UNIVERSITA' DEGLI STUDI DI PERUGIA
DIPARTIMENTO DI MEDICINA E CHIRURGIA
CLMMC V anno
Patologia Sistemica VI (M-Z)
AA 2023-24

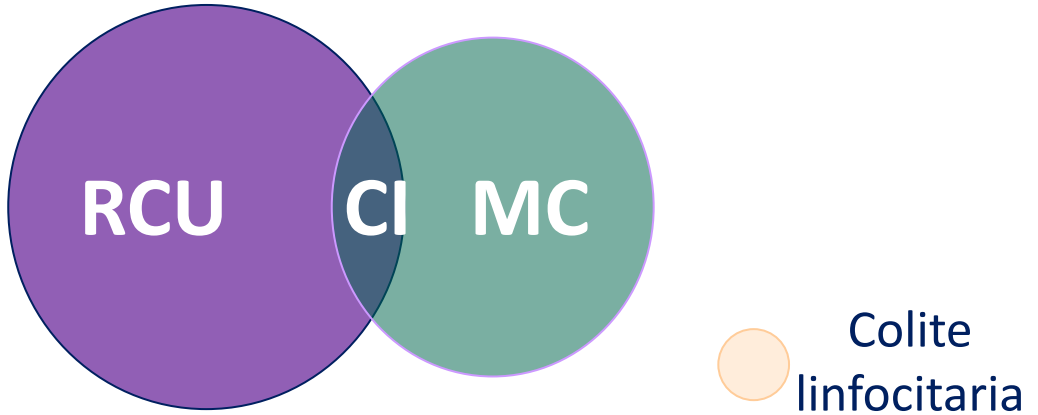
Inflammatory bowel disease

Prof. Stefano Fiorucci
Direttore Scuola di Specializzazione in Malattie apparato digerente
Università di Perugia
Stefano.fiorucci@unipg.it
www.unipg.gastroenterologia.it

Testo consigliato Harrison's Principles of Internal Medicine – 19-20° Ed.

Malattie infiammatorie croniche intestinali (MICI)

- Morbo di Crohn (M.C.)
- Rettocolite ulcerosa (RC.U.)
- Coliti in determinate (circa il 15%) (C.I.)
- Colite linfocitaria (collagenosica)



IBD definition

- **Inflammatory bowel disease (IBD)** is an immune-mediated chronic intestinal condition that comprises two chronic relapsing and remitting inflammatory disorders of the gastrointestinal tract, **ulcerative colitis and Crohn's disease.**
- The cause of these diseases **is unknown**.
- Each is a **lifelong disease**, characterized by recurrent episodes of diarrhea, which is often bloody, with abdominal pain, malaise, and weight loss.
- Unlike in Crohn's disease, gut inflammation in **ulcerative colitis affects only the colon and rectum**.

IBD definition

UC and CD are related, but considered separate disorders with somewhat different treatment options.

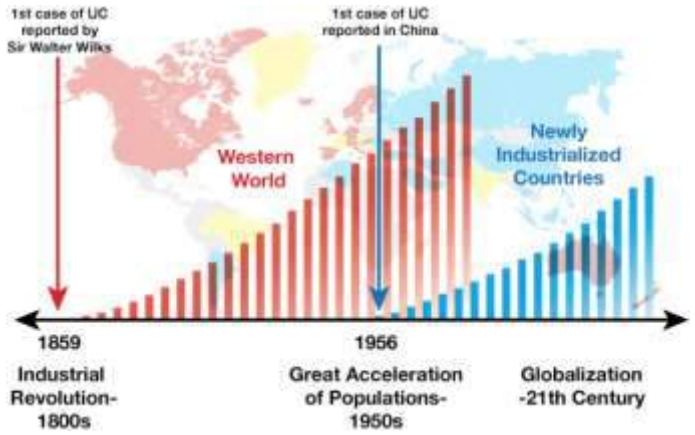
The basic distinctions between UC and CD are **location and phenotypes.**

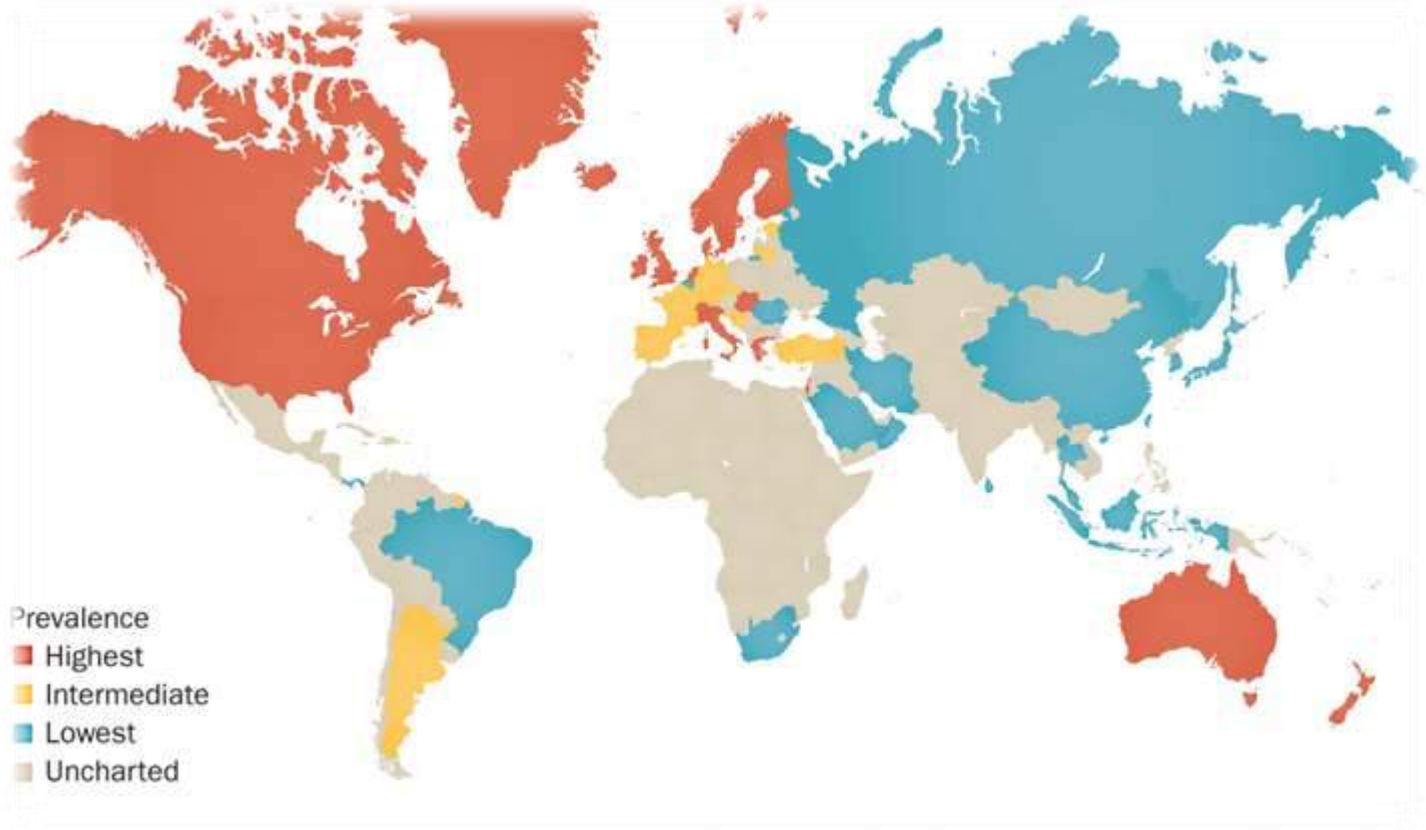
However, as many as 10% of patients with IBD have features and symptoms that match the criteria for both disorders, at least in the early stages **(this is called indeterminate colitis).**

IBD: Crohn vs ulcerative colitis

Feature	Crohn's disease	Ulcerative colitis
Clinical features		
Diarrhea	Fairly common	Very common
Rectal bleeding	Fairly common	Very common
Sites of involevment		
Ileum and colon (ileocolonic region)	50% of patients	Never
Ileum	30% of patients	Never
Colon	20% of patients	Exclusively
Upper parts of GIT	Infrequent	Never
Endoscopic findings	Discontinuous lesions, cobblestoning, aphthous and linear ulcerations, strictures	Continous lesions, pseudopolyps
Histologic findings	Transmural inflammation	Mucosal/submucosal inflammation

