

### CLINICAL PRESENTATION

- Crohn's disease (CD) is a complex, chronic inflammatory disease of the gastrointestinal tract characterized by widespread discontinuous inflammation, most commonly affecting the terminal ileum and proximal colon.
- Cardinal symptoms of CD include diarrhea, abdominal pain, and weight loss. Additional EIMs typically affect joints, eyes, and skin in up to 50% of patients.
- Up to one-third of patients have evidence of complications of CD at diagnosis, including intestinal strictures and fistulas.
- The disease burden is high with a time-dependent risk for surgery (1-, 5- and 10-year risk about 19%, 28% and 40%).

EIMs: extra-intestinal manifestations

### SYMPTOMS AND SIGNS OF CD

Fatigue, fever, abdominal pain, diarrhea, weight loss, anemia, micronutrient deficiencies, elevated inflammatory markers (CRP, ESR, fecal calprotectin), strictures, fistulas and/or abscesses

CRP: C-reactive protein, ESR: erythrocyte sedimentation rate

### EPIDEMIOLOGY IN EUROPE

#### Incidence (annual rate of new cases):

Up to 22.8 cases per 100,000 population per year

#### Prevalence (number of existing cases):

Up to 331 cases per 100,000 population

### INITIAL DIAGNOSIS AND MONITORING

The diagnosis of CD should be based on a combination of clinical history and examination, serum and stool biomarkers, cross-sectional and endoscopic imaging, and histology.

#### Diagnostic investigations

- Many CD patients present with abnormal complete blood counts (leukocytosis, anemia, and thrombocytosis) and elevated inflammatory markers (CRP and ESR).
- CRP and fecal calprotectin are both highly sensitive markers for IBD but lack specificity to rule out other causes of inflammation.
- Cross-sectional imaging (MR enterography or CT enterography) to identify ulcerations and inflammation and guide clinical and endoscopic assessment as well as classification on the basis of location, phenotype, and severity (Montreal or Paris classification).

#### Endoscopy

- The hallmark of CD is a patchy distribution of inflammation and skip lesions in the form of aphthous erosions or longitudinal cobblestone ulcers (Figure 1).
- Additional findings include erythema, mucosal edema (Figure 2), and luminal narrowing.

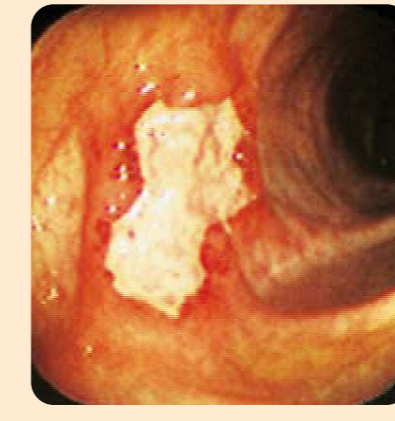


Figure 1: Aphthous erosion

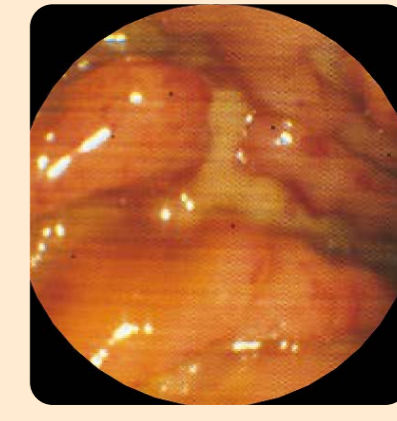


Figure 2: Erythema; mucosal edema

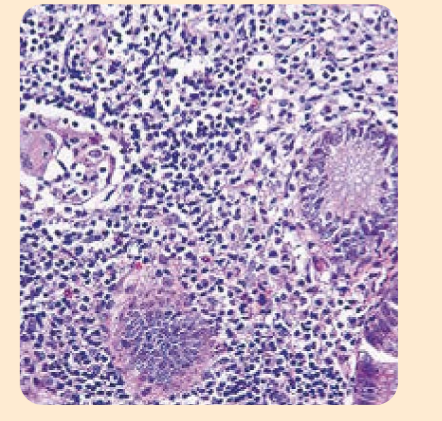


Figure 3: Granuloma; basal plasmacytosis

#### Histology

- The cornerstone of CD diagnosis remains two or more biopsies from inflamed regions showing (Figure 3):
- transmural inflammation with lymphoplasmacytic infiltrates
- discontinuous crypt distortion
- epithelioid granulomas
- irregular villous architecture

#### Differential diagnosis in CD

Ulcerative colitis, gastrointestinal infections (e.g., STDs, Herpes simplex virus), diverticulitis, Behçet's disease, intestinal lymphoma, intestinal tuberculosis, autoimmune enteritis, ischemic colitis, celiac disease, NSAID-induced ulceration.

