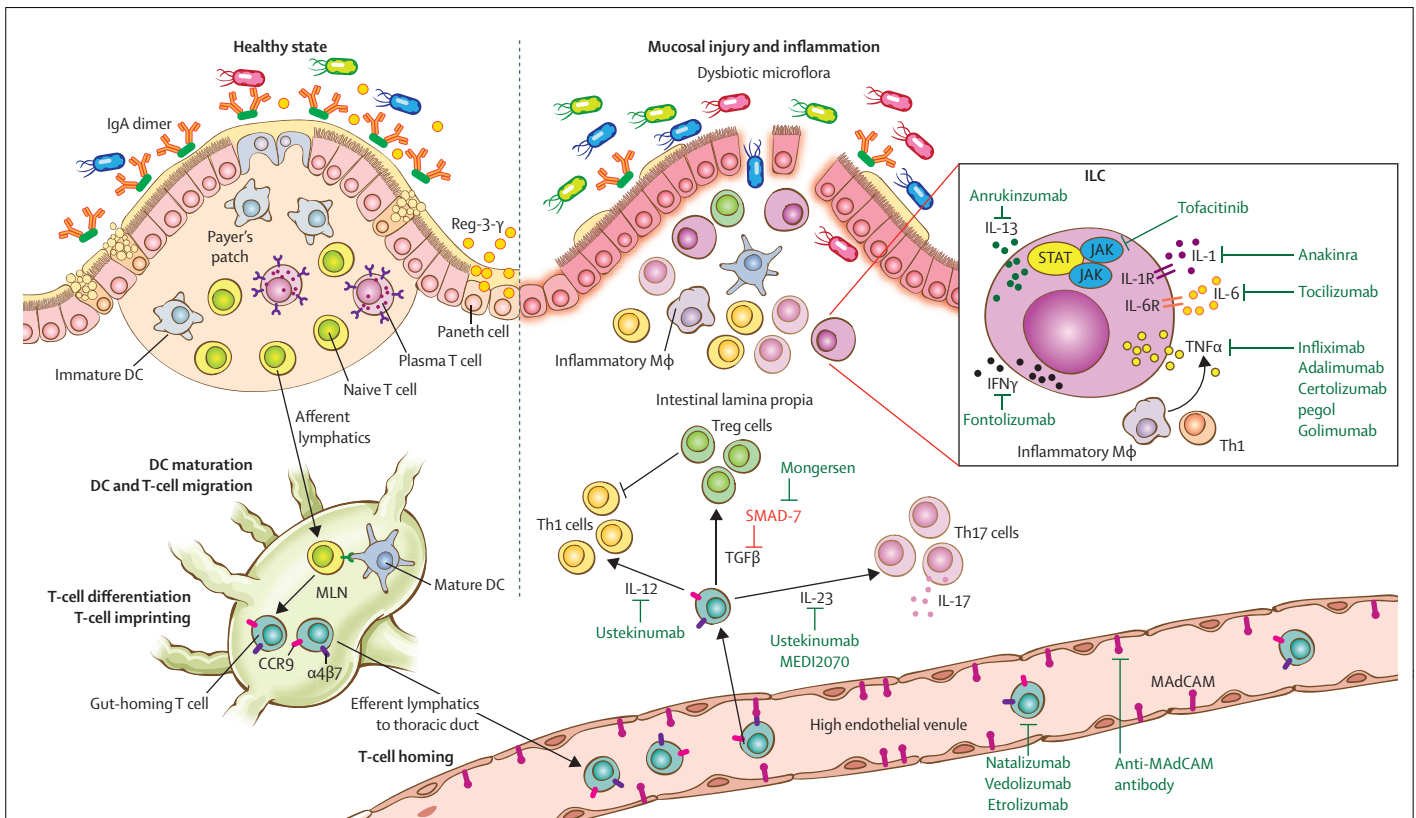
#### Intestinal immune system Crohn's disease

##### Barrier function defects

Multiple and overlapping immune pathways are dysregulated in Crohn's disease (figure 1). The intestinal epithelium, an important single layer of columnar epithelium, produces mucus and antimicrobial factors such as REG-3 $\gamma$ , establishing a buffer zone between the luminal contents and itself.<sup>29</sup> Disruption of this buffer zone by emulsifiers, which are ubiquitous in western diet,<sup>30</sup> or by mutations in the *MUC2* gene,<sup>31</sup> might promote bacterial translocation and is associated with IBD. Epithelial cells have a process called autophagy, in which unwanted cytoplasmic contents are targeted to the lysosome for degradation,<sup>32</sup> preventing the dissemination of invasive bacterial species.<sup>33</sup> Defects in autophagy-related genes such as *ATG16L1* and *IRGM* have been identified as important risk factors for Crohn's disease.<sup>9</sup> Defects in intestinal tight junctions are also associated with IBD.<sup>34</sup>

##### Innate immune defects

NOD-like receptors are innate immune proteins that mobilise the host defence to intracellular fragments of bacterial peptidoglycan by initiating NF- $\kappa$ B-dependent and MAPK-dependent gene transcription, producing protective cytokines. Dendritic cells, which are key antigen-presenting cells, are tolerogenic at steady state. However, in inflammatory conditions, they develop enhanced expression of *TLR2*, *TLR4*, and costimulatory molecules, and secrete proinflammatory cytokines.<sup>35</sup> Intestinal macrophages have essential housekeeping functions, such as the clearance of apoptotic or senescent cells and tissue remodelling at steady state.<sup>36</sup> Neutrophils are responsible for the early response to microbial stimuli, and probably modulate the adaptive responses beyond the acute state by the production of cytokines and reactive oxygen species. Innate lymphoid cells (ILCs), a heterogeneous population of cells, are critically involved in the maintenance of barrier integrity. They respond to microbial cues<sup>37</sup> and dietary input,<sup>38</sup> among other stimuli, by producing cytokines such as TNF $\alpha$ , interleukin 17, interleukin 22, and interferon  $\gamma$ . ILC3 and ILC1 have been implicated in Crohn's disease pathogenesis. Intra-epithelial and lamina propria ILC1 are expanded in the ileum of patients with Crohn's disease.<sup>39</sup> ILCs isolated from the inflamed colon of patients with Crohn's disease show increased gene expression of key ILC3 cytokines (*IL17A* and *IL22*), transcription factors (*RORC* and *AHR*), and cytokine receptors (*IL23R*).<sup>40</sup>



**Figure 1: Overview of the intestinal immune system in healthy-state patients or patients with Crohn's disease and their potential therapeutic targets**

