# Crohn's disease

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See Online for appendix

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**Crohn's disease is a relapsing systemic inflammatory disease, mainly affecting the gastrointestinal tract with extraintestinal manifestations and associated immune disorders. Genome wide association studies identified susceptibility loci that—triggered by environmental factors—result in a disturbed innate (ie, disturbed intestinal barrier, Paneth cell dysfunction, endoplasmic reticulum stress, defective unfolded protein response and autophagy, impaired recognition of microbes by pattern recognition receptors, such as nucleotide binding domain and Toll like receptors on dendritic cells and macrophages) and adaptive (ie, imbalance of effector and regulatory T cells and cytokines, migration and retention of leukocytes) immune response towards a diminished diversity of commensal microbiota. We discuss the epidemiology, immunobiology, amd natural history of Crohn's disease; describe new treatment goals and risk stratification of patients; and provide an evidence based rational approach to diagnosis (ie, work-up algorithm, new imaging methods [ie, enhanced endoscopy, ultrasound, MRI and CT] and biomarkers), management, evolving therapeutic targets (ie, integrins, chemokine receptors, cell-based and stem-cell-based therapies), prevention, and surveillance.**

## Introduction

Crohn's disease and ulcerative colitis are the two main components of inflammatory bowel disease.[1] Crohn's disease is a relapsing inflammatory disease, mainly affecting the gastrointestinal tract, and frequently presents with abdominal pain, fever, and clinical signs of bowel obstruction or diarrhoea with passage of blood or mucus, or both. Because its incidence and prevalence are rising (appendix p 1) in all ethnic groups and because of the systemic nature of the illness, Crohn's disease concerns an increasingly diverse group of clinicians.

## Causes and pathophysiology

### Genetics

Familial aggregation has been known for more than 70 years and large concordance studies in twins in northern Europe were early indicators of a genetic component in Crohn's disease. These data have been confirmed in other countries. A German nationwide study[2] showed that 35% of monozygotic pairs, but only 3% of dizygotic pairs, were concordant for the disorder. In 70% of discordant monozygotic pairs the first-born had inflammatory bowel disease.[2] Substantial phenotypic (location, behaviour, and age at diagnosis) concordance exists, both at diagnosis and longitudinally, in monozygotic twins.[3] Familial aggregation is confirmed.[4] Moreover, prevalence in Ashkenazi Jews is higher than in any other ethnic group and Jewish descent is an independent risk factor for the disorder. Genetic anticipation—ie, earlier disease onset in the offspring of parents with the disorder—has been confirmed.[5]

Genome wide association studies and computerised (*in silico*) meta-analyses have identified and confirmed 71 susceptibility loci for Crohn's disease on 17 chromosomes so far (appendix pp 2–3).[6] The identification of susceptibility loci has enhanced our understanding of the causes of the disorder by providing important clues about crucial and disturbed pathways of the intestinal immune system. Appreciation of the role of the innate immune response in Crohn's disease resulted from the discovery of relevant susceptibility loci in genetic research. Familial aggregation with occurrence of ulcerative colitis in one family explains why 17 of the loci that relate to Crohn's disease are shared within the 47 loci identified for ulcerative colitis.[7]

Genome wide association studies (appendix pp 2–3) also link inflammatory extraintestinal symptoms[8] (ie, ankylosing spondylitis, non-drug induced osteoporosis) and associated autoimmune diseases[9] (ie, asthma, multiple sclerosis, type 1 diabetes, autoimmune thyroid disease, and coeliac disease) known from epidemiological studies on a molecular level with shared susceptibility loci and can explain ethnic differences[10] in the distribution of these associated diseases (figure 1). However, although enhanced statistical models and increasing sample sizes from consortia will double the number of susceptibility loci identified in the future, this component still explains only a little more than 20% of the heritability of Crohn's disease, which together with the relatively low concordance rates in monozygotic twins, emphasises the importance of gene-gene, epigenetic, and environmental factors.[11] Furthermore, association (statistically significant correlation) does not equal causality, which is difficult to

### Search strategy and selection criteria

We searched PubMed, Cochrane, and Ovid databases with the MeSH terms "Crohn's disease" and "inflammatory bowel diseases", combined with the subheadings "epidemiology", "innate and adaptive immunity", "genetics", "diagnosis", "imaging", "endoscopy", "therapy", "surveillance", "prevention", and "complications". All relevant articles were critically reviewed and the most recent preferably cited. For basic science articles priority was given to studies involving human beings and for clinical research to randomised placebo controlled trials and meta-analyses. Relevant abstracts presented at major meetings were also taken into account for this Seminar. We focused on reports from the past 5 years, and the last search was done in December, 2011.

prove.[12] Identification of the causative gene variants in the many sequence polymorphisms in the regions of association can be very challenging, as suggested by new work on the *IRGM1* coding region involved in autophagy.[13]

### Environmental factors

Worldwide, north-south, east-west, and urban-rural gradients for incidence rates and prevalence of Crohn's disease have been identified.[14] However, a systematic geographic analysis,[15] new studies from southern hemisphere countries reporting rates that are much the same as those in the northern hemisphere (appendix p 1),[16] and reports of an increased incidence in rural, periurban regions[17] argue against an independent geographic component. Apart from genetics, several alternative explanations, mostly related to lifestyle, are possible. The importance of environment is suggested by increasing incidence rates in previously less affected ethnic groups such as Asians and Hispanics[10] and in immigrants from low incidence regions moving to areas with a traditionally high incidence.[18]

Industrialisation has greatly affected people's lives with a focus on career and higher education,[15] more adverse life events,[19] less women breastfeeding,[20] smaller families with less crowded living conditions, improved domestic hygiene and sanitation,[21] availability and quality of (hot) tap water,[22] adoption of a sedentary lifestyle,[23] exposure to air pollution,[24] consumption of a western diet[25] loaded with convenience foods (often containing excessive amounts of sugar and polyunsaturated fats), and increased tobacco use. Although all of these factors have been implicated in Crohn's disease, active[26] and passive[27] (even in childhood) smoking are best studied. Early tobacco use significantly increases the risk of developing the disorder.[28] Mechanistically, apparently neither nicotine nor carbon monoxide are the cause.

Crohn's disease frequently occurs after infectious gastroenteritis,[29] has a distinct mucosal flora (dysbiosis),[30] and increased numbers of intramucosal bacteria[31] often featuring adhesive species[32] and thus efforts to identify a causative infectious agent continue. The disorder resembles infectious granulomatous ileitis conditions including intestinal tuberculosis and Johne's disease, a zoonosis caused by *Mycobacterium avium paracellulare*, which induces similar immune responses to Crohn's disease.[33] Mycobacteria have been identified in tissues and blood of adult[34] and paediatric[35] (early onset) patients with Crohn's disease and they remain an important differential diagnosis in endemic areas.[36] Controlled trials with antituberculous drugs have failed.[37] Mycobacteria-related Crohn's disease research frequently comes from ruminant farming areas where alternative explanations including contaminated foods and drinking water[38] occur. However, mycobacteria still stand out from all other suspected infectious causes since genome wide association studies [6,39] showed shared susceptibility loci with leprosy (ie, *NOD2, LACC1*) and polymorphisms in autophagy (ie, *CARD9, IRGM1*) required for mycobacterial clearance. The association of Crohn's disease with measles or other viruses, *Listeria,* or *Yersinia* was not confirmed. However, animal research suggests that viral infections—as an environmental factor—might convert genetic susceptibility to disease outbreak.[40] Results of a meta-analysis suggest a link to contraceptives,[41] but not to measles-mumps-rubella[42] or BCG[43] vaccines. Although a meta-analysis[44] confirmed a substantial risk of development of Crohn's disease after appendicectomy, this finding probably results from diagnostic problems in patients with incipient Crohn's disease.

## Immunobiology

Crohn's disease seems to result from an impaired interaction of the intestinal commensal microbiota that is normally in a state symbiotic mutualism with the human host (immune system). Despite enormous progress in understanding the many facets of this ancient relation, distinction between primary inciting events and secondary occurrences is challenging.