NSAID: nonsteroidal anti-inflammatory drug  
STDs: sexually transmitted diseases

### DISEASE ACTIVITY ASSESSMENT

#### Location

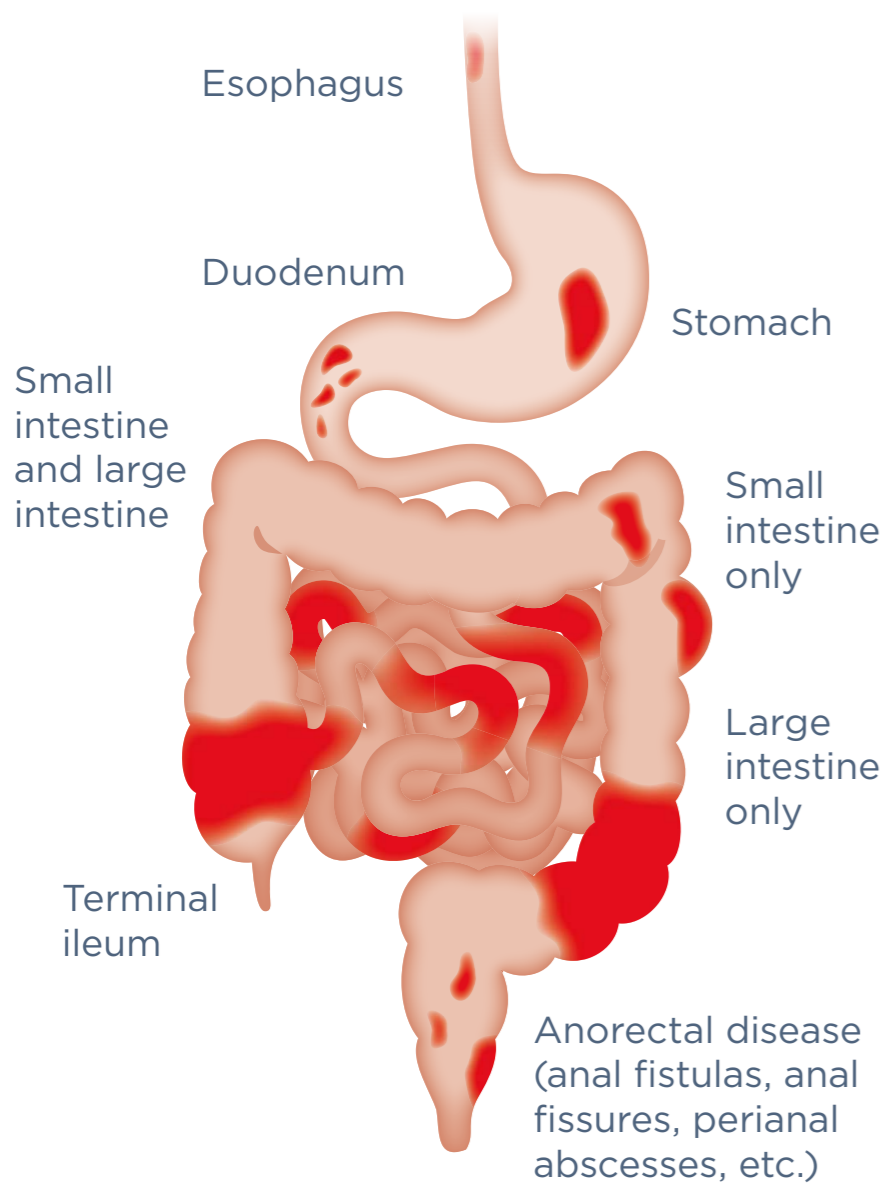


Figure 4: Patterns of segmental, discontinuous inflammation observed in different intestinal regions. Most commonly affected are the terminal ileum and proximal colon.