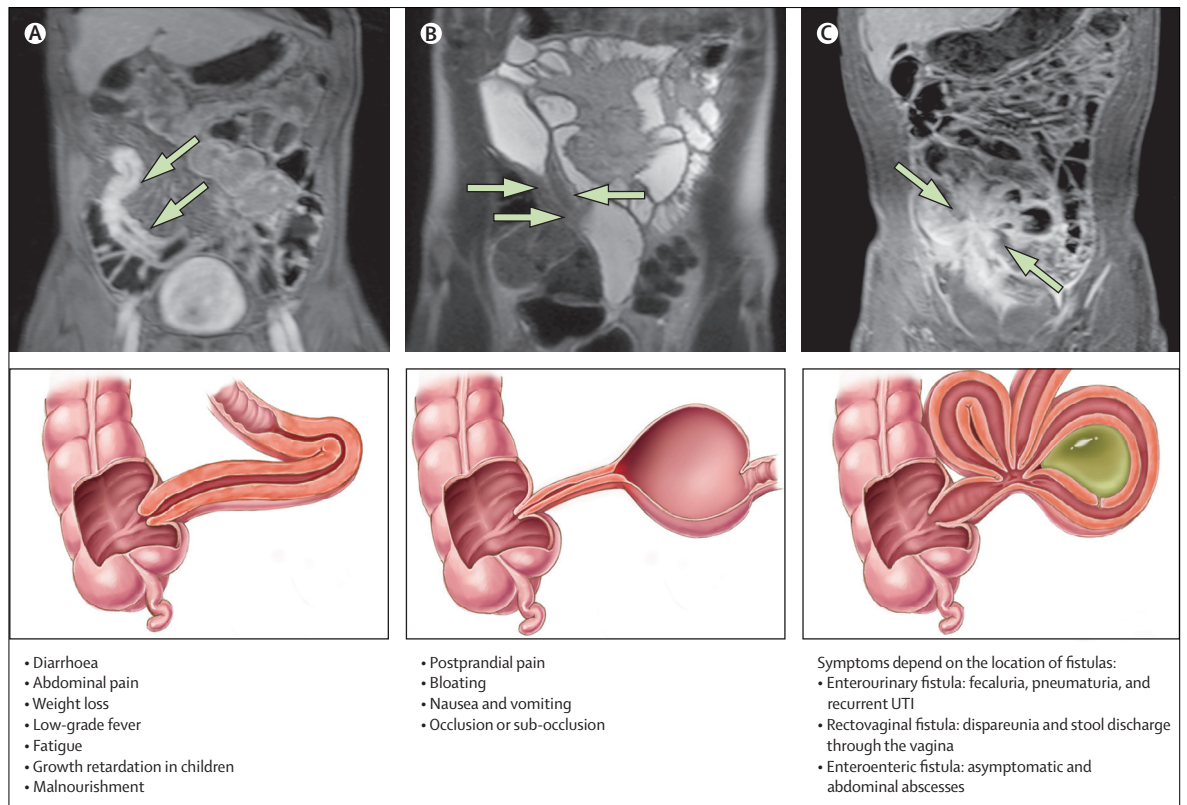
In the healthy state, intestinal epithelium and IgA dimers work in concert to regulate and separate luminal microflora from the mucosal immune system. Intestinal epithelium also contains specialised cells such as Paneth cells that produce antimicrobial peptides and M cells that sample luminal antigens. M cells are in close contact with antigen presenting cells such as DCs. Contact with the antigen leads to DC maturation and antigen presentation to T and B cells. DCs default to inducing a tolerising phenotype in the mucosa unless danger signals such as bacterial LPS induce the switch to an inflammatory or immunising DC phenotype. Intestinal DCs also imprint T and B lymphocytes to express gut homing molecules  $\alpha 4\beta 7$  and CCR9. Lymphocytes thus imprinted within the GI tract enter the systemic circulation. Upon reaching intestinal high endothelial venules, gut-imprinted  $\alpha 4\beta 7$ -expressing lymphocytes engage with locally expressed MAdCAM and egress circulation to enter into the intestinal lamina propria. Intestinal lamina propria has multiple families of T cells: Th1, Th17, and Treg. At steady state, Treg regulates the activity of Th1 and Th17, and prevents unchecked inflammation. During mucosal injury and inflammation such as in CD, the epithelial barrier is breached as a primary or secondary event, and the luminal microflora stimulates a proinflammatory immune response by DCs and inflammatory M $\phi$ . Regulatory ability of Treg is outstripped by inflammatory activity of Th1 and Th17. Additionally, ILCs, homeostatic at steady state, contribute to the cytokine production—perpetuating inflammation. Mucosal injury and damage is associated with dysbiosis, which perhaps perpetuates the inflammatory cascade. Improved understanding of the mucosal immune system has led to an expanding array of therapeutic targets. Of these, TNF $\alpha$  antagonists and homing inhibitors are in clinical practice and others are in early to advanced stages of clinical development. Only promising and currently used therapies (green) are mentioned in this figure. DC=dendritic cell. LPS=lipopolysaccharide. GI=gastrointestinal. MAdCAM=mucosal addressin cell associated molecule. CD=Crohn's disease. MLN=mesenteric lymph node. Th1=T-helper-1 cell. Th17=T-helper-17 cell. Treg=regulatory T cell. M $\phi$ =macrophage. ILCs=innate lymphoid cells. IFN=interferon. IL=interleukin. TGF=transforming growth factor. Illustration by Jill Gregory. Printed with permission of ©Mount Sinai Health System.

Furthermore, there is a reciprocal reduction in ILC3 cells that produce interleukin 22 (a cytokine that promotes barrier integrity<sup>41</sup>).<sup>39</sup> The Th17/interleukin-23 pathway in ILCs has been implicated in the pathogenesis of Crohn's disease.<sup>9</sup> Paneth cells are specialised secretory cells located at the base of the crypts of Lieberkühn. Genetic defects, including mutations in *NOD2*, *ATG16L1*, *LRRK2*, *XBPI*, and *IRGM* lead to alterations in Paneth cell function and survival, resulting in reduced secretion of antimicrobial proteins.<sup>42</sup>

#### Adaptive immune cells in Crohn's disease

CD4-positive T-helper cells can be functionally classified as Th1, Th2, Treg, Th17, Tfh, and Th9 cells.<sup>43</sup> Intestinal inflammatory infiltrate in Crohn's disease contains Th1 and Th17 cells. These effector T-cell responses to

bacteria or fungi are implicated in the pathogenesis of the disease.<sup>44</sup> Additionally, impaired functional activity of intestinal Treg cells has been reported in Crohn's disease.<sup>45</sup> B lymphocytes are less well investigated in the disease. Antimicrobial antibodies such as anti-*Saccharomyces cerevisiae* antibody, anti-I2 antibody, anti-outer membrane porin C antibody, anti-flagellin antibody, and antiglycan antibodies, are often seen at increased titres in patients with Crohn's disease. Their presence suggests that intestinal B cells mount an immune response to luminal microbes in these patients, but their pathogenic role remains unclear. Additional disruptions of the B-cell system in patients with Crohn's disease include an increase in lamina propria plasma cells and skewing of antibody production away from dimeric IgA to IgG and monomeric IgA.<sup>46</sup>



**Figure 2: Behaviour of CD as per Montreal classification represented in MRE and illustrated with typical symptoms**  
(A) T1-weighted MRE imaging with fat saturation after injection of gadolinium chelates shows mural thickening and enhancement in the distal ileum (arrows) in a patient with active CD. (B) T2-weighted MRE imaging shows a narrowed luminal segment with thickened wall and upstream dilation (arrows), suggesting the presence of a stricture. (C) T1-weighted MRE imaging with fat saturation after injection of gadolinium chelates shows multiple converging enhancing loops of small bowel suggestive of enteroenteric fistulas (arrows). Lower illustration shows a deep and transmural fissure or ulcer leading to the formation of an abscess. CD=Crohn's disease. MRE=magnetic resonance enterography. UTI=urinary tract infection. Illustration by Jill Gregory. Printed with permission of ©Mount Sinai Health System.