### Microbiota

Metagenomic research suggests that up to four major bacterial phyla (Bacteroidetes, Firmicutes, Actinobacteria, and Proteobacteria) consisting of thousands of mostly anaerobic species colonise the human gut with a steep, stomach-acid driven, proximal-distal gradient. Species diversity in the gut normally also varies according to temporal,[45] individual,[46,47] dietary,[48] and drug induced[49] factors. However, healthy intestinal microbiota variation is overall stratified and not continuous.[50] Comparative studies showed clustering[51] and reduced diversity especially within the Firmicutes and Bacteroidetes phyla in patients with Crohn's disease.[31,52,53] A reduction of *Faecalibacterium prausnitzii* (a Firmicute), was associated with an increased risk of postoperative recurrence of ileal Crohn's disease and its experimental restitution had anti-inflammatory effects.[54] Crohn's disease is not caused by diminished commensal diversity alone, but requires a susceptible genotype—as confirmed by research in mice with human-relevant susceptibility mutations.[55]

### Intestinal barrier

The first line of defence of the mucosal immune system is a polarised single layer of epithelial cells covered by mucus biofilm secreted from goblet cells with interspersed bacteria.[31] Decreased expression of the mucin gene *MUC1* in the inflamed terminal ileum in patients with Crohn's disease suggests that mucin cover becomes insufficient.[56] This hypothesis is supported by genome wide association studies[6] that link *MUC1, MUC19,* and *PTGER4* to the disorder.[6] The paracellular route of fluxes between neighbouring epithelial cells is normally blocked by tight junctions. In Crohn's disease this tight seal becomes leaky,[57] possibly because of changes in the expression of tight-junction proteins such as claudins,[58]

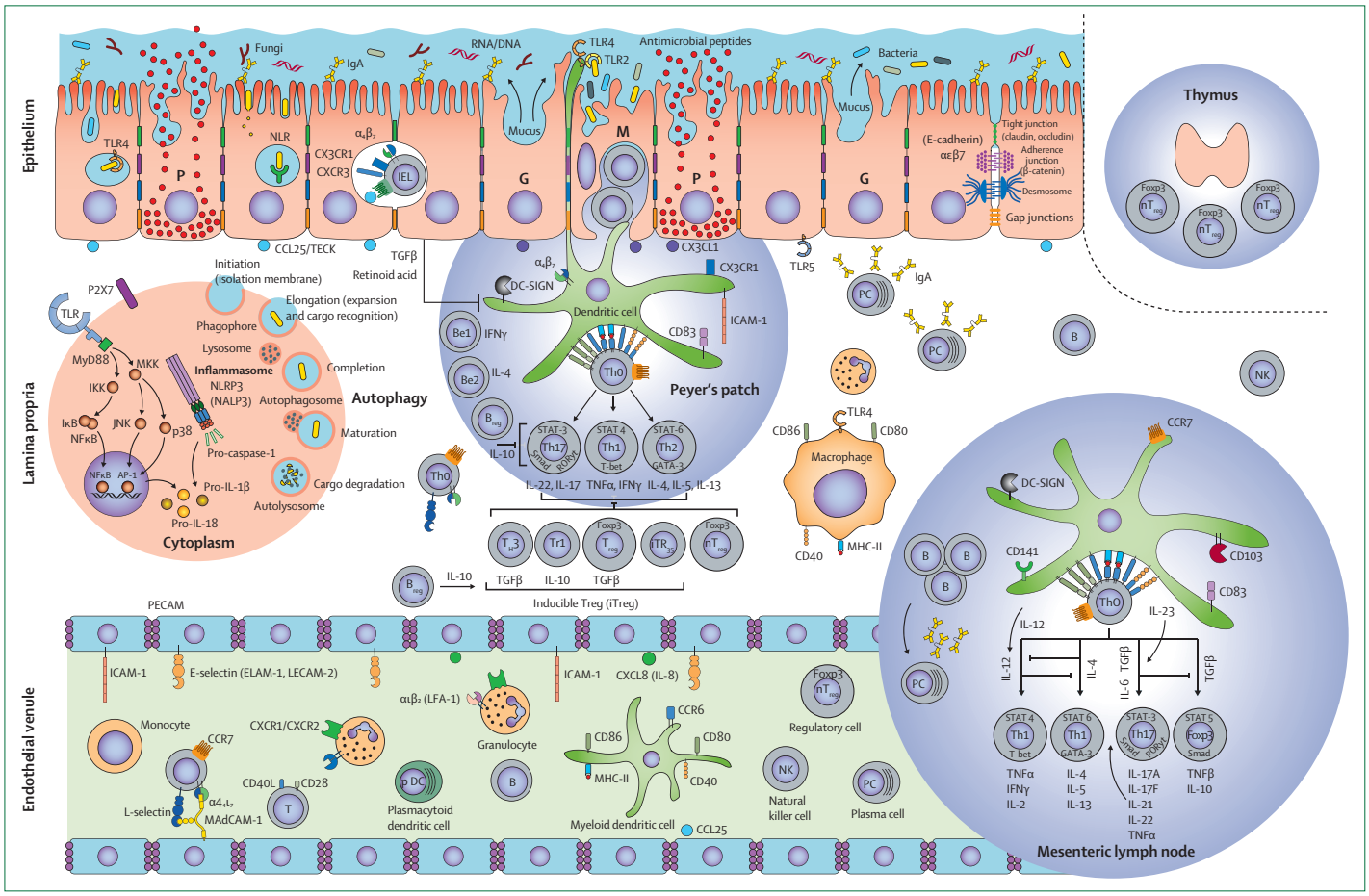


***Figure 1:*** **Healthy small intestinal immune system**
AP-1=activator protein 1. B=B cell. Be=B effector cell. Breg=regulatory B cell. CD=cluster of differentiation. CCL=C-C motif chemokine ligand. CCR=C-C motif chemokine receptor. CXCL=C-X-C motif chemokine ligand. CXCR=C-X-C motif chemokine receptor. DC-SIGN=dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin. ELAM=endothelial-leucocyte adhesion molecule. FoxP3=forkhead box P3. G=goblet cell. GATA=GATA binding protein. ICAM=intercellular adhesion molecule. IFN=interferon. Ig=immunoglobulin. IL=interleukin. IEL=intraepithelial lymphocytes. JNK=c-Jun N-terminal kinases. KK=IκB kinase. LECAM1=leukocyte endothelial cell adhesion molecule. LFA=lymphocyte function-associated antigen. M=microfold cell. MAdCAM=mucosal vascular addressin cell adhesion molecule. MKK=mitogen-activated protein kinase kinase. MyD88=myeloid differentiation primary response gene 88. NKκB=nuclear factor κ B. NK=natural killer cell. NLR= nucleotide binding domain like receptor. NLRP=NACHT, leucine-rich repeat, and pyrine domains-containing protein. P2XR=P2X receptor. p38=p38 mitogen-activated protein kinases. P=paneth cell. PC=plasma cell. PECAM=platelet endothelial cell adhesion molecule. pDC=plasmamacytoid dendritic cell. RORγ=RAR-related orphan receptor γ. Smad=Sma and Mad related family. STAT=signal transducer and activator of transcription. T=T cell. nTreg=naturally regulatory T cells. iTreg=inducible regulatory T cells. iTR35=interleukin-35-dependent induced regulatory T cell. Tr=T regulatory cell. T-bet=Th1-specific T box transcription factor. TECK=thymus-expressed chemokine. TGFβ=transforming growth factor β. Th=T helper cell. TNFα=tumour necrosis factor α. TLR=toll-like receptor.

resulting in increased permeability and access of luminal antigens to the lamina propria, which is densely populated with immune cells. In-vitro and animal studies link tight-junction proteins[59–61] and permeability changes that are mediated by myosin light chain kinase[59,62] to activated T cells, the prototypical Crohn's disease cytokines tumour necrosis factor (TNF) α[59,62] and interferon γ[61], and intestinal microbiota via NOD2.[62] Permeability defects have been reported in clinically healthy first degree relatives of patients with Crohn's disease who have a *NOD2* mutation.[6,63] Paneth cells are also highly specialised epithelial cells. They defend the mucosal barrier by excretion of antimicrobial peptide granules, such as α-defensins, and regulate the makeup of the commensal microbiota.[64] Paneth cells from patients with Crohn's disease carrying the 300T→A variant of the autophagy gene *ATG16L* have fewer, dysmorphic, and functionally impaired granules than do those with other variants.[65] Additional evidence linking Paneth-cell dysfunction and ileal inflammation to polymorphisms in *XBP1* and *NOD2* comes from animals.[66,67] Endoplasmic reticulum stress in the highly active secretory goblet and Paneth cells is mechanistically linked to autophagy and might disturb the unfolded protein response of these cells and induce inflammation.[68]