#### Scoring systems

The Crohn's Disease Activity Index (CDAI) is commonly used to assess disease activity in clinical practice and clinical studies (not depicted). The Montreal classification (see below) aids in phenotyping disease location (see Figure 4), type, and age at diagnosis. This is complemented by assessment of endoscopic findings using endoscopic indexes such as the Crohn's Disease Endoscopic Index of Severity (CDEIS) or its simplified version: the Simple Endoscopic Score for Crohn's Disease (SES-CD) which is more commonly used in clinical routine.

#### Classification of Crohn's disease

Montreal classification	
Age at diagnosis	<b>A1</b> ≤ 16 years   <b>A2</b> 17-40 years   <b>A3</b> > 40 years
Location	<b>L1</b> Ileal   <b>L2</b> Colonic   <b>L3</b> Ileocolonic   <b>L4</b> Isolated upper disease (in addition to L1-3)
Disease behavior	<b>B1</b> Non-stricturing, non-penetrating   <b>B2</b> Stricturing (stenosis/strictures)   <b>B3</b> Penetrating (abscesses/fistulas)   <b>p</b> Perianal disease (in addition to B1-3)

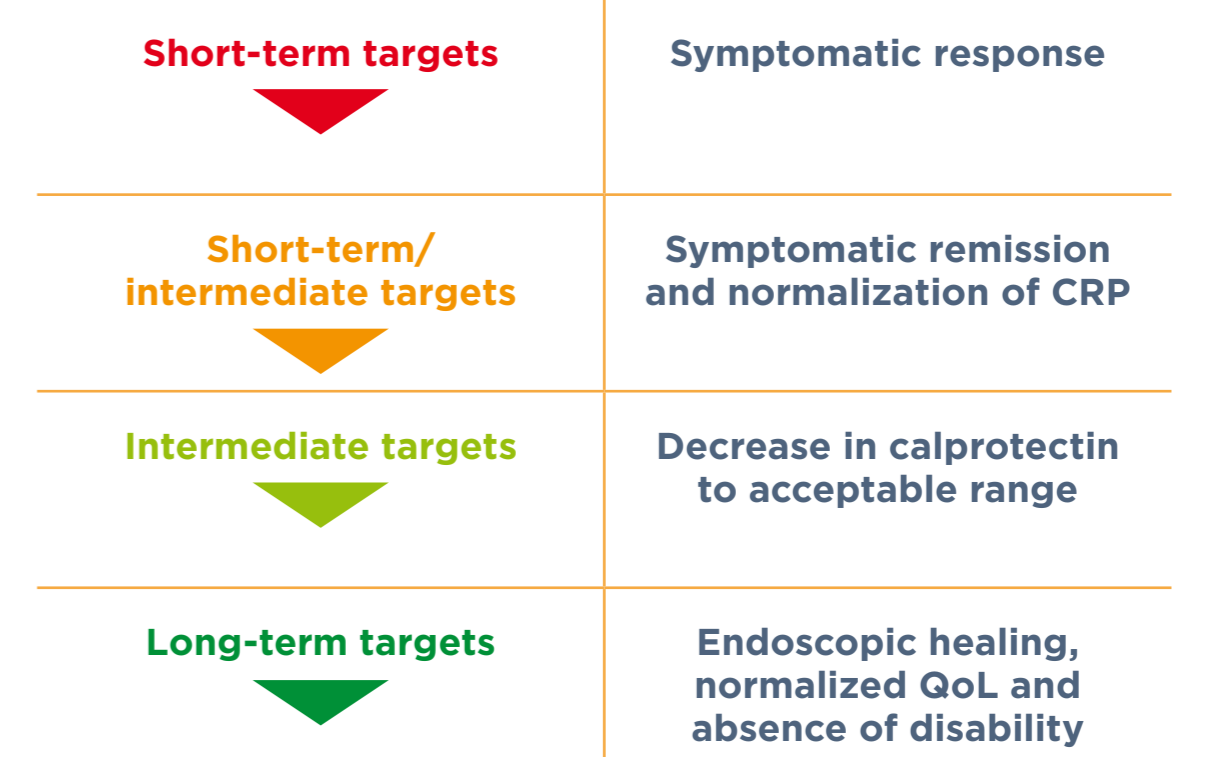
#### Classification by endoscopic findings (Simple Endoscopic Score - Crohn's Disease [SES-CD])