#### Immune cell homing to the intestinal mucosa

Lymphocytes are imprinted during activation by dendritic cells with specific trafficking programmes. Dendritic cells residing in Peyer's patches or small bowel draining lymph nodes metabolise vitamin A to produce retinoic acid and induce the expression of  $\alpha 4\beta 7$  integrin and CCR9 on T and B lymphocytes. Cells thus imprinted enter into circulation, and upon re-entering the gut vasculature engage their respective ligands: MAdCAM-1 for  $\alpha 4\beta 7$  and C-C motif chemokine 25 for CCR9.<sup>47</sup> Although no specific homing defects have been described in patients with Crohn's disease, vedolizumab, an  $\alpha 4\beta 7$  antagonist, is used to treat patients.

#### Clinical presentation and diagnosis

Presenting symptoms can be heterogeneous and insidious. Clinical presentation depends on disease location, severity of inflammation, and disease behaviour (figure 2). The most common scenario is a young patient presenting with right lower quadrant abdominal pain, chronic diarrhoea, and weight loss. Fatigue and anorexia are common symptoms. In patients with colonic involvement, rectal bleeding or bloody diarrhoea might

be the major symptoms. High fever should always raise the suspicion of a septic complication. Approximately a third of patients present with perianal disease.<sup>48</sup> Up to 50% of patients present with skin, joint, or eye extra-intestinal manifestations that can precede diagnosis. Some of these manifestations, such as erythema nodosum and pauciarticular large joint arthritis (type 1), are associated with active intestinal disease. Others, such as axial arthropathies or primary sclerosing cholangitis, are independent of disease activity.

Crohn's disease diagnosis relies on a combination of symptoms, radiology, endoscopy, and histological criteria (table 1).<sup>49–52</sup> Smoking and family history of IBD are well known risk factors. Information about recent travelling, gastrointestinal infections, and medications should be sought. Physical examination should assess signs of systemic toxicity, malnutrition, dehydration, anaemia, or malabsorption. Patients might have a tender mass in the right lower quadrant, representing thickened bowel loops, thickened mesentery, or an abscess. Careful examination of the perianal region should be routine in patients with established or suspected Crohn's disease. Perianal disease can present as skin lesions (ulcerations



and skin tags), anal canal lesions (stenosis, fissures, and ulcers), and fistulas with or without abscesses. Eccentrically located fissures, even if asymptomatic, should raise concerns about Crohn's disease. The presence of anal pain or tenderness and purulent discharge suggests an underlying abscess (appendix).

After diagnosis is established, disease activity, severity, extent, and behaviour should be assessed using cross-sectional imaging, and patients should be phenotyped (table 2).<sup>53,54</sup>

### Diagnostic investigations

Typical laboratory findings include thrombocytosis, increased acute phase proteins (particularly C-reactive protein), and anaemia. C-reactive protein is a biomarker used to monitor disease activity, but correlates poorly with endoscopic findings, and a third of patients never present with increased concentrations.<sup>55</sup> Hypoalbuminaemia and vitamin deficiencies might be present, especially in extensive small bowel disease. About 60–70% of patients might have antimicrobial antibodies in their serum, the most prevalent being anti-*Saccharomyces cerevisiae* antibody IgA.<sup>56</sup> The sensitivity and specificity of these antibodies is too low for diagnostic purposes. However, patients who present with high titres and increasing numbers of positive markers have an increased likelihood of developing more aggressive phenotypes.<sup>57</sup> Stool biomarkers, including faecal calprotectin, are being increasingly used as screening tests and to assess disease activity in IBD. Faecal calprotectin concentrations correlate with neutrophil infiltrates in the gut and represent a surrogate marker of intestinal inflammation with high sensitivity and specificity for the diagnosis of IBD.<sup>58</sup> A faecal calprotectin concentration of less than 40 µg/g in patients with symptoms suggestive of irritable bowel syndrome has been shown to be associated with a 1% chance of IBD, so this marker can be useful in the primary care setting to screen patients for colonoscopy.<sup>59</sup> In patients with established Crohn's disease, faecal calprotectin correlates well with endoscopic activity and is a useful biomarker with which to monitor disease activity, assess response to therapy, predict clinical relapse, and postoperative recurrence.<sup>58,60</sup> The cutoff point for differentiating mucosal inflammation is assay-dependent and might vary between 50 and 250 µg/g.<sup>61</sup> In the postoperative setting, a faecal calprotectin concentration of more than 100 µg/g has high sensitivity for prediction of endoscopic recurrence.<sup>60</sup>

Endoscopy remains the gold standard for diagnosis. Segmental inflammation, aphthoid, and longitudinal and serpiginous ulcerations are typical findings. Serpiginous ulcerations interspersed with nodular oedematous mucosa produces the so-called cobblestone pattern (appendix). Because mucosal healing has emerged as an important therapeutic goal, colonoscopy has gained an important role in monitoring disease activity.<sup>62</sup> Routine use of a scoring system such as the Simplified Endoscopic Score

Disease features	
Ulcerative colitis	Rectal bleeding, tenesmus, and faecal urgency are the major symptoms; disease is limited to the colon (backwash ileitis is present in 10% of extensive colitis cases); rectum is usually involved (possible exceptions: patients with PSC and paediatric patients might present rectal sparing) and there is no substantial perianal disease; inflammation is limited to the mucosa, in a continuous and symmetrical way; typically histology shows crypt architecture distortion, crypt abscesses, and ulceration <sup>49</sup>
Infectious enterocolitis	Typically, there is an acute onset of symptoms (<4 weeks), and epidemiological setting or recent travel history might be present; exclude <i>Clostridium difficile</i> infection if recent antibiotic exposure or admission to hospital; microbiological examination of stool, serology, and histology might reveal the causative agent; histology, if done normally, shows no basal plasmacytosis and architectural changes; self-limited
Microscopic colitis	Typically affects women aged 50 years or older, who present with chronic watery diarrhoea and normal appearing mucosa on endoscopy; histology is essential for diagnosis with two histological sub-types of microscopic colitis: lymphocytic colitis and collagenous colitis; typical histological features include an increased number of intra-epithelial lymphocytes (>20 per 100 epithelial cells) with minimal crypt architecture distortion, increased chronic inflammatory infiltrate (plasma cells, eosinophils, and lymphocytes) in the lamina propria, or the presence of an abnormal surface sub-epithelial collagen layer with abnormal thickness (>10 µm) compared with normal surface sub-epithelial collagen layer (5–7 µm)
Intestinal tuberculosis	Endoscopically might mimic CD; ileocecal location most common; suspicion should be raised in immigrants from endemic areas or in immunocompromised patients; chest radiograph might reveal suggestive lesions in 50% of patients, and CT might display calcified and necrotic-looking mesenteric lymph nodes; caseating granulomas are seen in histology as opposed to epithelioid granulomas; positive Ziehl-Neelsen, culture, and PCR normally lead to diagnosis <sup>50</sup>
Behçet's disease	Might present with intestinal inflammation and EIM; presence of recurrent oral and genital ulcerations should raise suspicion; uveitis and skin involvement are frequent; other vasculitic lesions might be present; positive pathology test supports the diagnosis <sup>51</sup>
NSAID's associated enteropathy	Multiple erosions and ulcerations in a patient with a history of long-term use of NSAIDs or aspirin; small intestine concentric diaphragmatic strictures (thin, concentric, and diaphragm-like septa with pinhole-sized lumen) are typical of NSAID injury and can lead to obstructive symptoms; histology non-specific; <sup>52</sup> typically resolves upon drug withdrawal

PSC=primary sclerosing cholangitis. CT=computed tomography. PCR=polymerase chain reaction. EIM=extraintestinal manifestations. NSAIDs=non-steroidal anti-inflammatory drugs. CD=Crohn's disease.