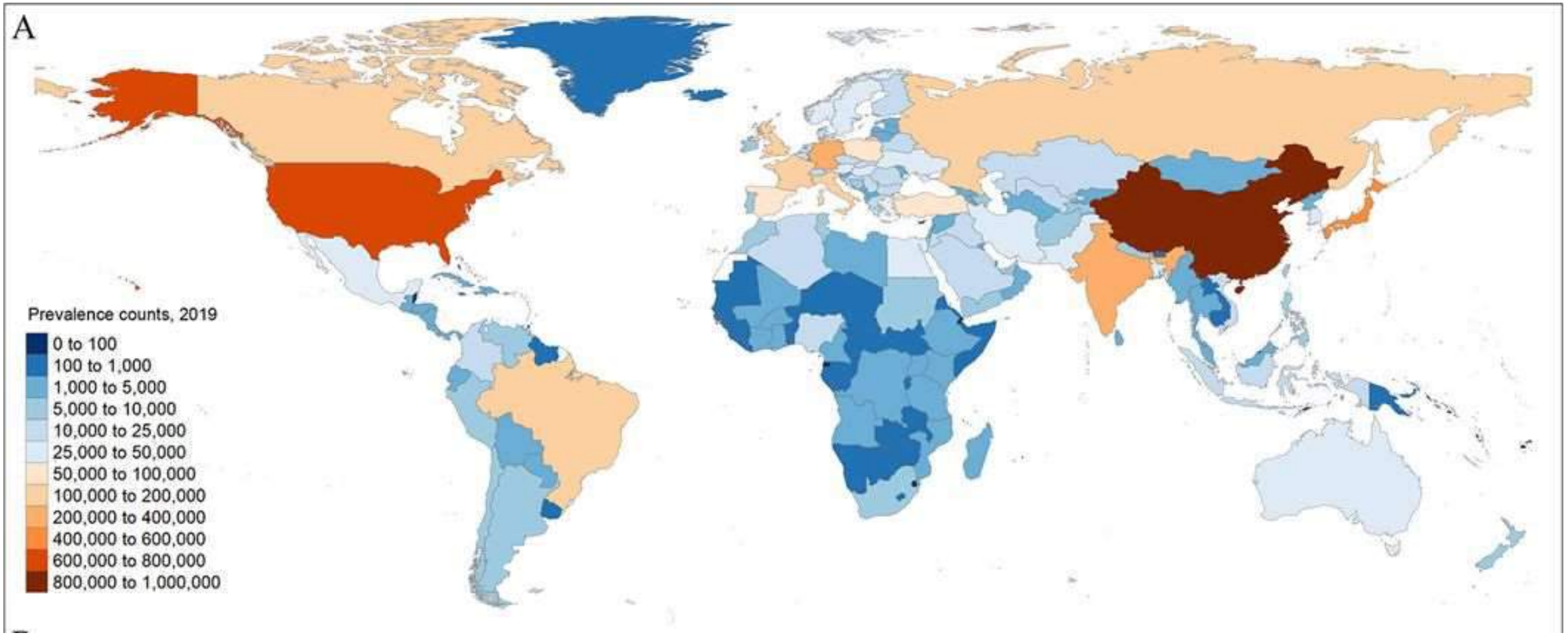
The global prevalence of IBD in 2015



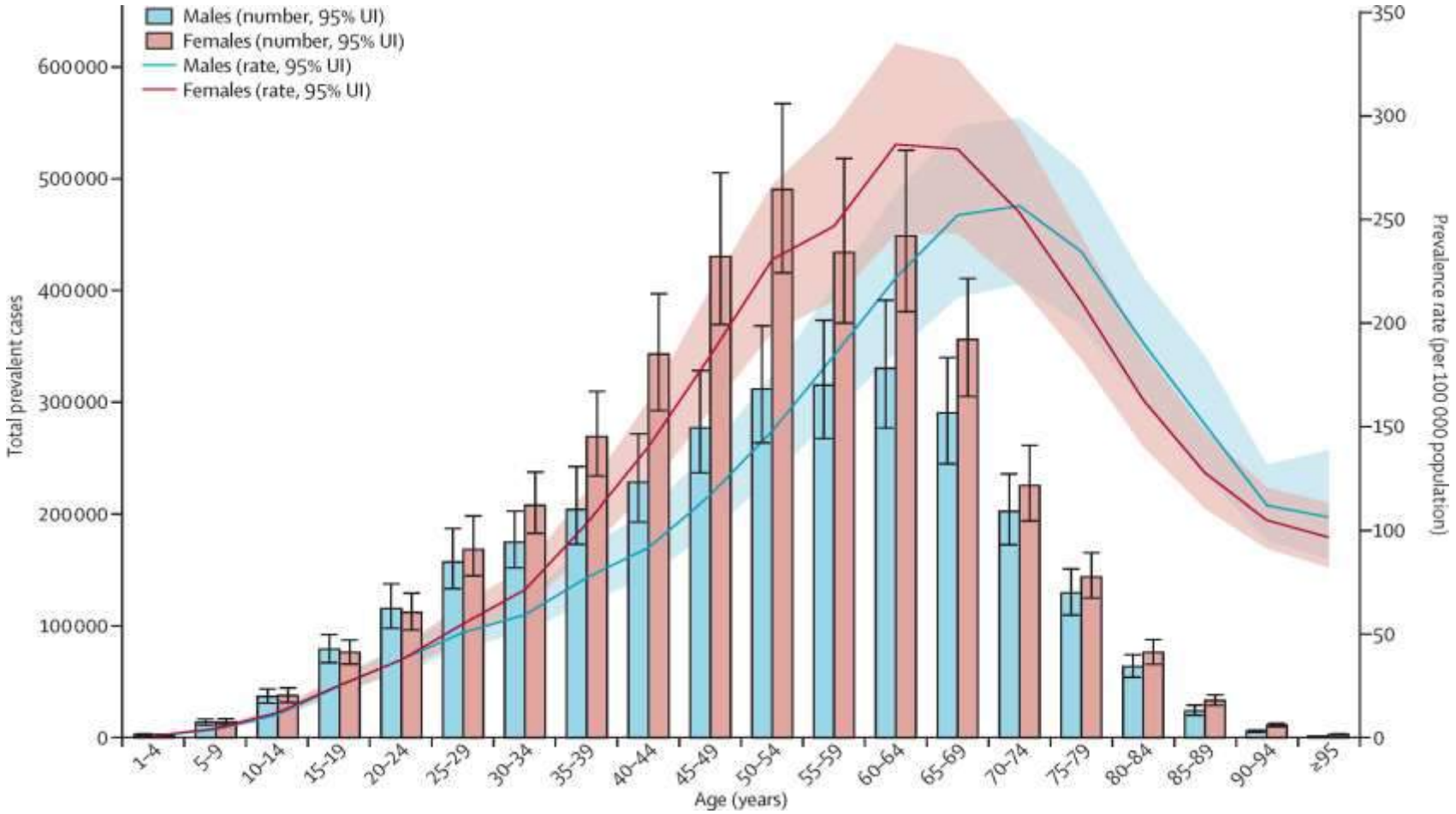


Kaplan, G. G. (2015) The global burden of IBD: from 2015 to 2025 *Nat. Rev. Gastroenterol. Hepatol.*
doi:10.1038/nrgastro.2015.150

The global prevalence burden of IBD in 204 countries and territories.



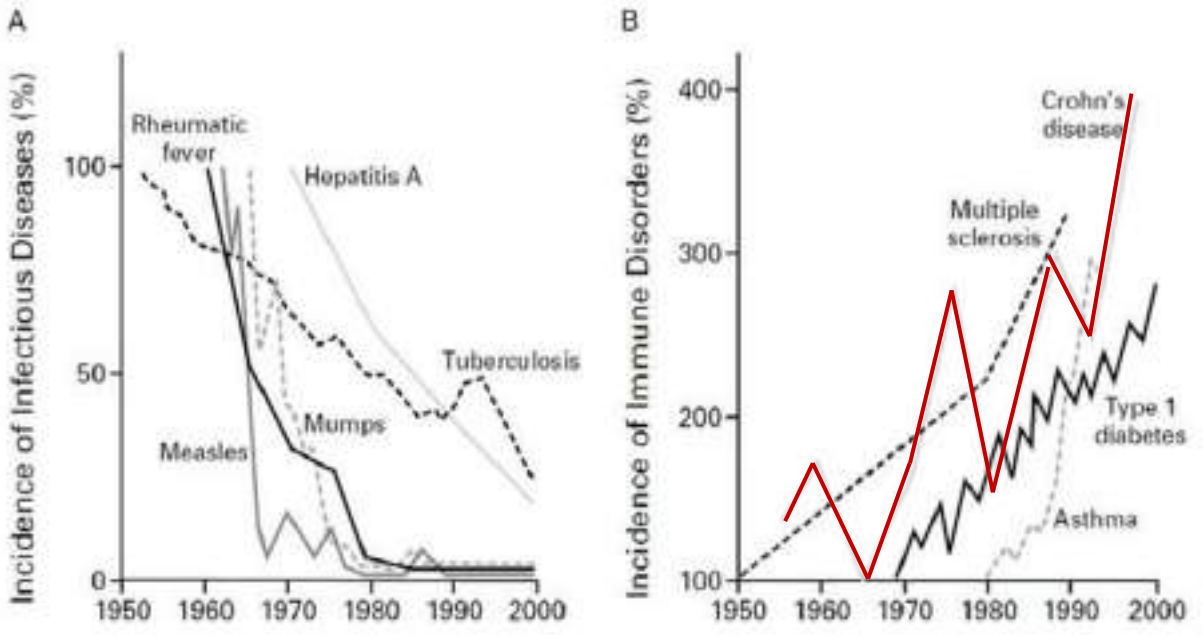
Rui Wang et al. BMJ Open 2023;13:e065186



The Lancet Gastroenterology & Hepatology 2020 517-30DOI: (10.1016/S2468-1253(19)30333-4)

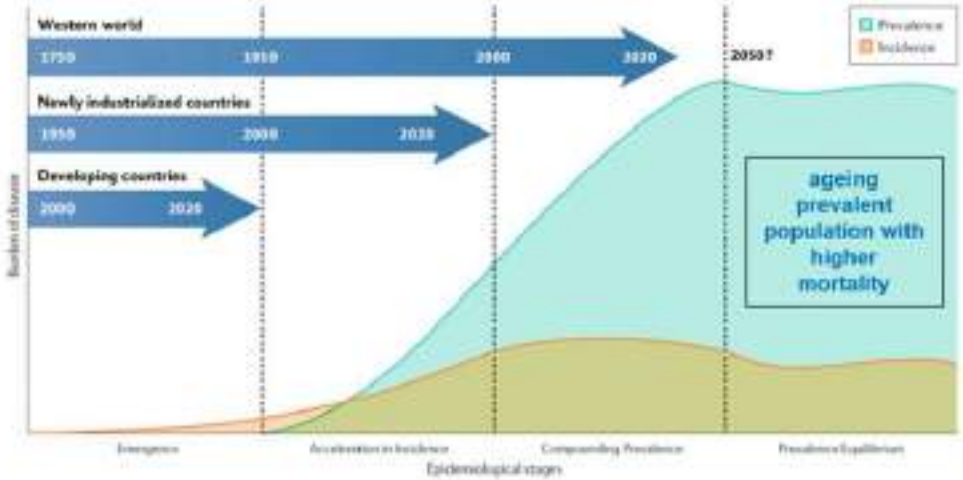
IBD historical trends

Autoimmune diseases
a modern epidemic?



Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. N Engl J Med. Sep 2002;347(12):911-920

The four epidemiological stages in the global evolution of IBD and estimated prevalence in Italy

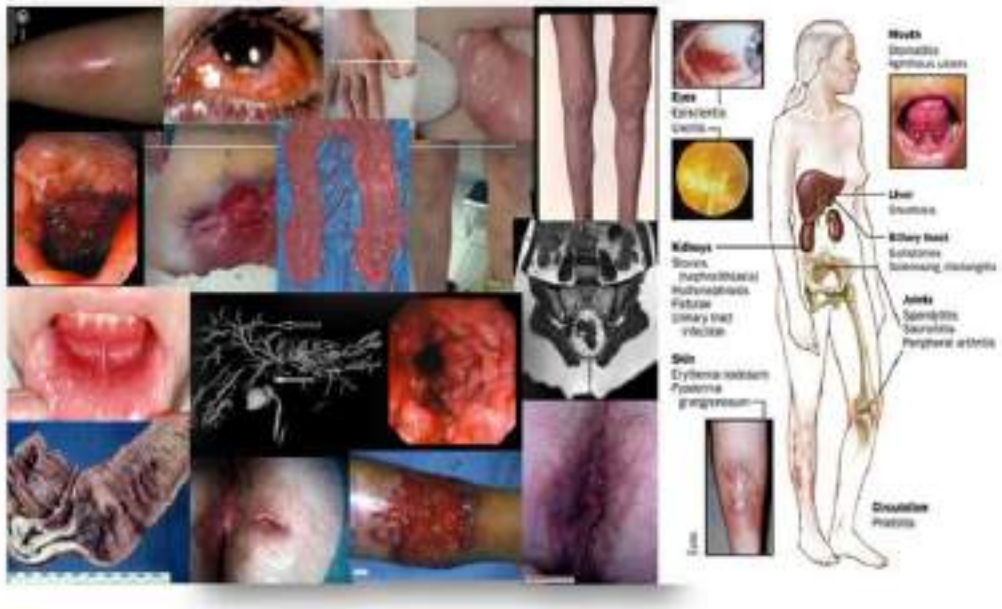


IBD
1) Early onset
2) Chronic
3) Low mortality

L'incidenza di RCU e MC in Italia è stimata intorno ai 10-15 nuovi casi su 100.000 abitanti all'anno

Prevalenza circa 400 casi/100.00 abitanti 0.3-0.4% della popolazione (stimata 240.000 casi)

Disease burden



Intestinal and extraintestinal phenothypes in IBD: clinical, social, economic burden of disease