## Microbial sensing, innate immunity, and autophagy

Microbe associated molecular patterns such as lipopolysaccharide, peptidoglycan-derived muramyl dipeptide, lipoteichoic acid, single and double stranded RNA and

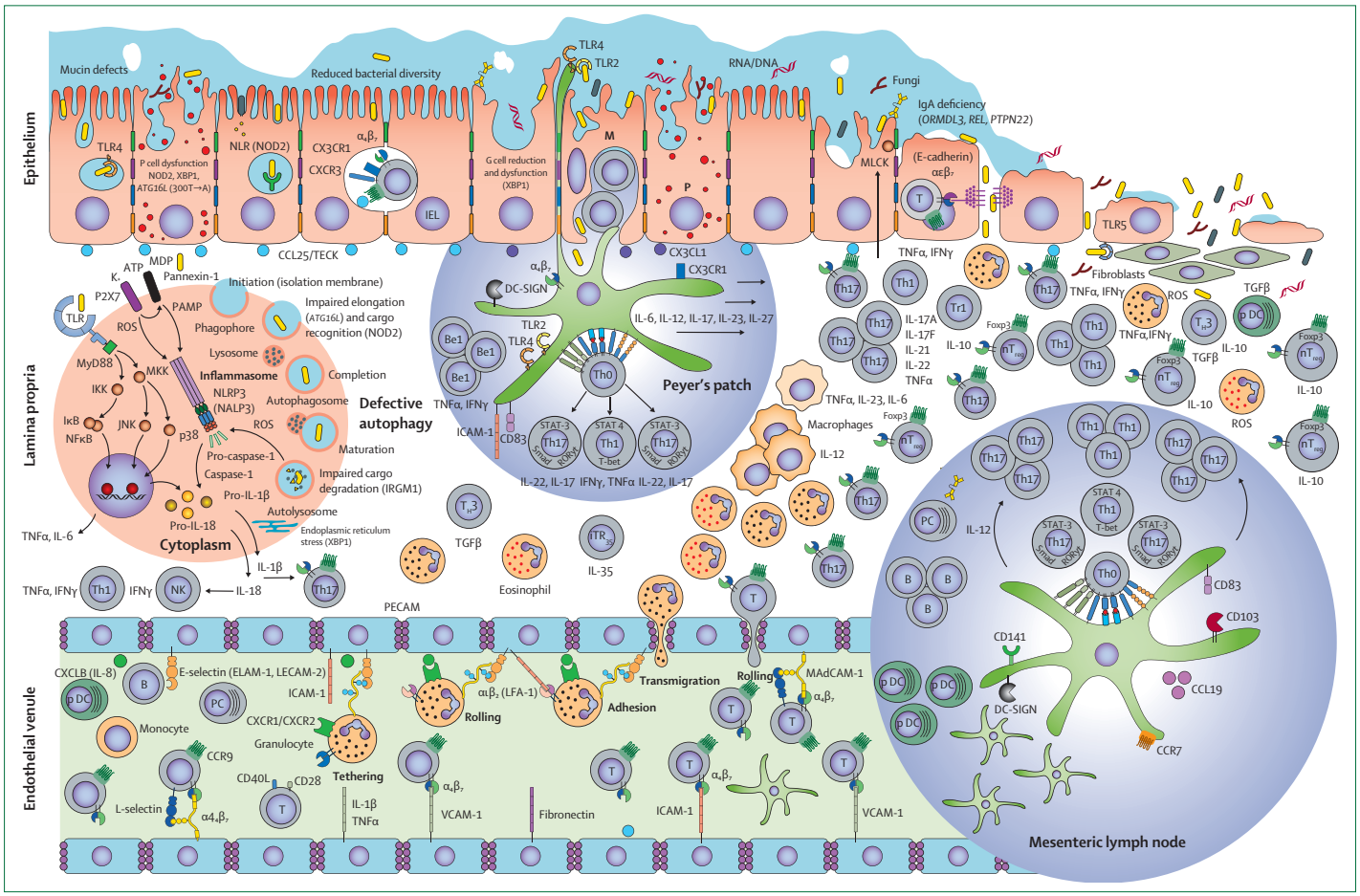


***Figure 2:*** **Intestinal immune system in Crohn's disease**

For therapeutic targets see text and appendix p 6. AP-1=activator protein 1. B=B cell. Be=B effector cell. Breg=regulatory B cell. CD=cluster of differentiation. CCL=C-C motif chemokine ligand. CCR=C-C motif chemokine receptor. CXCL=C-X-C motif chemokine ligand. CXCR=C-X-C motif chemokine receptor. DC-SIGN=dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin. ELAM=endothelial-leucocyte adhesion molecule. FoxP3=forkhead box P3. G=goblet cell. GATA=GATA binding protein. ICAM=intercellular adhesion molecule. IFN=interferon. Ig=immunoglobulin. IL=interleukin. IEL=intraepithelial lymphocytes. JNK=c-Jun N-terminal kinases. KK=IκB kinase. LECAM1=leukocyte endothelial cell adhesion molecule. LFA=lymphocyte function-associated antigen. M=microfold cell. MAdCAM=mucosal vascular addressin cell adhesion molecule. MDP=muramyl dipeptide. MKK=mitogen-activated protein kinase kinase. MLCK=myosin light-chain kinase. MyD88=myeloid differentiation primary response gene 88. NKκB=nuclear factor κ B. NLR= nucleotide binding domain like receptor. NLRP=NACHT, leucine-rich repeat, and pyrine domains-containing protein. NOD=nucleotide-binding oligomerisation domain. P2XR=P2X receptor. p38=p38 mitogen-activated protein kinases. P=paneth cell. PAMP=pathogen-associated molecular patterns. PC=plasma cell. PECAM=platelet endothelial cell adhesion molecule. pDC=plasmamacytoid dendritic cell. RORγ=RAR-related orphan receptor γ. ROS=reactive oxygen species. Smad=Sma and Mad related family. STAT=signal transducer and activator of transcription. T=T cell. nTreg=naturally regulatory T cells. iTR35=interleukin-35-dependent induced regulatory T cell. Tr=T regulatory cell. T-bet=Th1-specific T box transcription factor. TECK=thymus-expressed chemokine. TGFβ=transforming growth factor β. Th=T helper cell. TNFα=tumour necrosis factor α. TLR=toll-like receptor. VCAM=vascular cell adhesion protein.

methylated DNA (CpG), and luminal dietary components are recognised by different innate immune-cell populations of the intraepithelial and lamina propria mucosal spaces through pattern recognition receptors such as Toll-like receptors (TLR) and nucleotide binding domain (NOD) like receptors (NLR). Dendritic cells express the widest range of pattern recognition receptors and interpret microbial patterns to direct other immune cells towards immunity or tolerance. They form transepithelial dendrites that enable them to directly sample luminal antigens.[69] Their distribution[70] and phenotype[70,71] correlate with disease activity[72] in Crohn's disease, and increased expression of *TLR2*[73] and *TLR4*[71] and exaggerated lipopolysaccharide response[71] have been reported. The dichotomic role of TLR is shown by data from animals in which commensal induced TLR signalling through MyD88[74] prevents intestinal inflammation, whereas deletion of *TLR5*[75] drives it. The ability of dendritic cells to induce tolerogenic regulatory T cells ($T_{reg}$) might be lost in Crohn's disease.[76] Cytosolic NLR are another major group of pattern recognition receptors—some have a caspase recruitment domain (ie, NOD1 and NOD2) and others a pyrin domain. *NOD2* polymorphisms are strongly associated with Crohn's disease[6] and experimental evidence links them to a weakened inflammatory cytokine response towards muramyl dipeptide[77] and ineffective autophagy,[78] and to *IL10* transcription.[79] Impaired autophagy[80] of invasive

***Panel 1:*** **Evidence based diagnosis techniques for a patient with suspected Crohn's disease**

**Medical history**
Start of symptoms; blood or mucus, or both, in stool; cramps incontinence; nocturnal diarrhoea; travel and dietary history; recent intestinal infections; non-steroidal anti-inflammatory drug use; appendicectomy status; active or passive smoking; family history of Crohn's disease or inflammatory bowel disease; recent gastroenteritis. Screen for extraintestinal symptoms.