**Table 1: Features of some disease entities considered in the differential diagnosis of Crohn's disease**

for Crohn's disease is recommended to allow comparison between assessments (appendix). Finally, colonoscopy has an important role in colorectal neoplasia surveillance and in managing complications, such as strictures.<sup>62</sup> Upper endoscopy is not routinely recommended in adults with Crohn's disease without upper gastrointestinal symptoms. Diagnostic small bowel capsule endoscopy is reserved for cases in which endoscopic studies have been negative despite suggestive symptoms or in colonic IBD-unclassified. Its negative predictive value for small bowel Crohn's disease is very high. Although small bowel capsule endoscopy has better diagnostic accuracy for identifying small bowel mucosal lesions than other imaging modalities, the clinical significance of minor small bowel lesions, and therefore, the clinical usefulness of this method in the therapeutic management of patients with Crohn's disease remains to be determined prospectively.<sup>62</sup>

Suggestive histological features include a chronic focal, patchy, discontinuous, and transmural inflammatory

Montreal classification	
<b>Age at diagnosis</b>	
<16 years	A1
17–40 years	A2
>40 years	A3
<b>Disease location</b>	
Ileal disease	L1
Colonic disease	L2
Ileocolonic disease	L3
Upper-isolated gastrointestinal disease*	L4
<b>Disease behaviour</b>	
Non-stricturing and non-penetrating	B1
Stricturing	B2
Penetrating	B3
Perianal disease†	p

The Montreal classification (updated from initial Vienna classification) categorises patients according to their age at diagnosis, disease location, and disease behaviour because these variables have important prognostic information. In 35–45% of cases, disease is located in the terminal ileum and proximal colon. 30% of patients have disease confined to the small intestine, specifically the terminal ileum, and in approximately 20% of cases disease is limited to the colon. Upper-isolated gastroduodenal disease is reported in less than 5% of patients. Isolated jejunal involvement is rare. \*L4 is a modifier that can be added to L1–L3 classification when concomitant upper gastrointestinal disease is present. †Perianal disease (p) is also a disease modifier that can be added to B1–B3 classification when concomitantly present. For example, a patient diagnosed at age 21, with ileocolonic disease complicated by an abdominal abscess and perianal disease would be classified as A2L3B3p. A paediatric modification of the Montreal classification—the Paris classification<sup>31</sup>—has been developed to take into account specific phenotypic differences in this age range (eg, effect of disease in growth).

**Table 2: Montreal classification of Crohn's disease**

infiltrate, and goblet cell preservation. Transmural lymphoid aggregates and pyloric gland metaplasia are common findings. The histological hallmark of Crohn's disease is the epithelioid granuloma, which is seen in only about 15% of mucosal biopsies but in up to 70% of cases in surgical specimens.<sup>49,63</sup> In most cases, the clinical significance of histology is low.

Cross-sectional imaging tests such as ultrasonography, CT-enterography, or MR-enterography have gained increasing importance in the management of Crohn's disease. CT-enterography or MR-enterography should be done at diagnosis to assess the extent of disease and presence of complications such as strictures or fistulas, thereby providing information about disease behaviour (appendix).<sup>64</sup> During follow-up, cross-sectional imaging is increasingly used to assess disease activity, complications, and response to therapies.<sup>65,66</sup> When available, MR-enterography should be preferred to reduce the risk of cumulative radiation exposure. Ultrasonography is non-invasive and cheaper than CT-enterography or MR-enterography, and when done by an experienced operator it has similar sensitivity and specificity for assessing disease activity and complications; however, its accuracy is lower for proximal disease and for colonic segments, and gas interpositions often lead to incomplete exploration.<sup>65</sup> Patients with

perianal fistulas or abscesses, or both, should be assessed with pelvic MRI for accurate assessment and delineation of fistulous tracts.<sup>67</sup>

### Definition of disease activity and severity

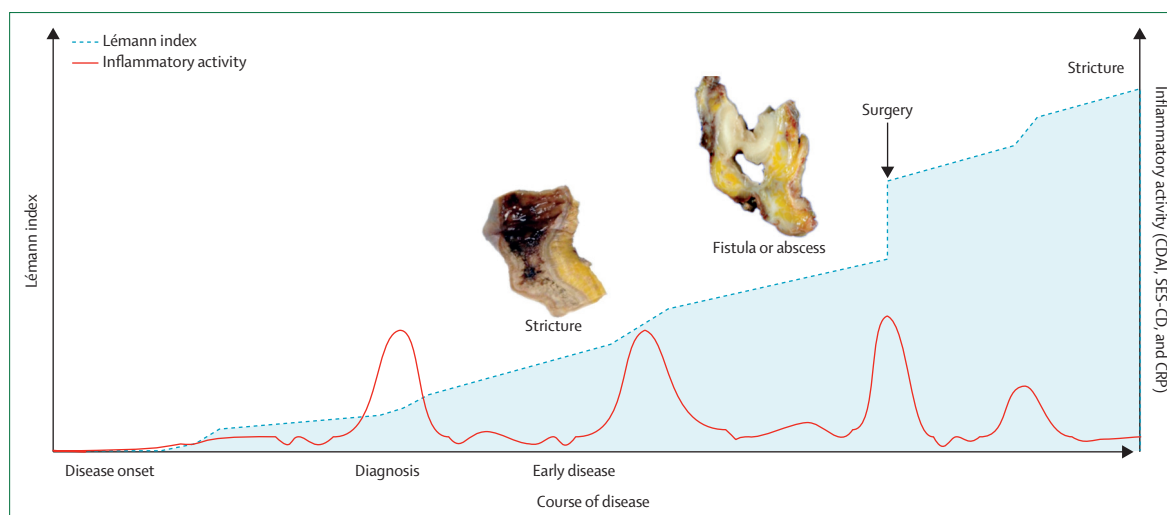
Disease activity refers to the assessment of disease at a given timepoint, and it is important for choosing the induction therapy, assessing the need for admission to hospital, or efficacy of a drug. A more clinical classification categorises disease into mild, moderate, or severe depending on response to therapy, presence of malnutrition, dehydration or systemic toxicity, presence of abdominal tenderness, mass or obstruction, and degree of weight loss and anaemia (appendix).<sup>68</sup> Symptoms do not necessarily correlate with objective assessment of disease activity such as endoscopy, cross-sectional imaging (appendix), or biomarkers (CRP or faecal calprotectin). Therefore, symptoms alone should not generally guide therapeutic decisions.<sup>69</sup> Disease severity takes into account the effect of disease in the individual patient, the cumulative complications and surgical resections, the disability produced by disease, the inflammatory burden of disease, and the disease course.<sup>70</sup>