Inflammatory Bowel Disease

Clinical[1,2]

- Chronic and unpredictable disease marked by alternating periods of exacerbation and remission
- Surgery up to 40% of CD patients and 20% of UC patients within 10 years from diagnosis
- High prevalence of extraintestinal manifestations

Social[3,4]

- Significant impact on quality of life
- Daily activity impairment
- Relationship difficulties with partners, family, and friends
- Negative effect on psychological well-being

Economic[5,6]

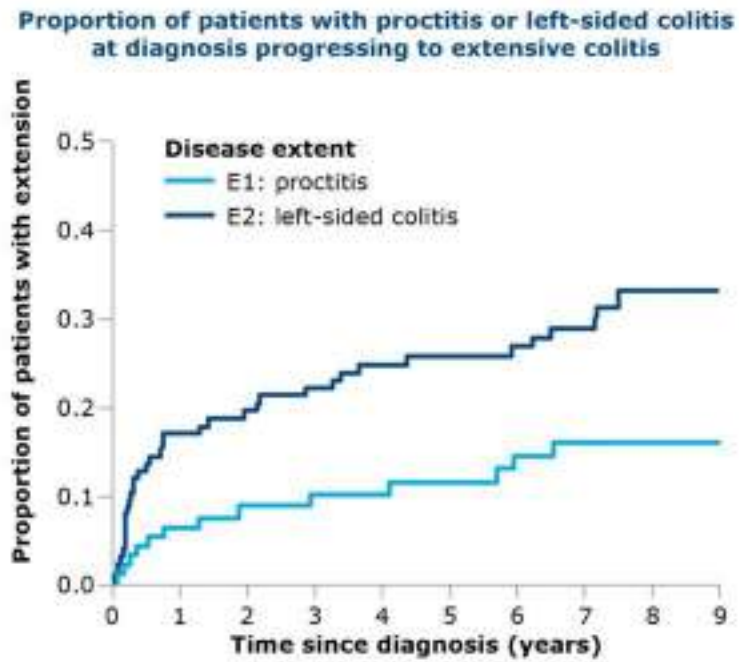
- Direct Healthcare costs
  - €2000–€10,000 per patient annually in Europe
  - $3300–$11,477 per patient annually in USA
- Indirect costs related to lost work productivity and long-term disability

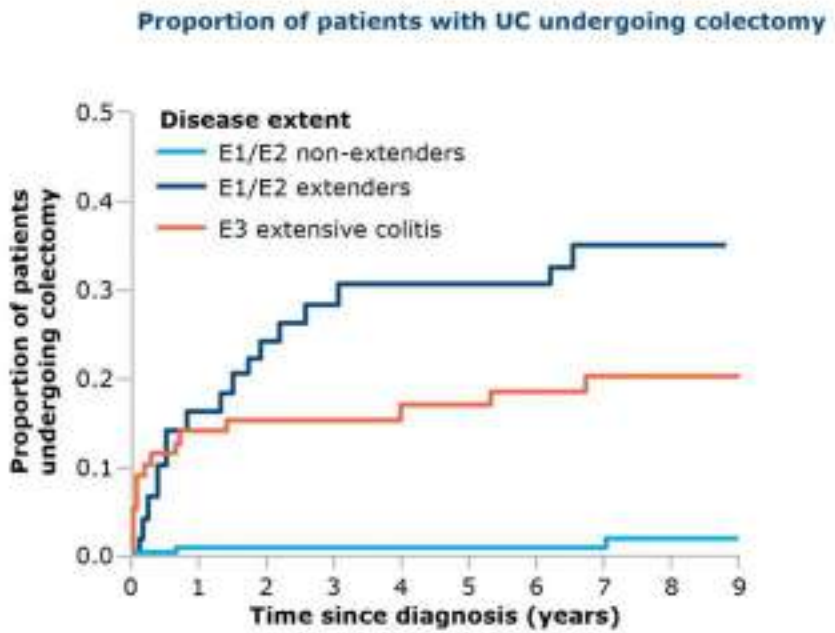
1. Ungaro R, et al. Lancet. 2017 Apr 29;389(10080):1756-1770; 2. Torres J, et al. Lancet. 2017 Apr 29;389(10080):1741-1755. 3. Devlen J et al. Inflamm Bowel Dis. 2014;20(3):545-552. 4. Rubin DT et al. Dig Dis Sci. 2010;55:1044-1052. 5. Cohen RD et al. Aliment Pharmacol Ther. 2010;31:693-707. 6. Burisch J, et al. Lancet Gastroenterol Hepatol. 2020;5:454-464

 pictures

Ulcerative colitis as a progressive disease: disease extension results in worse behaviour

Copenhagen County, Denmark (2003–2005)



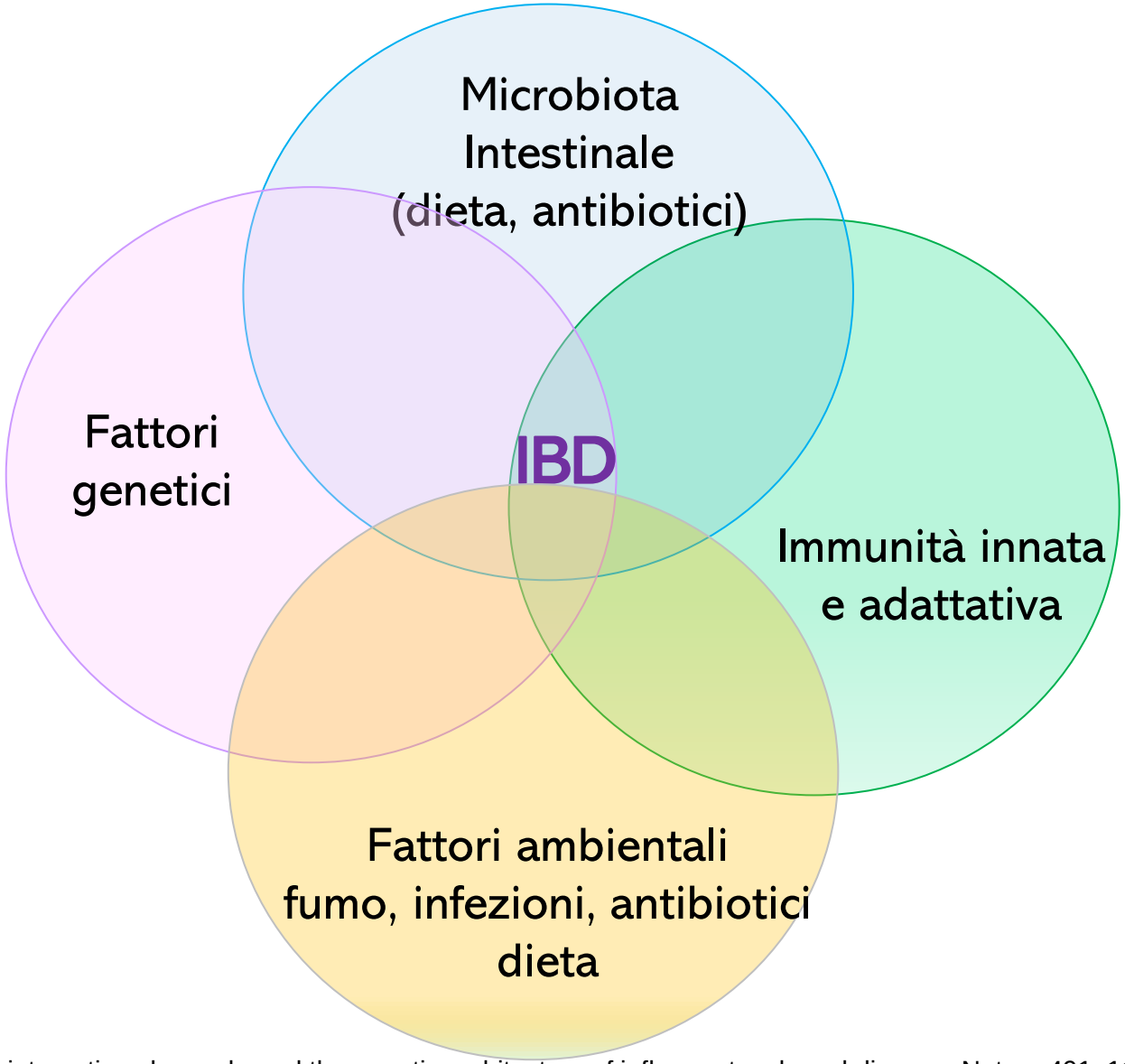


IBD pathogenesis

A consensus hypothesis is that:
in genetically predisposed individuals, both **exogenous** factors (e.g., abnormal microbiota) and **host factors** (e.g., intestinal epithelial cell barrier function, innate and adaptive immune function) **cause a chronic state of dysregulated mucosal immunity** that is further modified by specific environmental factors (e.g., smoking for Crohn).

Jostins, L. et al. Host–microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature 491, 119–124 (2012).
Hunt, K. A. et al. Negligible impact of rare autoimmune-locus coding-region variants on missing heritability. Nature 498, 232–235 (2013).

IBDs pathogenesis



Jostins, L. et al. Host–microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature 491, 119–124 (2012).
Hunt, K. A. et al. Negligible impact of rare autoimmune-locus coding-region variants on missing heritability. Nature 498, 232–235 (2013).