**Physical examination**
Heart rate, blood pressure, weight, height, body-mass index, abdominal examination, perianal inspection for fistulas, digital-rectal examination, look for extraintestinal symptoms (in the eyes, skin, joints, and muscles).

**Laboratory studies**
Electrolytes, blood urea nitrogen, creatinine, complete blood count with differential, erythrocyte sedimentation rate, liver function tests, bilirubin, transferrin, ferritin, vitamin B12, folic acid, urine strip. C-reactive protein, faecal calprotectin.

**Microbial studies**
Stool cultures. *Clostridium difficile.*

**Pathology and histology**
At least two biopsy samples from at least five segments including the ileum. Inflammatory cell infiltrate (lymphocytes, plasma cells) with focal crypt irregularity and independent granulomas.

**Endoscopy**
Ileocolonoscopy (spared rectum, ileal inflammation, skip lesions, cobble stoning, fissural and longitudinal ulcers, strictures, fistulas). Oesophagogastroduodenoscopy with biopsies when symptoms occur in the upper gastrointestinal tract.

**Imaging studies**
CT and MRI enterography or enteroclysis scanning for extraintestinal asymptoms if suspected (from history or physical examination). Scanning for fistulas or abscesses if suspected (from history or physical examination). Small bowel capsule endoscopy (wireless capsule endoscopy) if terminal ileum could not be intubated or when other imaging studies are negative. Magnetic resonance cholangiopancreatography if primary sclerosing cholangitis is suspected. Endoscopic retrograde cholangiopancreatography with balloon dilation and bile sampling for cytology patients primary sclerosing cholangitis and dominant strictures.

**Consultation of other specialists**
Surgery, rheumatology, dermatology, ophthalmomology, urology, obstetrics and gynaecology (when rectovaginal fistulas are suspected) if indicated in patients with established or suspected extraintestinal symptoms.

Evidence level and recommendation grade according to consensus guidelines of the European Crohn's and Colitis Organization are available in the appendix p 4.

microbes (xenophagy) and failure to induce an appropriate adaptive effector T-cell response[78] in cells mutant for the *ATG16L*[81] or *NOD2*[78] autophagy genes that are linked to Crohn's disease underscores the importance of this process.

### Adaptive immunity and leucocyte migration

The adaptive immune system in Crohn's disease is now thought to mediate and perpetuate, but probably not start, intestinal inflammation. The disorder is characterised by an imbalance of effector T cells (predominantly T helper [Th]1 or Th17 cells defending the mucosa against bacteria, fungi, and against viruses through secretion of interferon γ, TNFα, and interleukins 17 and 22) versus naturally regulatory T cells (secreting interleukin 10, and transforming growth factor [TGF] β or interleukin 35[82]) originating from the thymus (nTreg) and inducible (iTreg) cells such as Tr1, Th3, and iTr35 in the mucosa.[83] These two main opposing phenotypes, Th17 and Treg, originate from the same precursor and their differentiation, which is controlled by the transcription factors RORγT/FOXP3, is inversely regulated.[84] GWAS support the imbalance model by linking loci that are crucially involved in Treg (ie, *IL10, IL2RA, SMAD3*) and Th1 and Th17 (ie, *CPEB4*) differentiation to Crohn's disease.[6] Moreover, individual homozygous *IL10R* gene mutations derange the tightly regulated cytokine-T-cell balance and coincide with early onset Crohn's disease.[85] Circumstantial evidence such as autoantibodies, lack of mucosal IgA, overlap with loci associated with immunoglobulin A deficiency in GWAS,[6,86] and production of interleukin 10 and TGFβ by regulatory B cells suggest a role for such cells in this disorder. Innate and adaptive leukocyte migration is mediated by selectins, integrins (ie, $\alpha_4\beta_7$) and their ligands from the immunoglobulin superfamily (ie, ICAM-1, MAdCAM-1), fibronectin, and chemokine receptors (ie, c-c motif chemokine receptor 9) and chemokines (ie, c-c motif chemokine ligand 25). The rapid recruitment and inappropriate retention of leucocytes is a hallmark of Crohn's disease (figures 1, 2).

## Diagnostic approach with assessment of phenotype and disease activity

Crohn's disease is a clinical diagnosis that integrates history and physical findings with objective data from imaging and laboratory studies, including histopathology, and should neither be based nor excluded on any one variable or result (panel 1). Important differential non-infectious (ie, irritable bowel syndrome or Behçet's disease[87]) and infectious[88] diagnoses (ie, *Yersinia* or enteroviruses) that mimic Crohn's disease need to be considered with particular attention to endemic diseases such as tuberculosis (appendix p5).[36,89]

Once the diagnosis of Crohn's disease is established, patients should be phenotyped according to the Montreal classification (figure 3)[90] and screened for extraintestinal manifestations[8] and associated autoimmune diseases.[9] An assessment of disease activity (appendix p 6, 7) in combination with phenotype and endoscopic features helps to stratify patients and allows physicians to pick the best possible therapeutic regimen, since these factors are important predictors of disease course and complications. Whereas the anatomical location is mostly stable,[91] behaviour of Crohn's disease according to the Montreal classification varies substantially during the course of the disease. In a population based study[92]