Variable	0	1	2	3
Size of ulcers	None	Aphthous ulcers (0.1-0.5 cm)	Large ulcers (0.5-2 cm)	Very large ulcers (> 2 cm)
Ulcerated surface	None	< 10%	10-30%	> 30%
Affected surface	Unaffected	< 50%	50-75%	> 75%
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

Interpretation: 0-2 = Remission; 3-6 = Mild; 7-15 = Moderate; ≥ 16 = Severe

### DISEASE MONITORING AND SURVEILLANCE

In 2015, the STRIDE consensus identified both clinical and endoscopic remission as key goals in the medical management of CD, laying the foundation for a treat-to-target strategy in IBD. The STRIDE-II update confirmed the long-term targets, while adding absence of disability, improved quality of life, and normal growth in children as additional treatment targets as well as introducing symptomatic relief and biomarker normalization as short-term objectives.



QoL = Quality of Life; CRP = C-reactive protein  
Adapted from Turner et al, Gastroenterology, 2021, Fig. 2.

### OVERVIEW OF SELECTED DRUGS AND DRUG CLASSES APPROVED FOR CD IN EUROPE

This table does not constitute treatment recommendations. Please refer to local guidelines.

Therapeutic class	Target/mode of action	Active compounds approved for IBD treatment	Route(s) of administration	Setting
Second-generation corticosteroids**	Broad anti-inflammatory and immunomodulatory effects through downregulation of inflammatory cytokines and modulation of leukocyte activity and function.	Budesonide	Oral, topical (rectal)	Induction therapy of mild to moderate CD
First-generation corticosteroids***	Broad anti-inflammatory and immunomodulatory effects through downregulation of inflammatory cytokines and modulation of leukocyte activity and function.	Prednisolone, methylprednisolone, prednisone	Oral	Induction therapy of moderate to severe CD
Anti-TNF antibodies	Multiple mechanisms of action, including neutralization of TNF- $\alpha$ , reverse signaling, apoptosis, and cytotoxicity.	Infliximab, adalimumab, golimumab, certolizumab pegol	IV and SC injection	Induction and maintenance therapy of moderate to severe CD
Anti-IL-12/23 antibodies	Binds specifically to the p40 protein subunit shared by IL-12 and IL-23, thus preventing binding to the IL-12R $\beta$ 1 receptor expressed on the surface of immune cells.	Ustekinumab, risankizumab, mirikizumab	IV and SC injection	Induction and maintenance therapy of moderate to severe CD
Anti- $\alpha$ 4 $\beta$ 7 integrin antibodies	Inhibiting the binding of integrin $\alpha$ 4 $\beta$ 7 to MAdCAM-1, resulting in suppression of T-cell-mediated inflammation.	Vedolizumab	IV infusion	Induction and maintenance therapy of moderate to severe CD
JAK inhibitors	Anti-inflammatory effect through blockade of the JAK-STAT pathway.	Upadacitinib	Oral	Induction and maintenance therapy of moderate to severe CD
Thiopurines	Immunosuppressive effect through inhibition of purine synthesis.	Azathioprine, mercaptopurine	Oral	Maintenance therapy of steroid-dependent CD
Methotrexate	Immunomodulatory effect through multiple mechanisms, including inhibition of purine and pyrimidine synthesis, transmethylation reactions, translocation of NF- $\kappa$ B, JAK-STAT signaling, and NO production.	Methotrexate	IM or SC injection	Maintenance therapy of steroid-dependent CD

\*\* Second-generation corticosteroids (2nd Gen CS) refer to synthetic corticosteroids that have been structurally modified to enhance their potency, selectivity, and safety profile [Miehlke JGH 2018].

\*\*\* First-generation corticosteroids are also typically referred to as "systemic corticosteroids" since their systemic concentrations are typically high, causing more pronounced corticosteroid-related side effects than 2nd Gen CS.