### Natural history and predictive factors for complications

Crohn's disease is characterised by periods of clinical remission alternating with periods of recurrence. However, there is a disconnect between clinical symptoms and mucosal disease activity, which might explain why conventional strategies have failed to alter the course of the disease.<sup>71</sup> Persistent subclinical inflammation that occurs during clinical remission is thought to lead to complications (strictures, fistulas, and abscesses) and progressive bowel damage (figure 3).<sup>72</sup> Disease location in Crohn's disease tends to be stable,<sup>73,74</sup> but disease behaviour changes over time.<sup>2</sup> Bowel damage (stricture, fistula, or abscess) is present in a fifth of patients at diagnosis (figure 2).<sup>12</sup> The annual incidence of admissions to hospital is around 20%, and within 10 years of diagnosis half of patients will require surgery. A third will need multiple surgeries and about 14% of those with severe disease—especially with concomitant rectal involvement—will require a permanent stoma.<sup>75</sup> Extensive small bowel disease or multiple surgeries, or both, can result in intestinal failure and short bowel syndrome, a rare but fearful and irreversible complication.<sup>76</sup> Unfortunately, surgery is not curative; clinical recurrence is reported in 50% of patients, endoscopic recurrence in 80%, and surgical recurrence in 30%.<sup>77</sup>

### Risk factors for complicated disease

With various definitions of complicated disease, the predictors of a worse outcome identified in population-based studies are ileal or ileocolonic disease location, extensive small bowel disease, severe upper



**Figure 3: Disease course in a patient with CD**

CD is characterised by flare-ups followed by clinical remission. Subclinical inflammation, even during periods of clinical remission, often persists, leading to development of complications such as stricture or penetrating lesions that frequently require surgery. This progressive and destructive disease course (shaded area) therefore results in structural bowel damage over time leading to progressive loss of intestinal function and disability. Cumulative bowel damage can be measured using the Lémann index.<sup>66</sup> Inflammatory activity can be measured by clinical (CDAI), endoscopic (SES-CD) indexes, or biomarkers (CRP). CD=Crohn's disease. CDAI=Crohn's Disease Activity Index. SES-CD=simplified endoscopic activity score for Crohn's disease. CRP=C-reactive protein. Adapted from Pariente and colleagues,<sup>72</sup> by permission of Wolters Kluwer Health.

gastrointestinal disease, rectal disease, perianal lesions, early stricturing or penetrating disease, a young age at diagnosis, and smoking.<sup>78</sup> Smoking is also the most important risk factor for postoperative recurrence and need for second surgery.<sup>79</sup> These clinical risk factors have poor precision as predictors of outcome, and some have only been identified retrospectively. Therefore, the need to identify biomarkers that can predict disease course is gaining increasing importance. Serological markers have been associated with stricturing and penetrating complications and the need for surgery,<sup>77,80</sup> but their low sensitivity and inadequate availability has hampered their use in clinical practice. Likewise, genetic markers have not been shown to predict complications.<sup>81</sup> CD8-positive T-cell transcriptional signatures have been shown to predict disease course.<sup>82</sup> The field is likely to evolve to incorporate the use of composite algorithms that will allow better and more precise prognostication.<sup>83</sup>

Besides disease-specific complications, patients with Crohn's disease also have an increased risk for development of intestinal and extra-intestinal malignancies (table 3).<sup>84,85</sup>

## Management

### Treatment goals and therapeutic strategies

In the past, patients were started on aminosalicylates, steroids, or thiopurine, with escalation to more effective treatments only after these lines of therapy had failed (step-up therapy). This strategy failed to change the course of disease as reflected by high rates of surgery. Therefore, the treatment framework evolved from mere control of symptoms towards blocking progression of the

disease that leads to complications, bowel damage, and disability. Endoscopic healing, usually defined as no ulcerations, has emerged as a major therapeutic target in IBD because it correlates with reduced relapse rates and need for surgery, and less bowel damage.<sup>86</sup> Because clinical symptoms are not a reliable measure of the underlying inflammation, disease modification is thought to only be possible through treating beyond symptoms. In this context, deep remission (ie, clinical and endoscopic remission) is emerging as a new treatment goal.<sup>70</sup> However, prospective disease modification trials are needed to determine how these strategies will change disease course. Pending these studies, a top-down approach might be considered in patients with Crohn's disease and poor prognostic factors, severe disease, or complicated disease.<sup>87</sup> This approach is supported by the Randomised Evaluation of an Algorithm for Crohn's Treatment trial. In this trial, patients who were randomised to early combined immunosuppression had slower progression to surgery and lower rates of admission to hospital for disease-related complications than those in the conventional treatment group.<sup>88</sup> For the remaining patients, a rapid step-up approach and a treat-to-target strategy based on a tight monitoring of mucosal disease and biomarkers of inflammation is recommended,<sup>70</sup> despite paucity in trials specifically addressing this issue; furthermore, this strategy is not yet endorsed by some international societies that require patients only to step-up therapy after failing conventional treatment.<sup>89</sup> We propose in figure 4 an evolving treatment algorithm for clinical practice summarising this treat-to-target strategy.

Description of malignancies that can complicate Crohn's disease course	
<b>Intestinal malignancies</b>	
Colorectal cancer	Higher risk with extensive involvement (>30–50% of the colonic surface) of the colon; SIR in population-based studies is 1.7 (95% CI 1.0–2.5); patients with extensive Crohn's colitis should follow guidelines for colorectal neoplasia surveillance, similar to ulcerative colitis
Small bowel adenocarcinoma	Although the absolute risk is very low, it is estimated to be 20–30 times higher than in the general population; overall incidence has been estimated to be 0.5 per 1000 patient-years; tends to develop in strictured-inflamed segments, especially if CD is >8 years of duration; new onset of symptoms after a period of long remission or medically refractory strictures should trigger the suspicion for small bowel adenocarcinoma
Intestinal lymphomas	Most common type is B-cell non-Hodgkin lymphoma; absolute risk is very low (0.1 per 1000 patient-years), but still substantially increased by comparison with the general population
Anal cancer (complicating perianal fistula)	Incidence estimated to be about 0.2 per 1000 patient-years; adenocarcinoma or squamous cell carcinoma, usually complicating persistent chronic perianal fistulising disease (>10 years) or anal stenosis; although surveillance is recommended for patients with risk factors, the optimal surveillance protocol and modality is unknown
<b>Extra-intestinal malignancies</b>	
Lymphoma	Among thiopurine users, the highest risk for developing any type of lymphoma is observed in men older than 50 years of age and younger than 30 years (SIR for all lymphomas is 5.7; 95% CI 3.7–10.1); the most common type is post-transplant-like non-Hodgkin lymphoma, associated with the use of thiopurines and the reactivation of chronic latent EBV infection; early post-mononucleosis lymphoma might complicate thiopurine use, especially in men younger than 30 years and EBV negative; incidence has been estimated to be around 3 per 1000 patient-years
Hepatosplenic T-cell lymphoma	Very rare type of lymphoma, associated with 90% mortality; associated with the use of thiopurines and combination therapy with TNF $\alpha$ antagonists; men younger than 35 years are at the highest risk
Non-melanoma skin cancer	Increased risk (SIR 2.4 [95% CI 1.4–3.9]), especially with advanced age; ongoing (HR 5.9 [95% CI 2.1–16.4]) and past exposure (3.9 [1.3–12.1]) to thiopurines is a risk factor; it is not yet clear whether the use of biologicals increases the risk
Melanoma	Baseline risk might be increased in relation to general population (OR 1.52 [95% CI 1.02–2.25]); biologicals might increase this risk (1.88 [1.08–3.29]); this risk has not been confirmed for thiopurines
Urinary tract cancer	Adjusted incidence associated with the use of thiopurines 2.8 (95% CI 1.2–6.5)
Cervical dysplasia and cancer of the uterine cervix	Might be increased in women with IBD; whether thiopurine use increases this risk remains unclear; smoking, young age at diagnosis, and exposure to oral contraceptives might increase the overall risk
CD=Crohn's disease. SIR=standardised incidence ratio. EBV=Epstein-Barr virus. HR=hazard ratio. OR=odds ratio. IBD=inflammatory bowel disease.	
<b>Table 3: Intestinal and extra-intestinal malignancies associated with CD<sup>84,85</sup></b>	