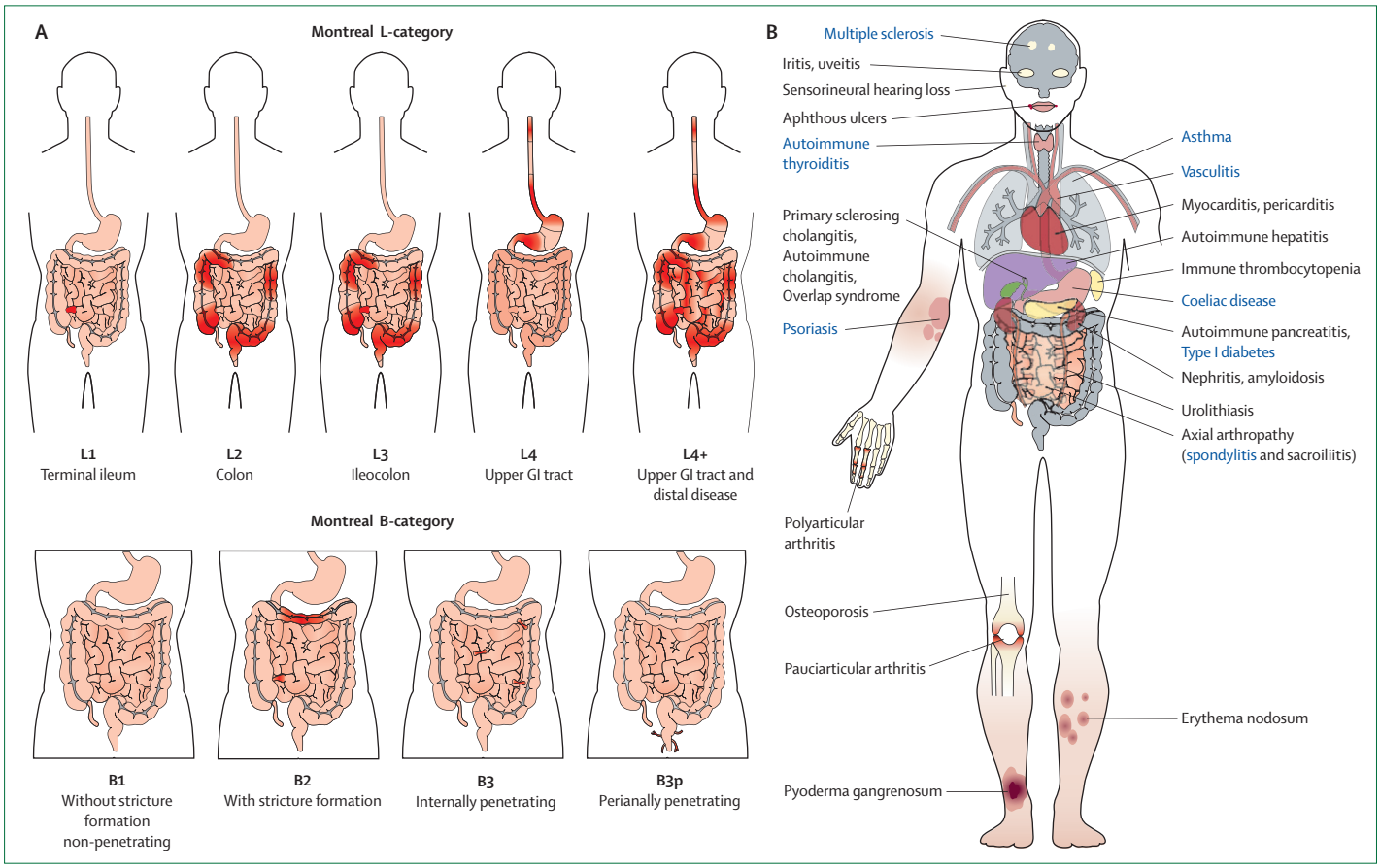


***Figure 3:*** **Phenotype of Crohn's disease**
(A) Montreal classification.[90] Classification by age is A1 <16 years, A2 17–40 years, A3 >40 years. (B) Major extraintestinal manifestations[8] and associated autoimmune disorders[9] (blue). GI=gastrointestinal. p=perianal disease modifier. p is added to B1–3 when concomitant perianal disease is present.

more than half of 306 patients were diagnosed between the ages of 17 and 40 years (Montreal category A2). Crohn's disease was located in the terminal ileum in 45% (L1), colon in 32% (L2), ileocolon in 19% (L3), and upper gastrointestinal tract in 4% (L4). Most patients (81%) had a non-stricturing non-penetrating phenotype (B1), 5% a stricturing (B2) and 14% a penetrating (B3 or B3p) phenotype. Almost a fifth (19%) of patients progressed to a more aggressive phenotype at 90 days and more than half (51%) at 20 years after initial diagnosis, especially when ileal and perianal involvement (fistulas) were present at the time of diagnosis.

## Diagnostic instruments

### Endoscopy

The gold standard for all patients with Crohn's disease is a full ileocolonoscopy with biopsies. Chromoendoscopy with methylene blue dye-spray targeted biopsies results in improved detection of dysplasia compared with conventional random and sequential biopsy methods.[93] Although digital alternatives such as narrow band imaging are less time consuming, they cannot be recommended as a standard technique because of increased rates of missed dysplasia.[94] Capsule endoscopy might be more sensitive compared with enterography or enteroclysis combined with CT (CTE) and MRI (MRE) in patients without endoscopic or clinical suspicion of stenosis.[95]

### CT and MRI enterography or enteroclysis

Enteroclysis is distinguished from enterography by the need to apply luminal contrast through an enteric tube. CTE offers the highest spatial resolution and has replaced small bowel fluoroscopy in leading centres. It is very sensitive, can show inflammation missed by other techniques, can detect complications such as obstruction, fistulas, and abscesses, and might even be cost effective. Its major disadvantage is high radiation exposure, although sophisticated mathematical algorithms of image acquisition and processing can reduce it. MRE is a non-radiating, non-iodine-contrast based alternative to CTE. With appropriate protocols it can provide movies to assess motility and detailed imaging of the bowel wall down to mucosal level. It is the preferred choice for repeated imaging, long-term follow-up and work-up of perianal fistula and abscess complications (figure 4).[96]

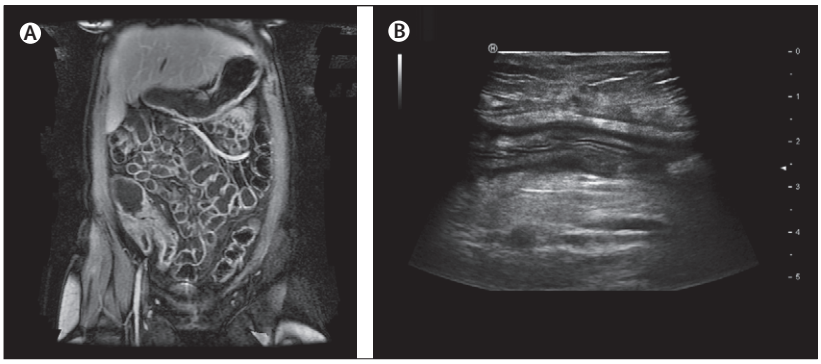


***Figure 4:*** **Stenosis in Crohn's disease**
(A) MR enterography of Crohn's disease restricted to the terminal ileum (Montreal category L1) with inflammatory stenosis. (B) Ultrasound image of an intestinal stenosis in Crohn's disease.

***Panel 2:*** **Key points when caring for a patient with Crohn's disease**

- Do a careful work-up considering important differential diagnoses
- Establish the complete disease phenotype including extraintestinal symptoms
- Screen for predictors and biomarkers of a complicated disease course
- Individualise therapeutic guideline recommendations to your patient
- Consider involving an inflammatory bowel disease expert for optimum treatment choice
- Educate and counsel your patient about disease and therapy associated risks and complications
- Enrol your patient in surveillance programmes and follow-up the patient closely

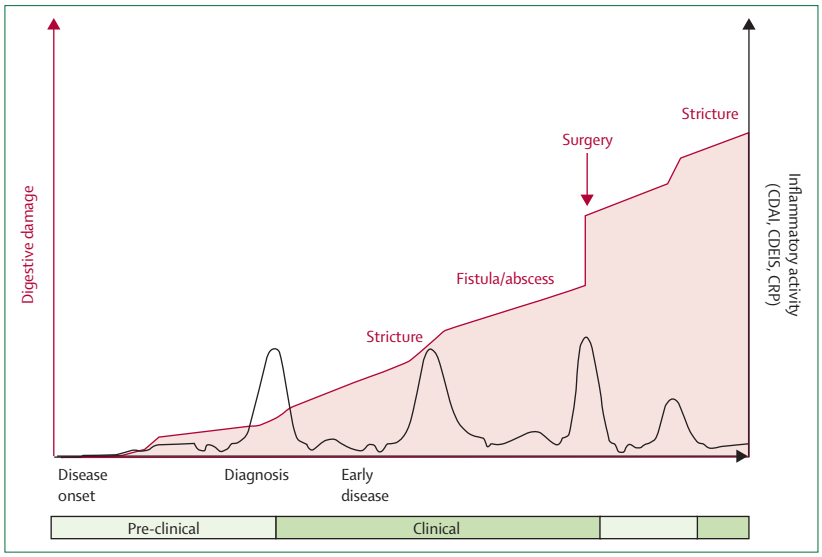


***Figure 5:*** **The Lémann score**
Exemplary visualisation of the Lémann score, a new technique to score and study intestinal damage in Crohn's disease. CDAI=Crohn's disease activity index. CDEIS=Crohn's disease of endoscopic severity. CRP=C-reactive protein. Adapted from Pariente and colleagues,[101] by permission of Wiley.

### Ultrasound (sonography)

Native and (gas or shell microbubble) contrast-enhanced abdominal ultrasound (figure 4) is a readily available, non-invasive imaging technique with an overall sensitivity and specificity that are much the same as with MRI and CT.[96] Prospective studies have shown utility for the initial diagnosis, assessment of disease activity, detection of fistulas, stenoses and abscesses, and significant correlation with histopathology, laboratory findings, validated disease activity indices, and endoscopy. Transrectal and endoscopic ultrasound can assist in perianal complications (figure 4).

### Biomarkers

X-ray based imaging procedures are an important source of exposure to ionising radiation and can result in high cumulative effective doses. Patients with Crohn's disease had a 2·5 times higher total effective dose than did those with ulcerative colitis in one study.[97] Efforts to follow-up patients with the least invasive procedures and to still base decisions on objective, cost-effective variables drives the discovery, development, and assessment of biomarkers.[98] The best studied follow-up biomarkers are C-reactive protein and the faecal granulocyte proteins lactoferrin and calprotectin. Several studies have confirmed good correlation with other laboratory tests, endoscopic and clinical disease activity indices, and possible predictive potential.