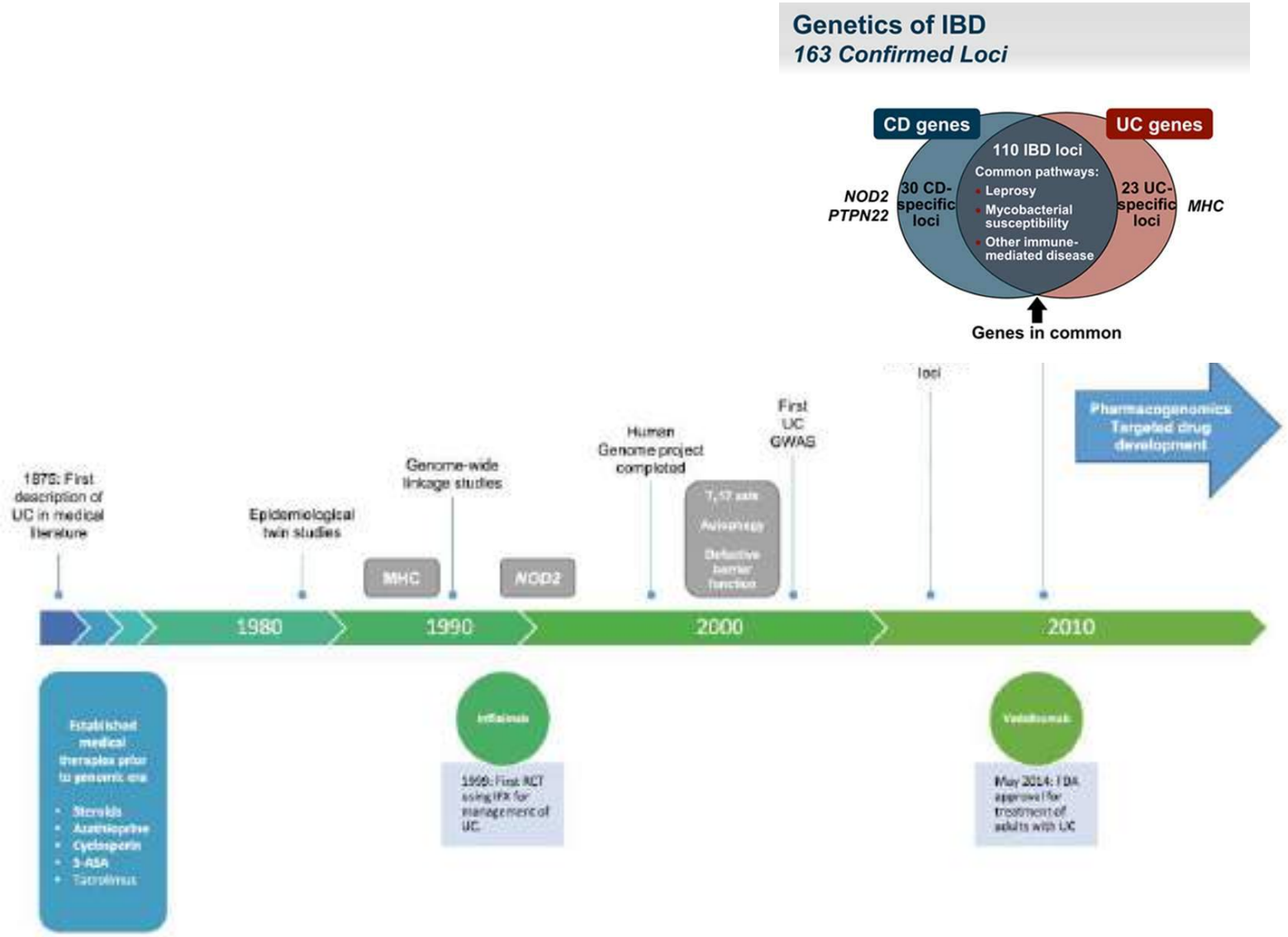
IBD genetics

IBD are polygenic disorders

that give raise to multiple clinical subgroups within UC and CD

Glocker, E.O. et al. Lancet. 2010; 376: 1272 . Inflammatory bowel disease and mutations affecting the interleukin-10 receptor.
Uhlig, H.H. and Schwerd, T. Inflamm. Bowel Dis. 2016; 22: 202–2125xThe diagnostic approach to monogenic very early onset inflammatory bowel disease.

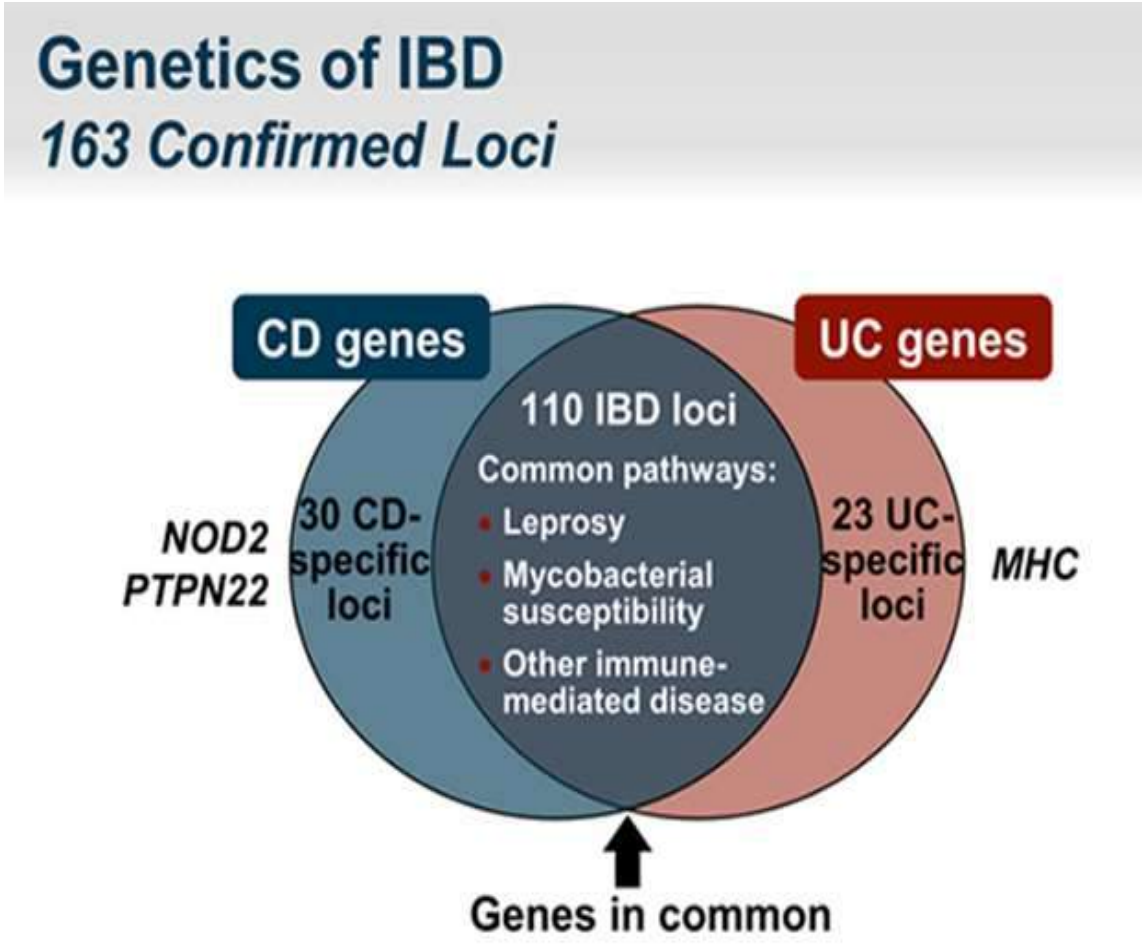
Timeline of genetic discoveries and recent drug developments in IBD.

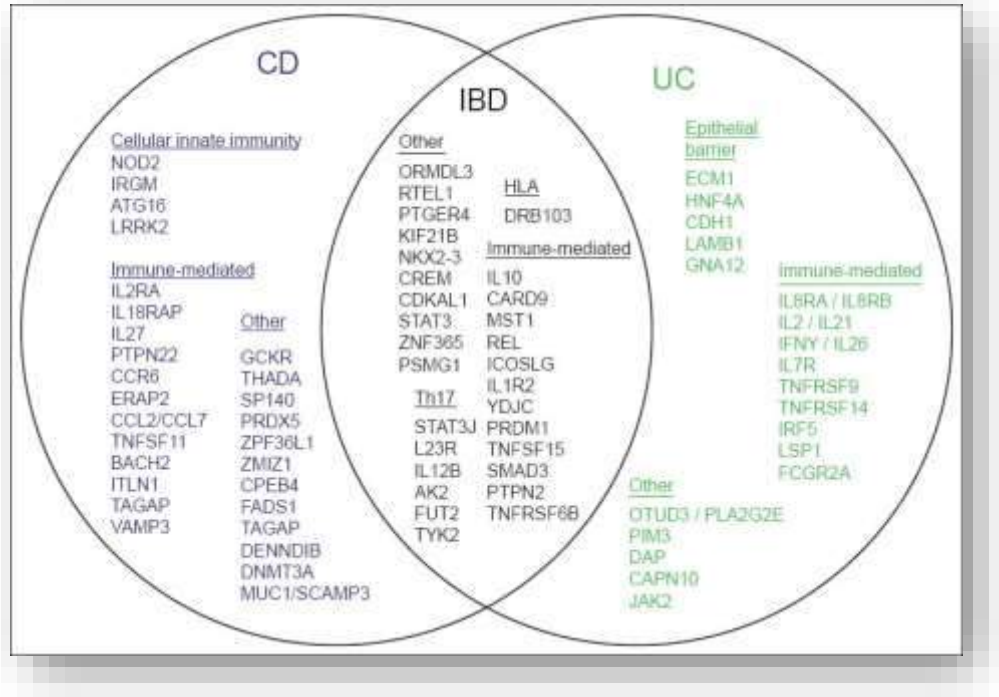


Sifuentes-Dominguez L and Patel AS 2016 [version 1; referees: 2 approved] F1000Research 2016, 5:240 (doi: 10.12688/f1000research.7440.1)

IBD genetic

Genome wide association studies (GWAS) have identified and confirmed **163 susceptibility loci for Crohn's disease on 17 chromosomes**





IBD genetics

In addition to the large group of patients with polygenic IBD, **some rare Mendelian disorders can present with IBD-like intestinal inflammation**.

The intestinal pathology in those patients is often indistinguishable from the more common polygenic IBD.

IBD genetics

The identification of genetic defects in the **IL-10 receptor (encoded by *IL10RA* and *IL10RB*)** and the *IL10* gene itself as the cause of severe infantile IBD by family association studies and candidate sequencing was a starting point for the identification of multiple high-impact monogenic disorders with high penetrance.