### Therapeutic agents Crohn's disease

The treatment of Crohn's disease involves an induction and maintenance regimen. The choice of medication depends on disease severity and response to previous therapies. The most widely used drugs in Crohn's disease are corticosteroids, immunosuppressants (thiopurines [azathioprine and mercaptopurine] and methotrexate), biologicals (anti-TNF [infliximab, adalimumab, and certolizumab pegol], and anti-adhesion molecules (vedolizumab). 5-aminosalicylates are not effective in the preoperative setting and have a low efficacy to prevent Crohn's disease postoperative recurrence.<sup>91</sup> Antibiotic use should be restricted to Crohn's disease complicated by fistulas or abscesses, or both. Encouraging results obtained

with some antibiotics such as rifaximin in luminal Crohn's disease await confirmation.<sup>92</sup> Although probiotics and faecal transplantation have no established role yet, they remain an area of active investigation.

### Corticosteroids

According to guidelines,<sup>93</sup> mild to moderately active disease should be treated with steroids (budesonide or prednisone). In case of localised ileal or ileocaecal disease, budesonide—a locally acting glucocorticosteroid—should be preferred to limit systemic side-effects, despite lower efficacy than that of prednisone.<sup>94</sup> Systemic steroids (prednisolone) should be used for all other disease locations. About 28% of patients become steroid dependent;<sup>95</sup> budesonide and prednisolone are not effective for maintaining remission, and steroid withdrawal with a steroid-sparing agent should be a major therapeutic goal because of the side-effects associated with prolonged exposure (eg, diabetes, bone loss, hypertension, and infections).<sup>94,96,97</sup>

### Nutritional therapy

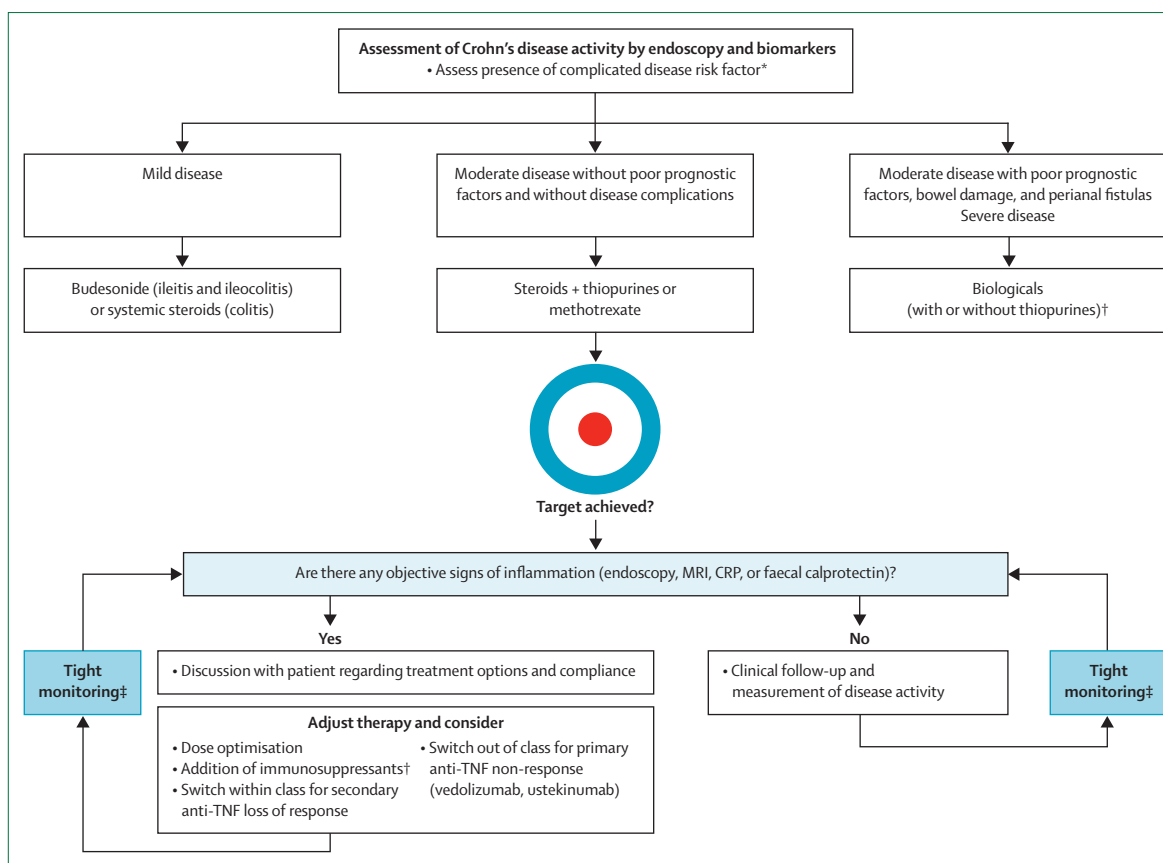
Nutritional support is a key component in the management of patients with Crohn's disease, who have weight loss or malnutrition, and before surgery. In children with Crohn's disease, exclusive enteral nutrition is recommended as first-line therapy to induce remission,<sup>98</sup> whereas in adult patients, the evidence is insufficient for nutrition to be recommended as a primary therapy.<sup>99</sup> Interest in dietary interventions is increasing but studies are needed.