## Medical management

Key points when caring for a patient with Crohn's disease are listed in panel 2. According to population based data from 1935–2008, 50% of adult patients with Crohn's disease have an intestinal complication within 20 years after diagnosis. Only 10% of patients have prolonged clinical remission. The annual incidence of admission to hospital is 20%. 50% of the patients require surgery within 10 years after diagnosis and the risk of postoperative recurrence is 44–55% after 10 years.[91] Life expectancy is slightly reduced. Treatment of Crohn's disease aims to achieve sustained clinical and endoscopic remission[99] (mucosal healing) and to interrupt the naturally progressive destructive disease course that culminates in intestinal failure and associated complications. Despite an abundance of instruments (appendix p 6), techniques and definitions that can objectively define disease modification and intestinal damage are still in evolution.[100] The newly proposed Lémann score could help in this process (figure 5).[101] Young age, immediate need for corticosteroids, perianal disease, colonic resection, repeated small bowel resection, a stricturing phenotype, substantial weight loss, and specific endoscopic lesions might predict a disabling disease course.[102]

### Smoking and nutrition

Patients with Crohn's disease should quit smoking. Smoking promotes a fistulising and stricturing

phenotype, aggravated disease course, and suboptimal response to medical therapy. Unlike in children, evidence to support exclusive therapeutic parenteral nutrition or enteral nutrition (including elemental diets) is insufficient in adult patients with Crohn's disease. However, nutritional deficiencies should be corrected.[103]

### Choice of the initial drug

Choice of the initial drug from an increasingly expanding matrix of medications (table) is directed by phenotype, disease activity, comorbidities, and other individual characteristics of the drug and patient. In most cases a fast acting short-term use agent (ie, steroids or anti-TNF) to achieve rapid symptom relief and disease control is combined with thiopurines or methotrexate for long-term maintenance. The selection should aim to balance efficacy with side-effects and long-term complications. For example, whereas methotrexate is poor choice for a woman of childbearing age or patients with pre-existing liver disease (eg, primary sclerosing cholangitis, autoimmune hepatitis, autoimmune cholangitis), this drug could be an excellent option for a patient with Crohn's disease and arthropathy, because both disorders will benefit from the same treatment. The initial choice should also incorporate the individual profile and make more potent compounds available to high-risk patients earlier and avoid inflexible, step-wise escalation of drug classes.[106] However, evidence to support a general top-down treatment model for all patients with this disorder is insufficient.

### Monotherapy versus combination therapy

Pivotal trials have shown the superiority of combination therapies with thiopurines and TNF blockers for improved symptom control and mucosal healing.[106,107] This advantage needs to be balanced with the increased risk of infectious[108,109] and malignant[109,110] complications. Although the idea of withdrawing either thiopurines or TNF blockers only one (underpowered) non-inferiority study supports the notion of withdrawing thiopurines.[111]

### When and how to escalate therapy

Indications for switching drug classes or agents include primary non-response, loss of response (mostly noted with biological agents because of varying degrees of immunogenicity and anti-drug antibodies), insufficient efficacy (ie, absence of mucosal healing[99]), and intolerance or unacceptable side-effects. Before escalation of therapies by bodyweight-based dose adjustment (steroids, thiopurines, and infliximab), shortening of the treatment interval (infliximab, adalimumab), combination or switch of therapeutic strategy, disease complications (ie, bile acid loss after surgery or novel strictures and newly acquired or coexisting infection) must be ruled out. Bacterial and viral infections can mimic Crohn's disease (appendix p 5) and escalation of immunosuppression in this setting can have fatal consequences.[108]

### Duration of therapy

Since no available treatment corrects the underlying genetic basis of this chronic illness, most physicians believe that patients need long-term treatment. However, experts disagree about if and when drug holidays should be offered.[104,103,112] Although acute complications such as infections can be successfully managed with prevention, pausing drugs, and timely use of antimicrobials, some experts continue to express concern about long-term use of thiopurines and biological agents, particularly if used in combination. Evidence to determine the ideal duration of therapy is scarce, since randomised controlled trials are usually designed to fit approval agency requirements and rarely provide data beyond a year. Registry studies provide additional data about the long-term safety of various medical therapies, albeit with the known limitations of such evidence.[113]

### Fistulising disease

Management of fistulising Crohn's disease (B3 or B3p) requires careful assessment of the fistula location, extent, and potential complications (ie, penetration of adjacent organs or abscesses). If internal fistulas and complicated perianal fistulas are suspected, imaging, MRI, or ultrasound can help to guide therapy. Whereas uncomplicated perianal fistulae can be managed with seton placement, abscesses and other complications require surgical intervention in addition to medical therapy, which is usually a combination of anti-TNF with antibiotics and thiopurines (table).

### Surgery and postoperative care

Surgery does not cure Crohn's disease, and should be used restrictively, although it should not be regarded as the last resort. In some situations such as localised symptomatic ileocaecal disease it can be considered as a potential alternative to medical management. Specific indications for surgery include abscesses, complex perianal or internal fistulas that are unresponsive or insufficiently responsive to medical therapy, fibrostenotic strictures with symptoms of partial or complete bowel obstruction, high grade dysplasia, and cancer.[114]

Smoking, a penetrating phenotype (B3 or B3p), and previous small bowel surgery increase the likelihood of postoperative recurrence. So far, thiopurines[115] are best studied in this setting, but preliminary data also exist for infliximab,[116] and additional trials investigating the efficacy of other biological agents for prevention of postoperative recurrence are underway (table).

## Management of disorders commonly associated with Crohn's disease

### Anaemia

Chronic anaemia can be a presenting symptom in Crohn's disease and is most often not caused by intestinal blood loss, but by disturbed iron metabolisation from

| | Mildly to moderately active localised disease (L1) | | | | Mildly to moderately active extensive disease (L2, L3, L4) | | | | Refractory and severely active localised disease (L1) | | | | Refractory and severely active extensive disease (L2, L3, L4) | | | | Perianal fistulas (B3p) | | | | Postoperative maintenance | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Induction | Dose | Maintenance | Dose | Induction | Dose | Maintenance | Dose | Induction | Dose | Maintenance | Dose | Induction | Dose | Maintenance | Dose | Induction | Dose | Maintenance | Dose | Maintenance | Dose |
| Sulfasalazine | NR | .. | NR | .. | EL1bRGA (only mild L2/3) | 3–6 g/day (oral) | | .. | NR | .. | NR | .. | NR | .. | NR | .. | NR | .. | NR | .. | NR | .. |
| Mesalazine | NR No, 2C | .. | NR No, 2C | .. | NR No, 2C | .. | NR No, 2C | .. | NR No, 2C | .. | NR No, 2C | .. | NR No, 2C | .. | NR No, 2C | .. | NR No, 2C | .. | NR No, 2C | .. | EL1bRGB* | .. |
| Prednisolone | EL1aRGA (moderate) Yes, 1C | 40–60 mg/day (oral) | NR | .. | EL1aRGA (L2/3) EL4RGC (L4) | 40–60 mg/day (oral) | .. | .. | EL1aRGA | 40–60 mg/day (oral) | .. | .. | EL1aRGA | 40–60 mg/day (oral) | .. | .. | NR | .. | NR | .. | NR | .. |
| Budesonide | EL2aRGB (mild) EL1aRGA (moderate) Yes, 1C | 9 mg/day (oral) | NR No, 2C | .. | NR No, 2C | .. | N/R No, 2C | .. | NR No, 2C | .. | NR No, 2C | .. | NR No, 2C | .. | NR No, 2C | .. | NR No, 2C | .. | N7R No, 2C | .. | NR No, 2C | .. |
| Metronidazole | NR | .. | NR No, 2D | .. | NR | .. | NR | .. | NR | .. | NR No, 2D | .. | NR | .. | NR No, 2D | .. | EL3RGD First line for simple fistulas Yes, 2C | 750–1500 mg/day (oral) | No, 2D | .. | EL1bRGA* No, 2D | 750–1500 mg/day (oral) |
| Ciprofloxacin | NR | .. | NR No, 2D | .. | NR | .. | NR | .. | NR | .. | NR No, 2D | .. | NR | .. | NR No, 2D | .. | EL3RGD First line for simple fistulas Yes, 2C | 1000 mg/d oral | No, 2D | .. | NR No, 2D | .. |
| Azathioprine | NR No, 2C | .. | EL1aRGB (first episode) Yes, 2C | 2–3 mg/kg/day (oral) | EL5RGD (L4) Yes, 2C | 2–3 mg/kg/day (oral) | EL1b,RGA Yes, 2C | 2–3 mg/kg/day (oral) | .. | .. | .. | .. | ICW anti TNF Yes, 2C | .. | ICW anti TNF Yes, 2C | .. | .. | .. | EL2bRGC Yes, 2C | 2–3 g/kg/day (oral) | EL1RGA Yes, 2C | 2–3 g/kg/day (oral) |
| Mercaptopurine | NR No, 2C | .. | EL1aRGB (first episode) Yes, 2C | 1·5 mg/kg/day (oral) | EL5RGD (L4) Yes, 2C | 1·5 mg/kg/day (oral) | EL1aRGA Yes, 2C | 1·5 mg/kg/day (oral) | .. | .. | .. | .. | ICW anti TNF Yes, 2C | .. | ICW anti TNF Yes, 2C | .. | .. | .. | EL2bRGC Yes, 2C | 1·5 mg/kg/day (oral) | EL1RGA Yes, 2C | 2–3 g/kg/day (oral) |