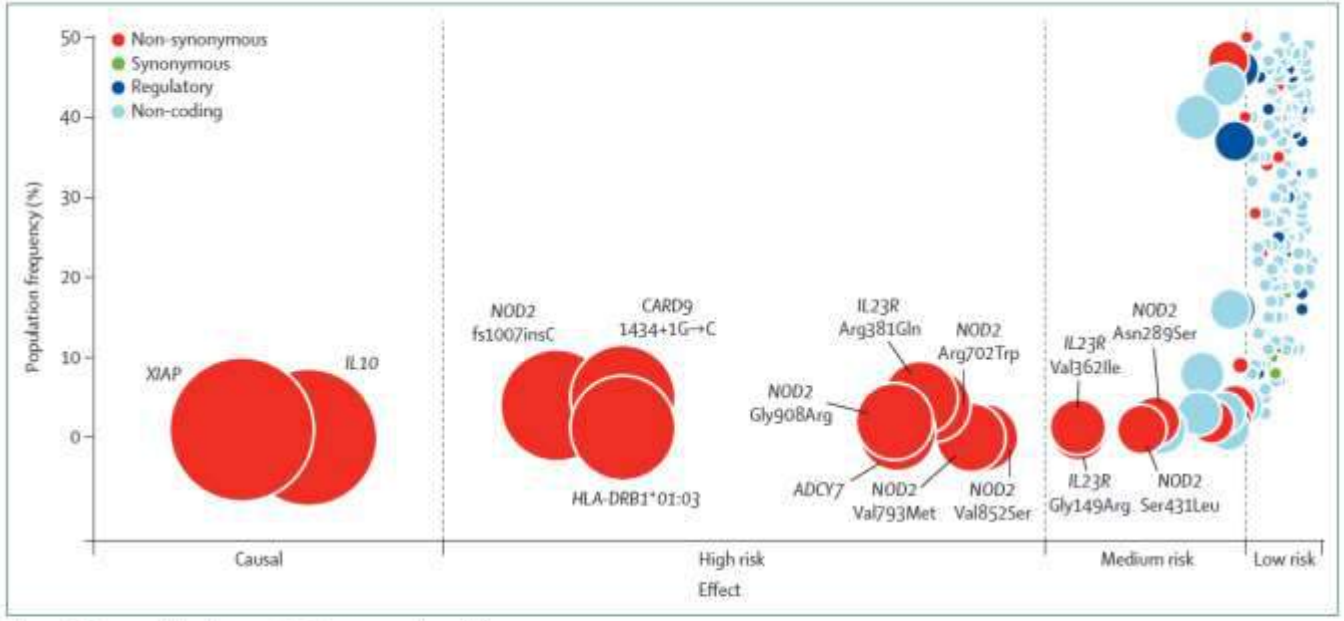
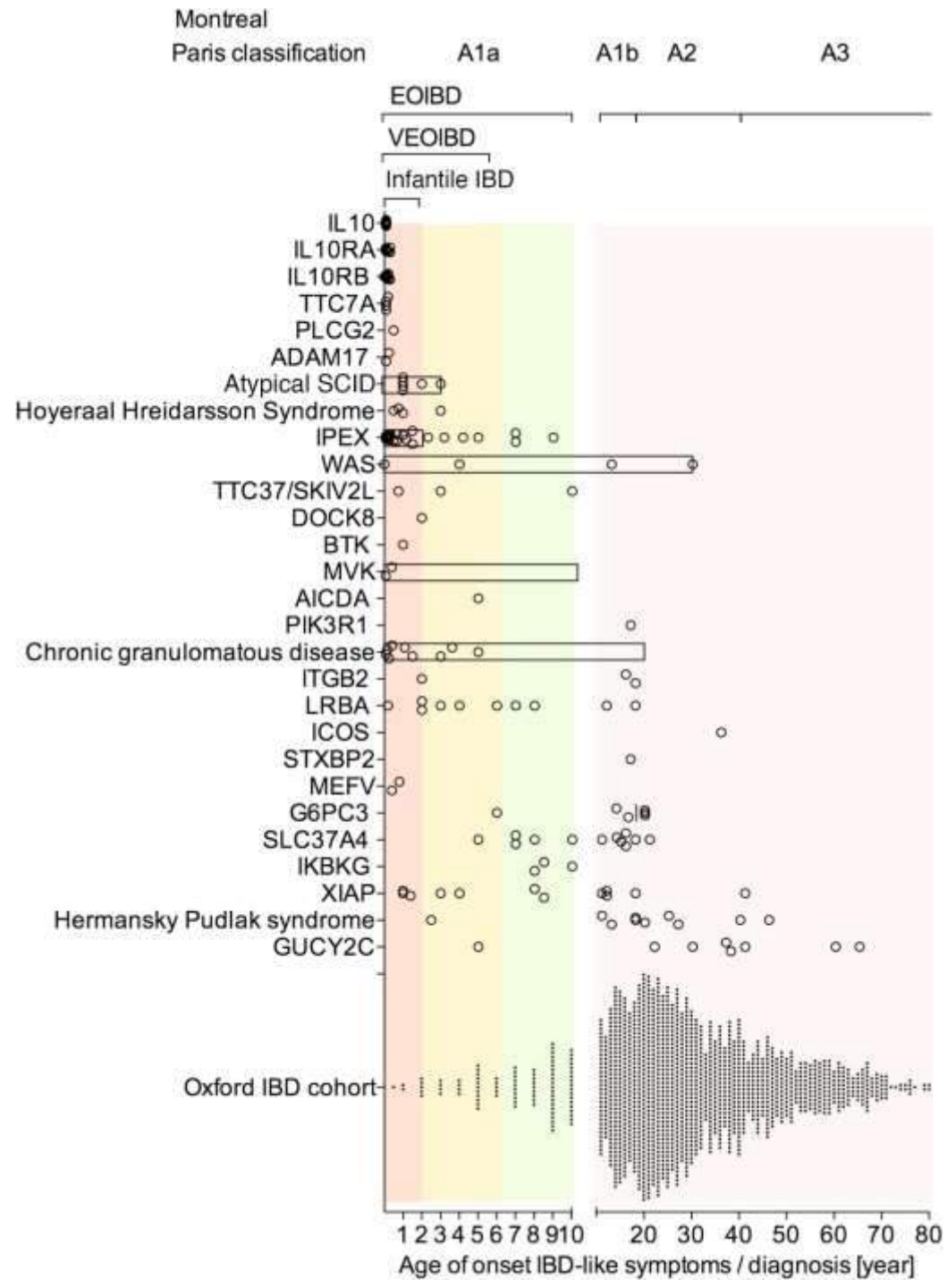
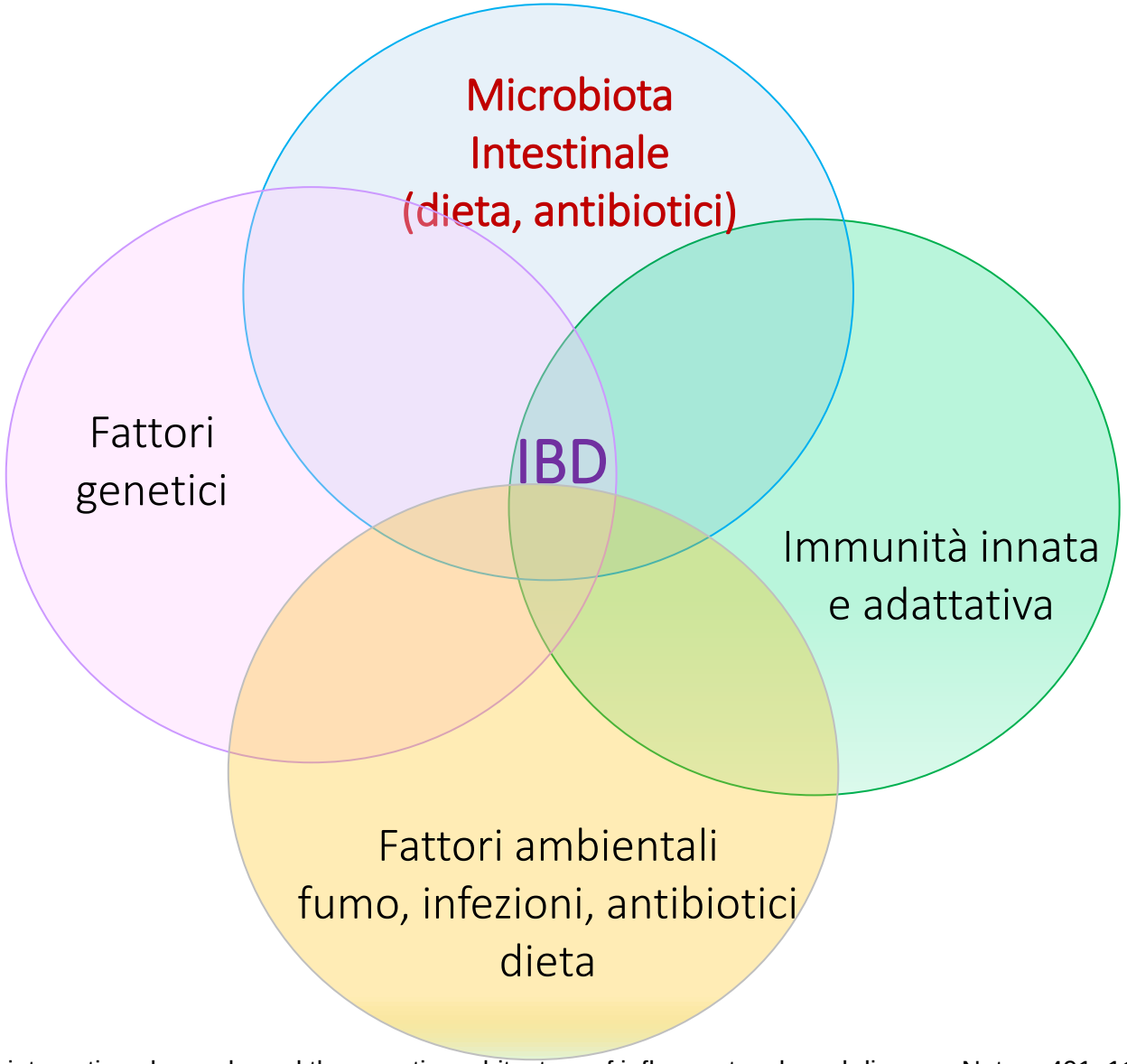


Figure 2: **The genetic landscape of inflammatory bowel disease**

Both rare and common variants contribute to inflammatory bowel disease risk. Known inflammatory bowel disease risk variants are plotted based on their minor allele frequency and relative effect. *XIAP* and *IL10* are added as representatives of causal rare variants identified in familial cases of very-early-onset inflammatory bowel disease. Variants are high risk (odds ratio [OR] >2), medium risk (1·2–2), or low risk (<1·2), with the position of the variant on the x-axis corresponding to its relative effect. The size of the circles represents effect size, with ORs from de Lange and colleagues,[17] or in cases where loci could be resolved to a single variant with high probability of being causal (posterior probability >50%), effect size was from Huang and colleagues.[18]



IBD pathogenesis



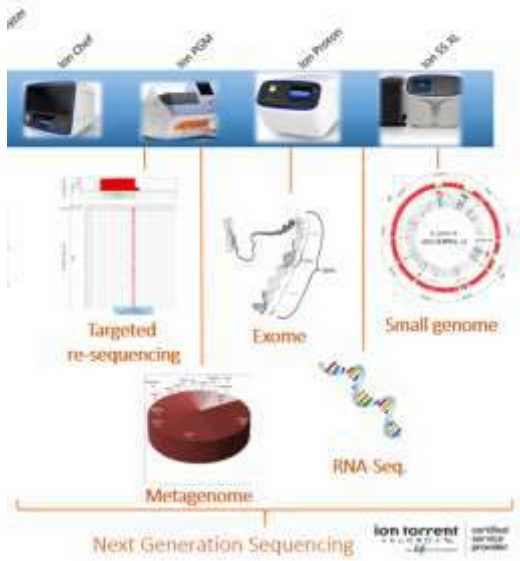
Jostins, L. et al. Host–microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature 491, 119–124 (2012).
Hunt, K. A. et al. Negligible impact of rare autoimmune-locus coding-region variants on missing heritability. Nature 498, 232–235 (2013).