### Immunosuppressants

Thiopurines and methotrexate should be considered only for maintenance therapy.<sup>100–102</sup> Several studies have reported that thiopurine use in Crohn's disease is associated with reduced need for surgery<sup>103,104</sup> and has modest benefit in maintaining remission.<sup>100</sup> Two controlled trials of early Crohn's disease failed to show that azathioprine has the potential for disease modification.<sup>105,106</sup> Furthermore, an increased risk of malignancies (lymphoma, non-melanoma skin cancers, myeloid disorders, and urinary tract cancers) is associated with these drugs.<sup>107–109</sup> Thiopurines should be used with caution in young men (aged <35 years) and in older people who are at increased risk of developing malignancy. Thiopurine metabolite monitoring might be helpful in detecting poor compliance to treatment, underdosing, resistance to thiopurines, preferential 6-MMP metabolism, and overdose or refractoriness to thiopurine.<sup>110</sup>

Despite some evidence of efficacy,<sup>101,111</sup> methotrexate has been underused in IBD, probably because IBD mainly affects young people and is contraindicated in pregnant women. Given a favourable risk–benefit ratio,<sup>112</sup> methotrexate is increasingly used to treat Crohn's disease as monotherapy or combination therapy, even though its efficacy in combination therapy requires additional investigation.<sup>113</sup>





**Figure 4:** Proposed algorithm for the treatment of CD based on a treat-to-target approach

Central to this algorithm is patient stratification, early introduction of immunosuppressants, and rapid escalation to biologicals (accelerated step-up strategy) or the early introduction of combination therapy (top-down strategy) based on patient prognostic factors associated with a tight and frequent control of inflammatory activity, and adjustment of therapy based on that assessment (treat-to-target).<sup>70,90</sup> CD=Crohn's disease. CRP=C-reactive protein. \*Poor prognostic factors include extensive small bowel disease, severe upper gastrointestinal disease, rectal disease, perianal lesions, early stricturing or penetrating disease, smoking and young age at diagnosis, and severe endoscopic lesions. †Consider anti-TNF monotherapy in patients at high risk of adverse events, including patients older than 65 years, with history of malignant disease, or male and younger than 35 years. ‡Suggested interval assessment for tight monitoring: clinical assessment every 3 months for patients with active disease (every 6–12 months for patients in remission), ileocolonoscopy (or cross-sectional imaging in patients who cannot be adequately assessed with ileocolonoscopy) every 6–9 months for patients with active disease, and biomarkers (CRP/faecal calprotectin) every 3–6 months.

#### Anti-TNF therapy

Three anti-TNF agents (infliximab, adalimumab, and certolizumab pegol) are effective to induce and maintain remission in Crohn's disease (see appendix for response and remission rates). Certolizumab is only available in North America, Switzerland, and a few other countries. Anti-TNF drugs are the most potent agents available to treat Crohn's disease, but their use is restricted to patients who have not responded to treatment with steroids or thiopurines according to drug labelling. Infliximab has been the only anti-TNF drug to show efficacy for the treatment of perianal disease in a randomised controlled trial.<sup>114</sup> Fistula healing was a secondary endpoint in the CHARM trial, in which adalimumab was also more effective than placebo for fistula healing<sup>115</sup> (for the management of perianal disease see the review by Gecse and colleagues<sup>116</sup>). Biosimilars were approved for the treatment of IBD in September, 2013, in Europe and in April, 2016, in the USA. Biosimilars should present no

meaningful differences in terms of efficacy and safety compared with their originators,<sup>117</sup> with the advantage of lower cost making them more accessible to a larger number of patients.

The SONIC trial (Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease) compared the efficacy of infliximab monotherapy, azathioprine monotherapy, and both drugs combined in patients with recent onset of moderate-to-severe Crohn's disease and no previous immunosuppressant or biological drug therapy.<sup>118</sup> Infliximab as monotherapy or combined with azathioprine was significantly more effective than azathioprine alone with regards to steroid-free remission and mucosal healing rates at 6 months.<sup>118</sup> A multicentre, open-label, randomised study compared the efficacy and safety of adalimumab monotherapy with adalimumab-azathioprine combination therapy. Although the clinical efficacy of combination therapy at 26 weeks was not significantly different from that of

adalimumab monotherapy, it led to a significantly better endoscopic improvement than monotherapy.<sup>119</sup>

All monoclonal antibodies have the potential for immunogenicity. Reducing the immunogenicity of anti-TNFs by the addition of an immunosuppressant drug might be an effective strategy for patients losing response to anti-TNF monotherapy over time.<sup>120</sup> Anti-TNF therapy is generally well tolerated in clinical practice but it was shown to double the risk of opportunistic infections in patients with IBD<sup>121</sup> and there are concerns it might increase the risk of melanoma skin cancer.<sup>84</sup> Although combination therapy does not seem to increase the risk of serious infections,<sup>122</sup> an increased risk of lymphoma has been observed in these patients, mainly driven by thiopurine use.<sup>122,123</sup>

#### *New biological drugs*

Vedolizumab is an intravenously administered monoclonal antibody that blocks  $\alpha 4\beta 7$  integrin, resulting in gut-selective anti-inflammatory activity. It is effective in the induction and maintenance of clinical remission in refractory and luminal Crohn's disease. Vedolizumab has been approved by the European Medicines Agency and the US Food Drug Administration in adults with moderately to severely active Crohn's disease who have had an inadequate response with anti-TNFs or immunosuppressants, lost response to anti-TNFs or immunosuppressants, or were intolerant to anti-TNFs or immunosuppressants, or who had an inadequate response with corticosteroids, were intolerant to corticosteroids, or showed dependence on corticosteroids.<sup>124</sup> Its efficacy is lower in patients in whom previous anti-TNF therapy was unsuccessful.<sup>125</sup> Ustekinumab is a monoclonal antibody directed against interleukin 12 and interleukin 23 through their common p40 subunit.<sup>126</sup> After an intravenous infusion for induction, it is administered subcutaneously every 8 weeks for maintenance therapy. Randomised controlled trials in patients with moderate-to-severe Crohn's disease have shown that ustekinumab is superior to placebo in anti-TNF naive and refractory patients.<sup>127</sup> It is less effective in patients in whom anti-TNF therapy has failed. The safety profile of both drugs looks favourable, but long-term safety needs to be formally investigated in post-marketing studies.

#### *Surgery*

Patients with refractory medical disease, who develop complications (abscesses or malignancy) or do not tolerate medical therapy, or both, are candidates for surgery. Likewise, patients presenting with obstructive symptoms and no evidence of inflammation, do not benefit from anti-inflammatory medications and might therefore need surgical resection. Occasionally, severe colonic disease, in combination with perianal sepsis, warrants colonic diversion for symptom control before anti-TNF therapy can be used safely.<sup>128</sup> The decision to operate should be discussed within a multidisciplinary

team, and should include appropriate preoperative imaging, patient counselling, optimisation of nutritional status, and prophylaxis for thromboembolic events.<sup>129</sup> Advances in minimally invasive surgery are being adopted into the management of Crohn's disease, allowing for shorter hospital stays, faster recovery times, and better cosmetic outcomes.<sup>130</sup>

#### *General health maintenance and follow-up*

Patients with Crohn's disease require periodic follow-up because of risk of flare-ups and long-term complications. Smoking cessation should be actively pursued. Patients should receive appropriate guidance on vaccinations, osteoporosis screening, and cancer or dysplasia surveillance (appendix).