(Continues on next page)

| | Mildly to moderately active localised disease (L1) | | | | Mildly to moderately active extensive disease (L2, L3, L4) | | | | Refractory and severely active localised disease (L1) | | | | Refractory and severely active extensive disease (L2, L3, L4) | | | | Perianal fistulas (B3p) | | | | Postoperative maintenance | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Induction | Dose | Maintenance | Dose | Induction | Dose | Maintenance | Dose | Induction | Dose | Maintenance | Dose | Induction | Dose | Maintenance | Dose | Induction | Dose | Maintenance | Dose | Maintenance | Dose |
| (Continued from previous page) | | | | | | | | | | | | | | | | | | | | | | |
| Methotrexate | NR<br>Yes, 2C | .. | EL1bRGA (first episode)<br>Yes, 2C | 15–20 mg weekly (IM) | EL5RGD (L4)<br>Yes, 2C | 25 mg weekly (IM) | EL1aRGA<br>Yes, 2C | 15–20 mg weekly (IM) | .. | .. | .. | .. | ICW anti TNF<br>Yes, 2C | .. | ICW anti TNF<br>Yes, 2C | .. | NR | .. | NR | .. | .. | .. |
| Infliximab | EL1bRGB (moderate)<br>Yes, 1B | 5 mg/kg every 0,2,6 weeks (IV) | EL1bRGB<br>Yes, 1A | 5 mg/kg every 8 weeks (IV) | EL1aRGB (moderate (L2/3) EL5RGD (L4)<br>Yes, 1B | 5 mg/kg every 0,2,6 weeks (IV) | EL1aRGB<br>Yes, 1A | 5 mg/kg every 8 weeks (IV) | EL1ARGB<br>Yes, 1B | 5 mg/kg every 0,2,6 weeks (IV) | Yes, 1A | 5 mg/kg every 8 weeks (IV) | EL1aRGB (L2/3)<br>Yes, 1B | 5 mg/kg 0,2,6 weeks | Yes, 1A | 5 mg/kg every 8 weeks (IV) | EL1bRGA<br>Yes, 1C | 5 mg/kg every 0,2,6 weeks (IV) | EL1bRGA<br>Yes, 2C | 5 mg/kg every 8 weeks (IV) | Multicenter study in progress (PREVENT trial) | .. |
| Adalimumab | EL1bRGB (moderate)<br>Yes, 1B | 160/80 mg on weeks 0/2 (SC) | Yes, 1A | 40 mg EOW (SC) | Yes, 1A | 160/80 mg on weeks 0/2 (SC) | EL1aRGB<br>Yes, 1B | 40 mg EOW (SC) | Yes, 1B | 160/80 mg on weeks 0/2 (SC) | Yes, 1A | 40 mg EOW (SC) | Yes, 1B | 160/80 mg on weeks 0/2 (SC) | Yes, 1A | 40 mg EOW (SC) | EL1bRGB<br>Yes, 1C | 160/80 mg on weeks 0/2 (SC) | EL1bRGB | 40 mg EOW (SC) | Published data available, but not in guideline | .. |
| Certolizumab | Yes, 1B | 400 mg on weeks 0/2/4 | Yes, 1A | 400 mg E4W (SC) | Yes, 1B | 400 mg on weeks 0/2/4 | Yes, 1A | 400 mg E4W (SC) | Yes, 1B | 400 mg on weeks 0/2/4 | Yes, 1A | 400 mg E4W (SC) | Yes, 1B | 400 mg on weeks 0/2/4 | Yes, 1A | 400 mg E4W (SC) | Yes, 1C | 400 mg on weeks 0/2/4 | .. | .. | .. | .. |
| Natalizumab | Yes, 2B | 300 mg on weeks 0/4/8 | Yes, 2C | 300 mg E4W (IV) | Yes, 2B | 300 mg on weeks 0/4/8 | Yes, 2C | 300 mg E4W (IV) | .. | .. | Yes, 2C | 300 mg E4W (IV) | .. | .. | Yes, 2C | 300 mg E4W (IV) | .. | .. | .. | .. | .. | .. |

Evidence level (EL) and recommendation grade (RG) listed according to consensus and position statements from the American College of Gastroenterology[104] and European Crohn's and Colitis Organization,[103,105] where available. Details can be found in the respective publications. Phenotype (L1, L2, L3, or L4) based on the Montreal classification. European Crohn's and Colitis Organization evidence levels and recommendations are graded and expressed according to the Oxford Centre for Evidence-Based Medicine. Recommendations denote the expert opinion of the authors. NR=not recommended. EOW=every other week. IM=intramuscular. ICW=in combination with. IV=intravenous. SC=subcutaneous. E4W=every 4 weeks. *Only after isolated ileal resection, inferior to all other prescriptions.

***Table:*** **Simplified evidence-based therapy matrix for Crohn's disease**

chronic inflammation. Intravenous iron substitution combined with erythropoietin is required and effective in some cases.[117]

### Arthropathy and osteoporosis

Peripheral (pauciarticular and polyarticular arthritis) and axial arthropathy (spondylitis and frequently isolated sacroiliitis) can precede intestinal symptoms in Crohn's disease. Pauciarticular arthritis (oligoarthritis) usually affects less than five large joints (eg, ankles, knees, hips, wrists elbows and shoulder), correlates with disease activity and responds to optimising medications, whereas polyarticular arthritis affects more than joints (mostly small joints of the hand) and is unrelated to disease activity. Pauciarticular and polyarticular arthritis respond to nonsteroidal anti-inflammatory drugs (preferably COX II inhibitors) and physical therapy, and ankylosing spondylitis also responds to anti-TNF. Patients with Crohn's disease are at risk for osteoporosis (because of steroid use, and diminished vitamin and mineral absorption) and inflammation-induced bone loss and should be supplemented with calcium and vitamin D while taking steroids or should receive a bisphosphonate before initiation of such treatment.[118]

### Pyoderma gangrenosum and erythema nodosum

Pyoderma gangrenosum and erythema nodosum are frequently associated with Crohn's disease and diagnosed on clinical grounds. Biopsies are generally not recommended and could induce additional eruptions in pyoderma because of pathergy. They need to be distinguished from therapy associated acneiform and psoriasiform skin lesions[119] and opportunistic infections. The diagnosis and management of other extraintestinal manifestations[8] and associated autoimmune disorders[9] (figure 3) is discussed elsewhere.[104,105]

## New therapeutic targets and strategies

Numerous compounds targeting various aspects (interleukins 6, 10, 11, 12, 17, and 23, TNFα and interferon γ, CD3 and CD4 T cells, leucocyte expansion and migration, antigen presentation by monocytes, macrophages and dendritic cells, oral tolerance, epithelial cell growth, microbial metabolism and composition) of the inflammatory process (figures 1, 2) with different compound classes (monoclonal antibodies, fusion proteins, small molecules, recombinant growth factors and oligonucleotides) have been proposed and engineered for Crohn's diease and other chronic inflammatory disorders. Some are in clinical development (appendix p 9). Most of these strategies were based on scientific data and conceptual frameworks derived from in-vitro experiments and studies with animals, few of which develop a true illness that resembles human Crohn's disease. Prediction at the bench of what will eventually work at the bedside is increasingly difficult. Perhaps individual genetic and environmental profiles derived from data from genome-wide association studies need to be incorporated in patient selection for future clinical trials. Because of space constraints we focus on three concepts (additional investigational compounds and concepts are provided in the appendix p 9).