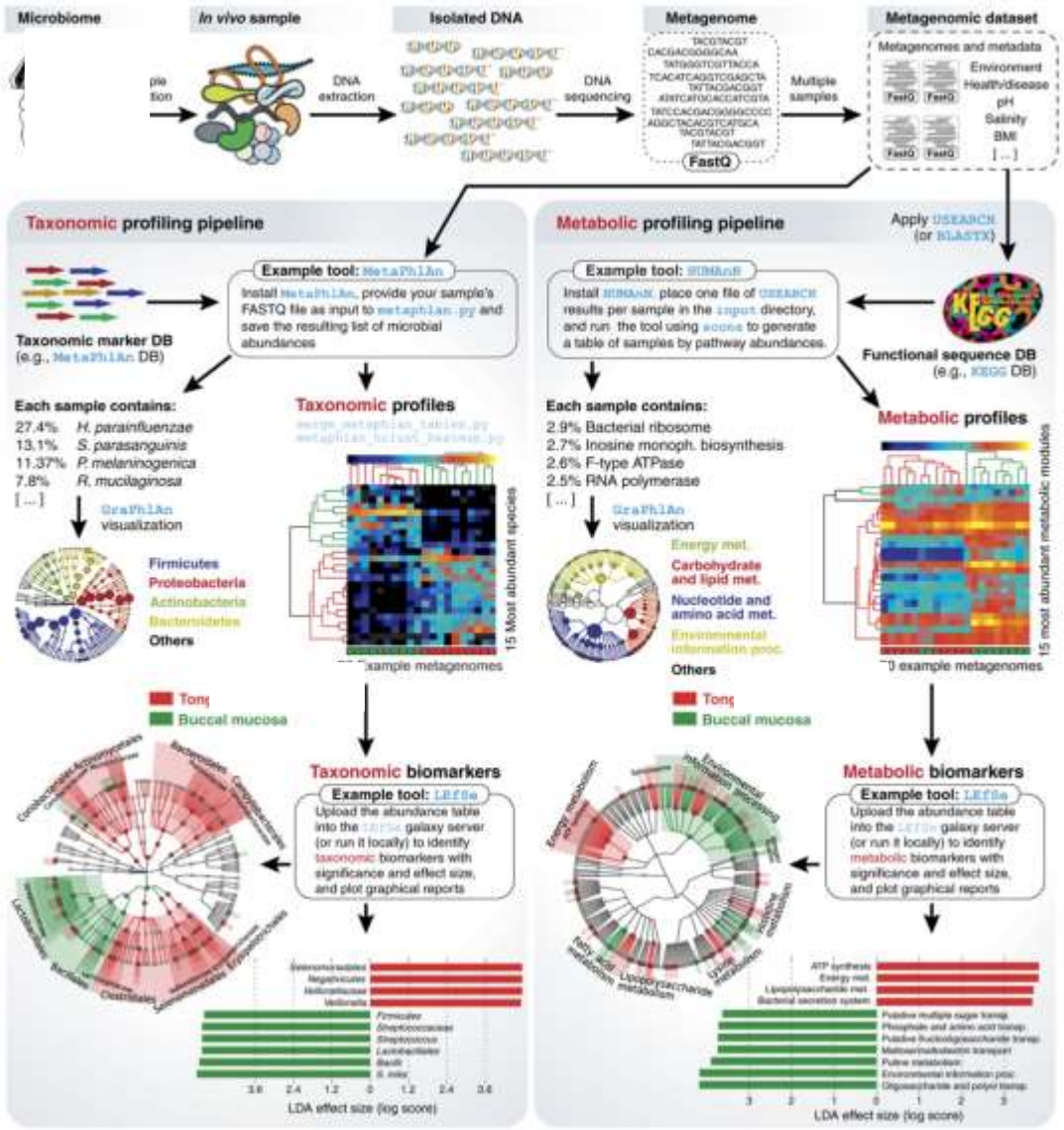
Crohn disease: Immunobiology

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.

A typical current computational meta'omic pipeline to analyze microbial communities.



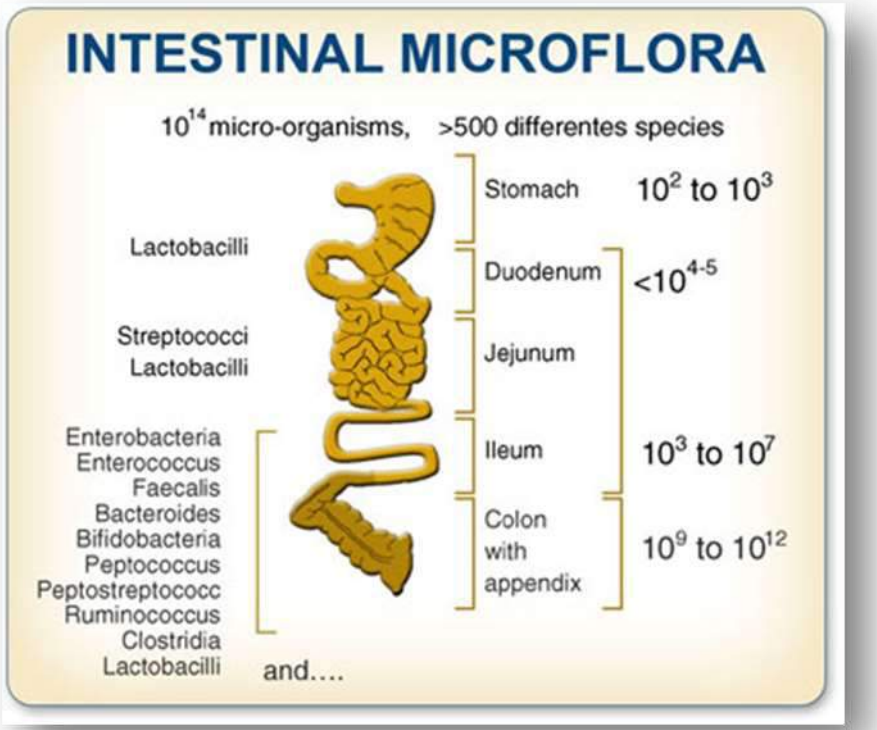


Nicola Segata et al. Mol Syst Biol 2013;9:666

The human microbiome

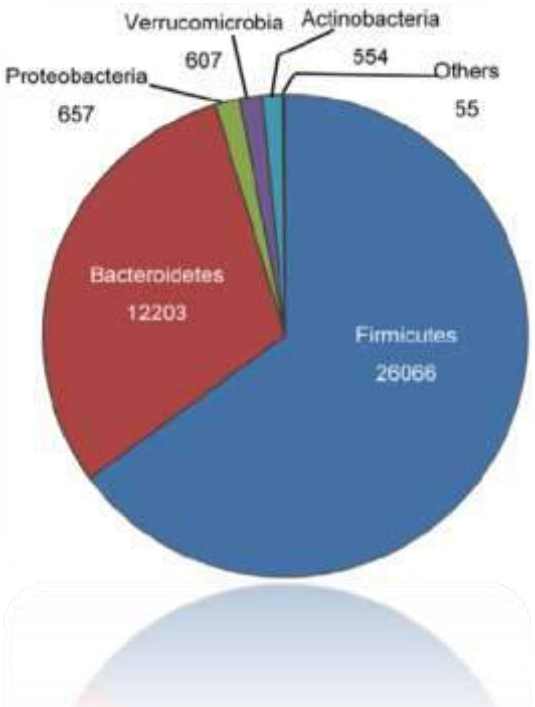
The *gut microbiota* is the community of microorganisms that normally live in the human digestive tract performing a number of useful functions for their hosts.

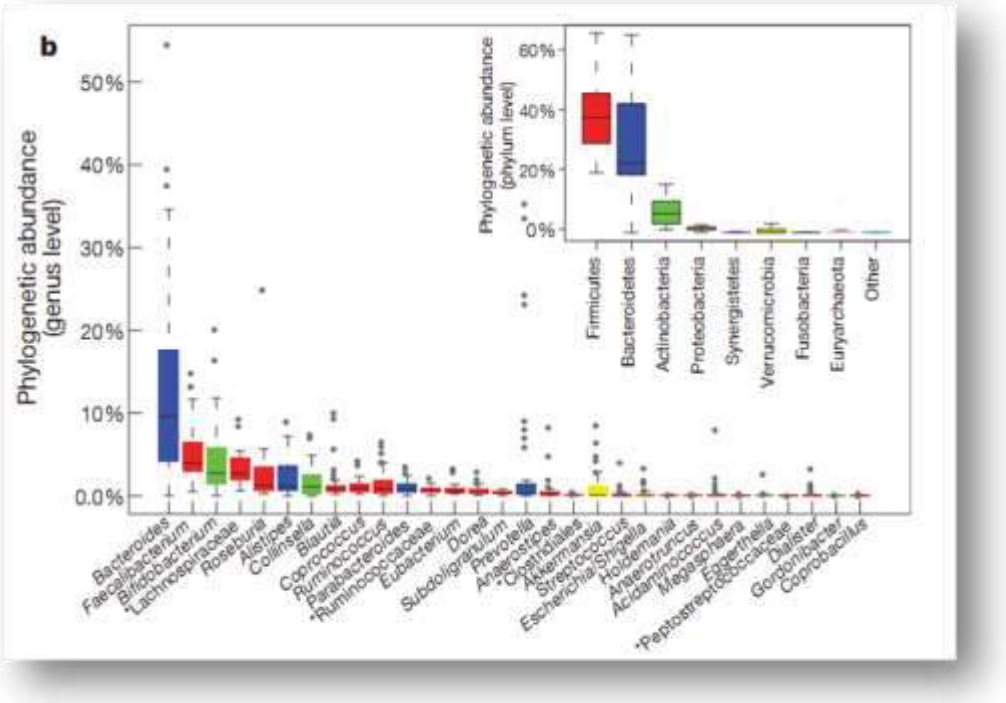
The average human body, consisting of about 10^{13} cells, has about ten times that number of microorganisms in the gut (**100 trillion**).



The human GI microbiota

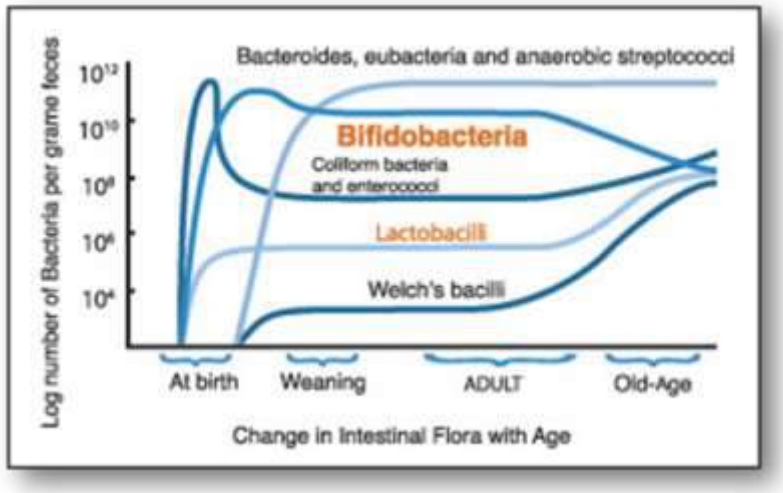
The gene catalogue - characterized by a metagenomic approach - indicates the microbe genome encodes for **3,364 non-redundant** genes suggesting that no more than ~**1,150 bacterial species** are abundant enough to be detected in the feces. With most individuals harboring approximately **160 different bacterial species and 99%** of intestinal microbiome derives from **30-40 species**