#### *Fertility and pregnancy*

Fertility rates for patients in remission without a history of pelvic surgery are the same as for the general population. Although there is no increased risk of congenital anomalies in pregnancies among women with IBD, there might be an increased risk of preterm birth (OR 1.85; 95% CI 1.67–2.05), small gestational age (OR 1.36; 95% CI 1.16–1.60), and stillbirth (OR 1.57; 95% CI 1.03–2.38).<sup>131</sup> These adverse events are mostly associated with active disease, and therefore adequate control of disease before and during pregnancy is crucial.<sup>132</sup> Most IBD medications, with the exception of methotrexate (which should be stopped at least 3 months before trying to conceive) are considered safe during pregnancy and breastfeeding.<sup>133</sup> A large prospective study<sup>134</sup> did not find any increased risk of congenital abnormalities or pregnancy complications for babies exposed in utero to thiopurines or biologicals. Infants exposed to combination therapy presented a slightly elevated risk of infections by age 12 months (relative risk 1.50 [95% CI 1.08–2.09]).<sup>134</sup> Biologicals (except certolizumab pegol) cross the placenta in the beginning of the second trimester, and drug concentrations in infants are four times higher than in their mothers.<sup>135</sup> Because the long-term implications of exposure to anti-TNF drugs are unknown, some societies<sup>136</sup> recommend discontinuing anti-TNF treatment by the end of the second trimester for women in deep remission with very low risk of relapse, although this recommendation is controversial.<sup>133</sup> The mode of delivery should be determined by obstetric indications; patients with active perianal disease should undergo caesarean section. Babies born to mothers who have been exposed during pregnancy to biologicals should not receive live vaccines during the first 6 months of life.

### **Future directions and controversies**

#### **Evolving therapeutic strategies and treatment goals**

The concept of targeting early Crohn's disease is emerging. Post-hoc data suggest that biological drug therapy is effective if introduced earlier in the disease course.<sup>137</sup>

Controlled trials in this specific population, using a treat-to-target approach and seeking prospective evidence regarding the need to achieve and maintain mucosal healing and deep remission, are eagerly awaited.<sup>138</sup>

### Personalisation of therapy and drug monitoring

The need to develop biomarkers that can predict response to therapies will become increasingly important for personalised medicine decisions in the near future.<sup>139,140</sup> The use of therapeutic drug monitoring to optimise anti-TNF drug concentrations holds great promise for dose optimisation in clinical practice, in view of the reported correlations between anti-TNF trough concentrations, anti-drug antibodies, and disease outcomes. Two controlled trials,<sup>141,142</sup> which investigated the clinical use of therapeutic drug monitoring based on drug concentration or symptoms, showed that trough-level-based dose intensification was not superior to dose intensification based on symptoms alone. Despite not being superior to symptom-driven dosing for achieving remission at 1 year, concentration-based dosing was associated with fewer flare-ups.<sup>141</sup> These rather disappointing results should be interpreted in the light of potential cost savings.<sup>143</sup> Furthermore, therapeutic drug monitoring is widely used in clinical practice and has indisputable value for assessment loss of response and guidance of therapeutic choices.

### Drug de-escalation

Stopping immunosuppressant monotherapy after a period of remission has been explored in randomised controlled trials and is associated with increased rates of relapse. Studies with patients who discontinued the immunosuppressants after combination therapy did not find that rates of relapse differed from those of patients who continued the drug.<sup>144</sup> As we move into an era of early diagnosis and early intervention with potent drugs, further de-escalation strategies will need to be explored. A prospective cohort study (STORI)<sup>145</sup> assessed the risk of relapse following anti-TNF withdrawal in patients on combination therapy with thiopurines or methotrexate. The estimated proportion of relapse over 2 years after stopping infliximab was 52.2% (standard error  $\pm 5.2\%$ ). Results from this trial showed that a subset of patients in deep remission had a very low risk of relapse. The ongoing SPARE trial (NCT02177071) is a three arm study comparing de-escalation strategies and exploring the concept of cycling therapy as a way of reducing costs and toxicity.<sup>144</sup>

### Emerging therapies

Mongersen is an oral anti-sense oligonucleotide that inhibits *SMAD7* mRNA production. This action restores TGF $\beta$ 1 signalling, leading to the suppression of proinflammatory cytokines. In a phase 2 study,<sup>146</sup> clinical remission was achieved in 65% of patients, with very mild side-effects. Janus kinase (JAK) inhibitors are a class of oral drugs targeting the JAK-signal transducer

and activator of transcription pathway. As a result, multiple cytokine signals are affected, highlighting the potential for these drugs to modulate several aspects of the adaptive and innate immune responses. Tofacitinib (a JAK1/JAK3 inhibitor) and filgotinib (a JAK1 inhibitor) are undergoing clinical testing in Crohn's disease.<sup>147</sup> New anti-adhesion molecules such as etrolizumab (rhuMab  $\beta$ 7) and anti-MAdCAM1 antibody are also under clinical trials. In 2016, a randomised controlled trial of patients with active complex perianal disease showed that intralesional injection of allogeneic, expanded, adipose-derived stem cells was more effective than was placebo at week 24 for fistula closure with absence of collections.<sup>148</sup>

As several biologicals are in the process of being approved for the treatment of Crohn's disease, choice among available agents is likely to become challenging in the future. Several parameters should be considered to help physicians through the decision making process, including the comparative effectiveness and long-term safety profile, availability and labelling, international guidelines, cost, and patient preferences.<sup>90</sup> Treatment algorithms for Crohn's disease are likely to evolve with the launch of new drugs and increasing use of biosimilars. Head-to-head trials and trials combining drugs targeting different pathways will be needed and will probably change the therapeutic landscape and prognosis of Crohn's disease.

### Prevention of disease

Crohn's disease has a preclinical period, during which dysregulated immunological pathways are evident, setting the stage for disease to manifest years later.<sup>149</sup> Insight into this stage of disease could offer numerous possibilities, including disease prevention. Despite anecdotal reports, there are no clear data regarding a robust vaccine or any other intervention to prevent Crohn's disease, since the antigenic drivers have not been established.

#### Contributors

JT, J-FC, and LP-B contributed to the manuscript concept and design. JT, SM, and LP-B drafted the manuscript. J-FC and LP-B critically revised the manuscript. All authors approved the final version of the manuscript.

#### Declaration of interests

JT has served as a consultant for AbbVie and Takeda, and as a speaker for Ferring and Falk. SM has served as a consultant for Pfizer, and receives research funding support from Takeda Pharmaceuticals. J-FC has served as consultant or advisory board member for AbbVie, Amgen, AstraZeneca, AB Science, Boehringer Ingelheim, Bristol Meyers Squibb, Celgene, Celltrion, Danone, Enterome, Evidera, Ferring, Genentech, Giuliani SPA, Given Imaging, Janssen & Janssen, Immune Pharmaceuticals, Intestinal Biotech Development, Kyowa Kirin Pharma, Lilly, Medimmune, Merck Sharp Dohme, Merck, Millennium Pharmaceuticals, Navigant Consulting, Neovacs, Nestle Nutrition Sciences Partner, Nutrition Science Partners, Pfizer, Prometheus Laboratories, Protagonist Therapies, Receptos, Sanofi, Schering Plough, Second Genome, Shire, Takeda, Teva Pharmaceuticals, Tigenix, UCB Pharmaceuticals, UEGW Abbvie Advisory Board, UEGW Abbvie Symposium, Vertex, and Dr August Wolff GmbH. LP-B has received consulting fees from Merck, Abbvie, Janssen & Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Therakos,

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