### Blockade of key cytokines

Interleukin 12 affects pathways shared by genetically related (appendix pp 2–3), but phenotypically different chronic inflammatory disorders such as multiple sclerosis, rheumatoid arthritis, and psoriasis. The p40 antibodies against interleukins 12 and 23 briakinumab (Abbott Laboratories, IL, USA)[120] and ustekinumab,[121] the latter of which is approved for psoriasis, initially showed equivocal effects in Crohn's disease, but more recently ustekinumab was effective in a phase 2b induction trial for this disorder and is expected to enter phase 3. Both antibodies show better results for remission at 4–6 months than shortly after diagnosis and thus could be developed as maintenance rather than induction agents.

### Blockade of leucocyte migration, adhesion, and homing

Vedolizumab (anti-α4β7, also known as MLN-02, LDP-02, and MLN0002) is a humanised monoclonal $IgG_1$ antibody targeting integrin $\alpha_4\beta_7$. Its activity is focused on $\alpha_4\beta_7$ MAdCAM-1 binding. Because MAdCAM-1 is expressed almost exclusively in the gastrointestinal tract it could have advantages compared with anti-$\alpha_4$ (ie, natalizumab and AJM300 [Ajinomoto Pharmaceuticals, Japan], which is associated with risk of progressive multifocal leukoencephalopathy.[122] Vedolizumab for Crohn's diease (and ulcerative colitis) is being assessed in phase 3 trials. PF-00547659 (anti-MAdCAM, Pfizer, USA) is a monoclonal $IgG_2$ antibody directed at MAdCAM that is being studied in Crohn's disease (and ulcerative colitis). It affects the same target as vedolizumab from the opposite direction and thus also blocks $\alpha_4^+\beta_7^+$, but not $\beta_7^-$ leucocyte adhesion to MAdCAM.[123] AJM300 (anti-α4) is an orally active small molecule that was assessed in one randomised placebo controlled trial in patients with Crohn's diease.[124] Etrolizumab (anti-β7, also known as rhuMAb Beta7 and PRO145223, Genentech, CA, USA) is a humanised monoclonal $IgG_1$ antibody targeting the integrin subunit $\beta_7$.[125] It blocks both $\alpha_4\beta_7$ and $\alpha_E\beta_7$ integrins and is in phase 1 and 2 trials for ulcerative colitis (NCT00694980, NCT01336465, NCT01461317).

GSK-1605786A and CCX282-B (both GlaxoSmithKline, UK) is an orally bioavailable small molecule that selectively blocks the human CCR9 receptor.[126] It has been studied in a multicentre, double-blind, placebo controlled, parallel group study in patients with Crohn's disease. Although the primary endpoint was not achieved, significant differences in clinical remission were recorded at week 12, and efficacy for maintenance of remission in patients who responded to this agent was shown in a placebo controlled maintenance trial.[127]

### Cell-based therapies

Although global blockade of key immune cells, such as T cells, through anti-CD3 has failed in Crohn's disease,[127] stem cell therapies derived from adult haemtopoietic,[128] mesenchmal stromal,[129] and adipose tissue[130] show promise. The best studied idea is the autologous, non-myeloablative haemtopoietic stem cell transplantation. In the largest series so far, all 24 patients studied went into remission. The percentage of clinical relapse-free survival after transplantation was 91% at 1 year, 63% at 2 years, 57% at 3 years, 39% at 4 years, and 19% at 5 years. The percentages of patients in remission, steroid-free, or medication-free at any post transplantation assessment interval more than 5 years after transplantation has remained at or greater than 70%, 80%, and 60%, respectively.[128] A new, multicentre study (ASTIC) assessing this therapy has been halted as of January, 2012 (NCT00297193). Autologous mesenchmal stromal stem cell transplantation was studied in a phase 1 trial.[129] Another approach involves locally applied adipose stem cells. A phase 2 trial reported healing of complex perianal fistulas in 71% of 24 patients who received adipose stem cells in addition to fibrin glue.[130] Stem cell based therapies attract criticism from some experts because autologous transplantation reintroduces the genetically defective immune cells, does not address the known genetic defects in various other cell types (namely epithelial cells) and because the conceptually potentially more effective allogeneic protocol carries substantial, myeloablation related mortality risks. Local injection of adipose stem cells has been criticised because its mechanisms are incompletely understood.

## Prevention, risk management, and surveillance

### Infection and vaccination

Almost all medications for Crohn's disease are associated with an increased risk of potentially life-threatening infections.[104,108] Prevention starts with selection of appropriate drugs for the specific clinical situation and screening for active infections before initiation of immunosuppressive drugs, including steroids and biological agents.[103] Special attention should be placed on tuberculosis, infectious hepatitis, cytomegalovirus, or HIV infection, and *Clostridium difficile* (appendix p 5). Another important aspect is ensuring an up-to-date immunisation status. Patients with Crohn's disease should be encouraged to complete their vaccinations before therapy according to annually updated authority recommendations for people with primary and secondary immunodeficiencies. Patients receiving natalizumab are at risk to develop progressive multifocal leukoencephalopathy, a serious and usually fatal CNS infection caused by JC polyoma virus;[131] these patients need special neurological monitoring. Natalizumab is only approved for Crohn's disease in selected jurisdictions under a special restrictive schedule.

### Family planning

Many approved Crohn's disease therapies are safe in the setting of conception and pregnancy.[132,133] Couples need to be counselled about potential effects of infliximab, adalimumab, and sulfasalazine on sperm quality and the potential effect of pelvic surgery on fecundity. Methotrexate is contraindicated in conception and pregnancy. Thiopurines and approved biological agents (except natalizumab because of absence of data) are generally regarded as safe with regard to conception, pregnancy, and breastfeeding and should be continued. Antibiotics, sulfasalazine, and methotrexate are contraindicated during breastfeeding. Women with Crohn's disease might have a higher risk of an abnormal Pap smear compared with healthy controls and those who use immunomodulators have a higher risk of an abnormal Pap smear associated with HPV infection and need close cervical cancer screening.[134]

### Malignancy

Patients with Crohn's disease are at risk for early small bowel and colorectal cancer.[135,136] The risk is even higher with a family history of sporadic colorectal cancer, uncontrolled inflammation, shortened colon, and multiple pseudopolyps.[137] If more than a third of the colon is affected (L3) patients should be enrolled in a surveillance programme 8 years after the onset of symptoms. Colonoscopies should be done ideally in remission every 1–2 years, when normal every 1–3 years thereafter. After 20 years the screening frequency defaults to the initial schedule. Patients with primary sclerosing cholangitis are especially at risk for right sided colorectal cancer and should undergo annual screening.[136,137] Dysplasia is managed according to the algorithm developed by Farraye and colleagues[137] (appendix p 10).

Thiopiurines[110] and TNF blockers[109] have been independently associated with development of mostly B-cell lymphomas. The rare hepatosplenic T-cell lymphomas[138] preferably affect males younger than 35 years and have a very poor prognosis. Thiopurines photosensitise human skin to UVA radiation. This sensitivity has been associated with an increased risk for non-melanoma skin cancer in Crohn's disease and requires protection against UVA and lifelong dermatological surveillance.[139]

#### Contributors

DCB did the literature search, designed the figures and tables, and wrote the first draft of the Seminar. DCB and WJS edited the report.

#### Conflicts of interest

DCB receives research support from Abbott, Astellas, Biocodex, Facet Biotech, and Shire; is a consultant for Abbott, AstraZeneca, Bayer Schering Pharma, Cellerix, (TiGenix), Genentech (Roche group), medac autoimmun, MSD, Otsuka, Facet Biotech, (formerly Protein Design Labs), and UCB; has received speaker's fees from Abbott, AstraZeneca, Dr Falk Pharma, Ferring, MSD, Otsuka, Shire, and UCB. All of his activities and contracts are in conformity with the "FSA-Kodex Fachkreise" (voluntary self-monitoring code for expert consultants to the pharmaceutical industry), have been checked by the legal Department of Charité Universitätsmedizin, Berlin, and have been approved by the directorate of the Faculty of Medicine Charité Universitätsmedizin Berlin. WJS has

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