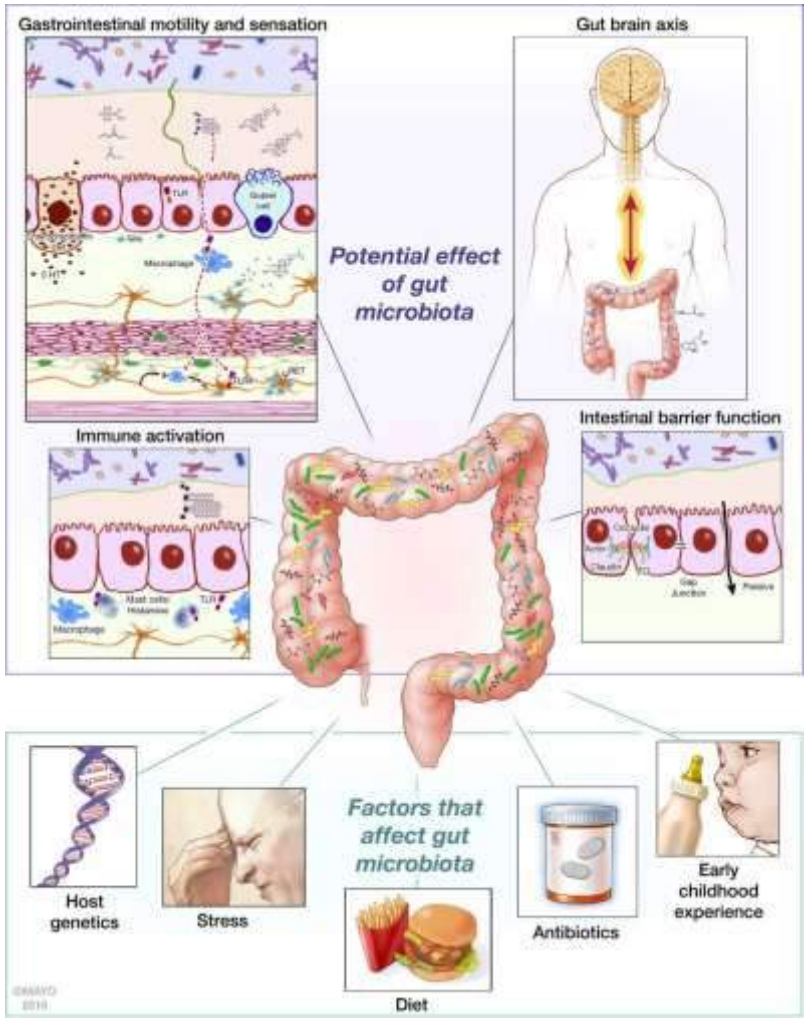




M Arumugam *et al. Nature* **000**, 1-7 (2011) doi:10.1038/nature09944

The structure of the human intestinal microbiota across the life cycle.



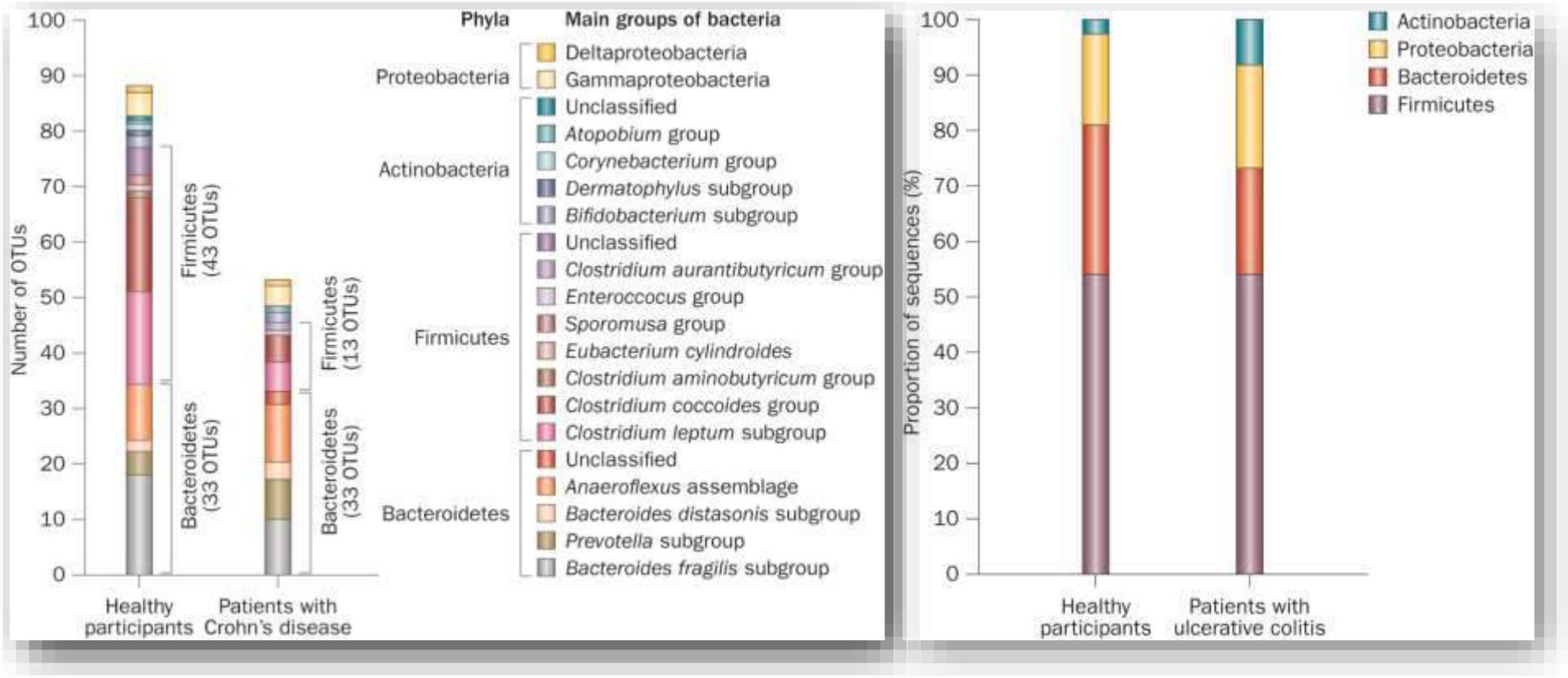


High fat/low fiber diet	BACTERIOIDES
Low fat /high fiber diet	PREVOTELLA

Kostic A D et al. Genes Dev. 2013;27:701-718

Reduction of bacterial diversity in patients with Crohn's disease (dysbiosis)

Crohn **UC**



Manichanh, C. *et al.* (2012) The gut microbiota in IBD
Nat. Rev. Gastroenterol. Hepatol. doi:10.1038/nrgastro.2012.152

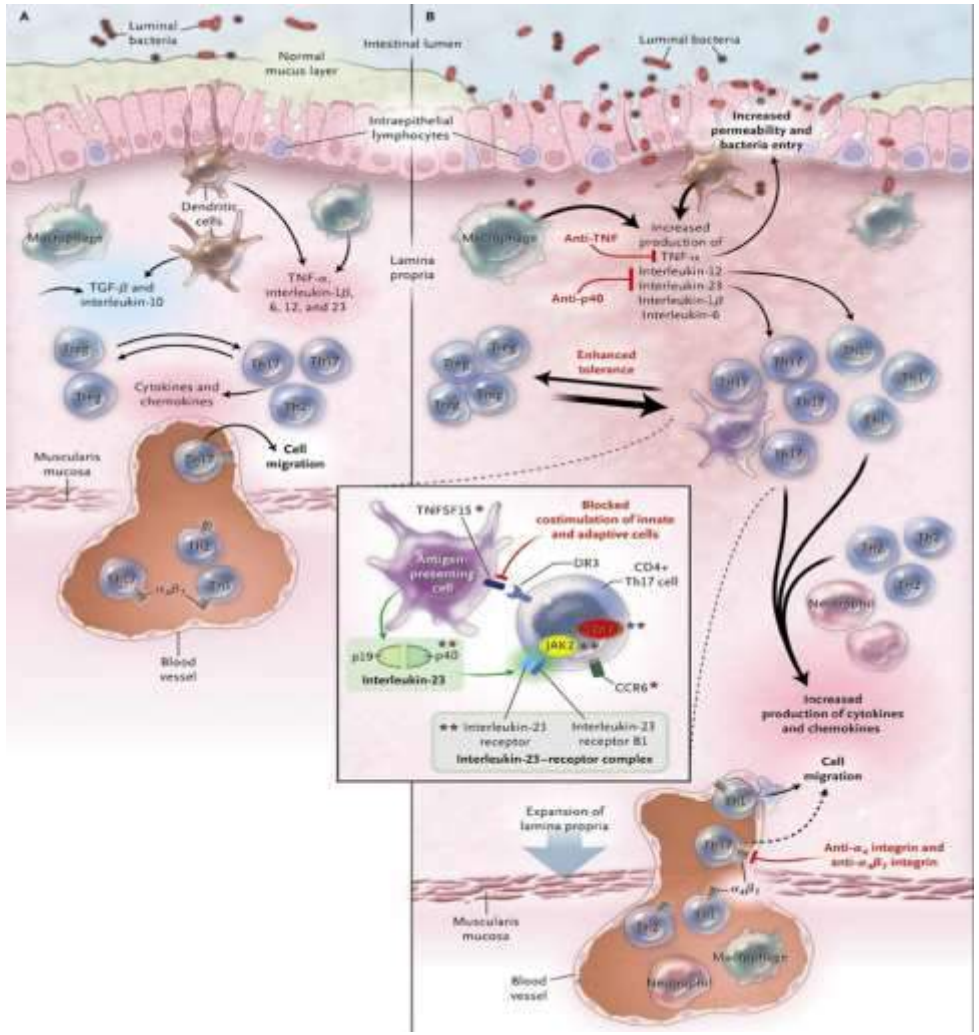
The intestinal microbiota in IBDs

TABLE 1 Microbial alterations in IBD as determined by high-throughput sequencing. Only studies including 10 or more patients per group have been included

Reference	Cohort description	Sample type	Findings
Rehman et al[183]	Adult (28 CD, 30 UC, 30 control)	Mucosal colonic biopsies	CD microbial signature • Reduced *Faecalibacterium prausnitzii*, *Bacteroides*, *Blautia*, *Ruminococcus*, *Roseburia*, *Coprococcus*, *Lachnospiraceae* UC microbial signature • Limited changes noted
Eun et al[184]	Adult (35 CD, 15 control)	Mucosal colonic biopsies (T) and subgroup of faecal samples (F; n = 25)	CD microbial signature • Increased Enterobacteriaceae, Fusobacteriaceae (T) • Increased Enterobacteriaceae, Pseudomonadaceae, Streptococcaceae and Erysipelotrichaceae (F) • Reduced Bacteroidaceae, Prevotellaceae, Lachnospiraceae and Ruminococcaceae and Veillonellaceae (T, F) • Reduced microbial richness (F)
Alipour et al[185]	Paediatric (n = 13 CD, 10 UC, 12 control)	Mucosal ileal biopsies	CD microbial signature • Limited changes noted UC microbial signature • Reduced microbial richness
Mar et al[186]	Adult (30 UC, 13 control)	Faeces	UC microbial signature • Reduced microbial richness • Reduced *Bacteroides*, *Prevotella* and a number of unclassified Lachnospiraceae and Ruminococcaceae • Enrichment of *Streptococcus*, *Bifidobacterium* and *Enterococcus* genera
Shah et al[187]	Paediatric (10 UC, 13 control)	Mucosal colonic biopsies	UC microbial signature • Reduced Verrucomicrobia, *Roseburia*, *Akkermansia* • Increased *Haemophilus*
Quince et al[170]	Paediatric (23 CD, 21 control)	Faecal	CD microbial signature • Reduced microbial richness • Reduced Lachnospiraceae, *Subdoligranum* and *Faecalibacterium* • Increased *Peptostreptococcus*, *Atopobium* and Enterobacteriaceae

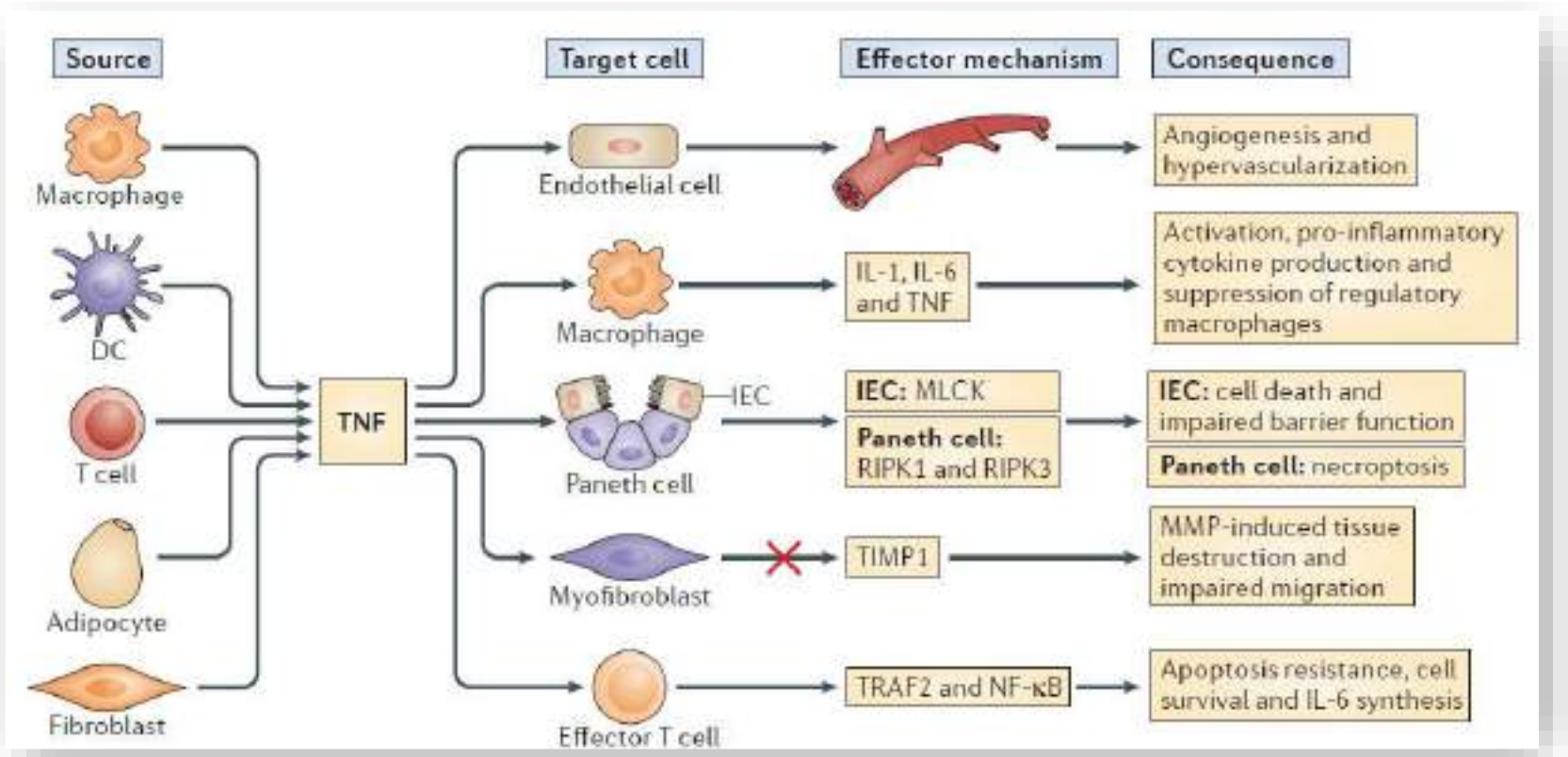
Aliment Pharmacol Ther. 2018 Jan;47(1):26-42. doi: 10.1111/apt.14384.
Review article: the gut microbiome in inflammatory bowel disease-avenues for microbial management.

IBD seem to result from an impaired interaction of the intestinal commensal microbiota that is normally in a state symbiotic mutualism with the human host



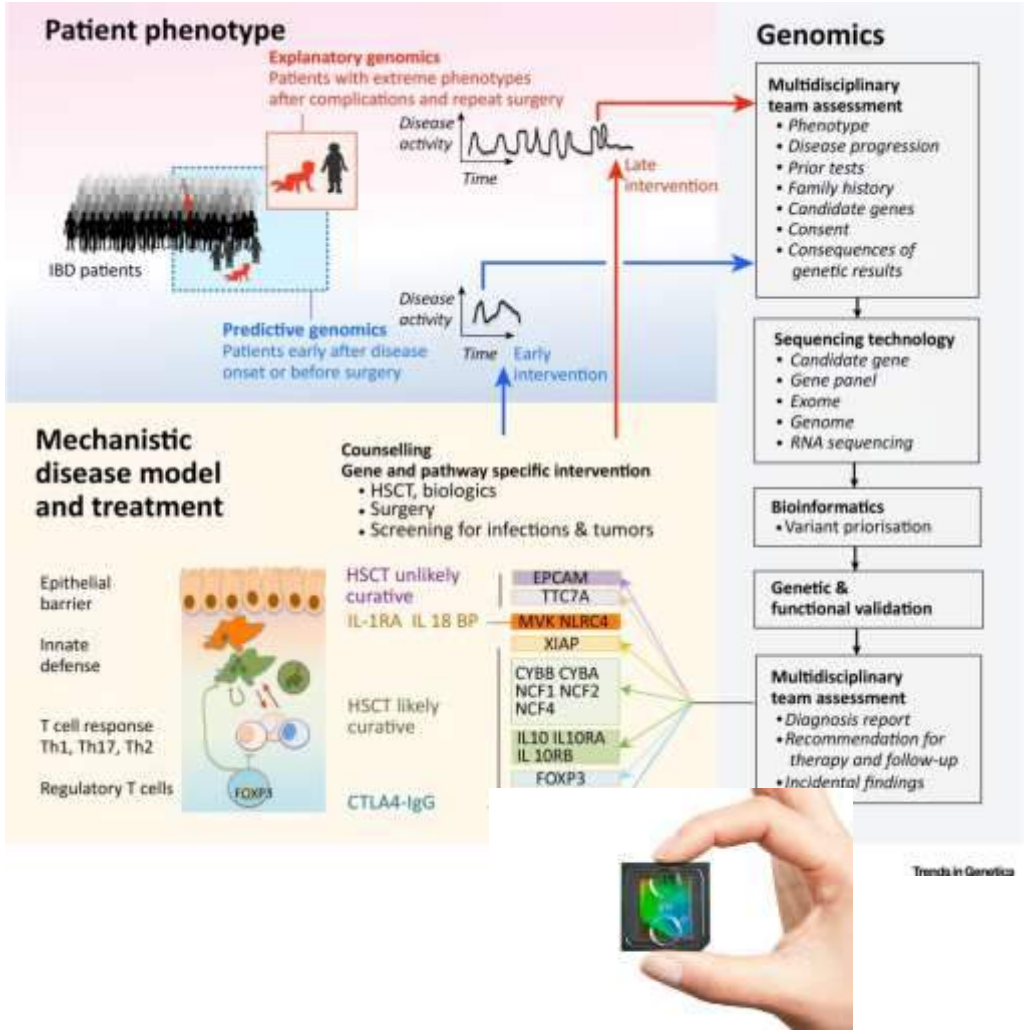
Despite enormous progress in understanding the many facets of this ancient relation, distinction between primary inciting events and secondary occurrences is challenging.

TNFα is a therapeutic target in IBDs

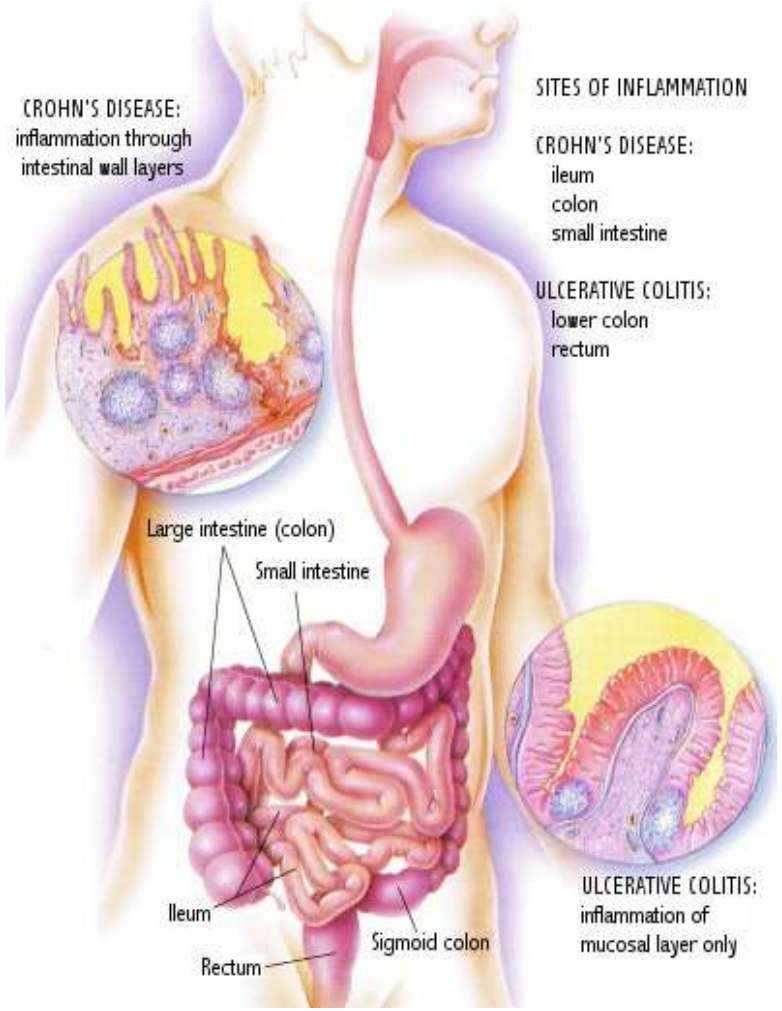


Nature Reviews Immunology | AOP, published online 22 April 2014; doi:10.1038/nri3661

Precision Medicine



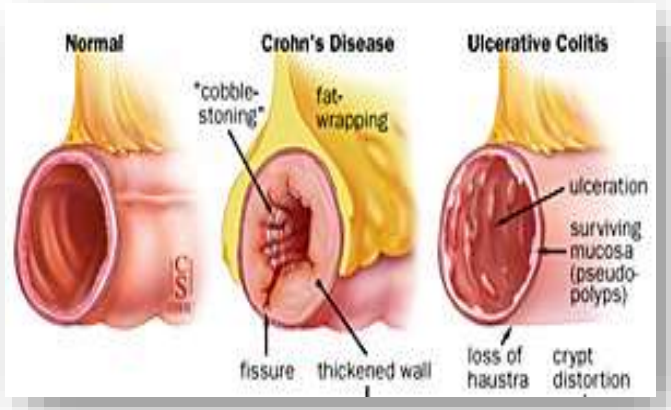
IBDs and Disease phenotype

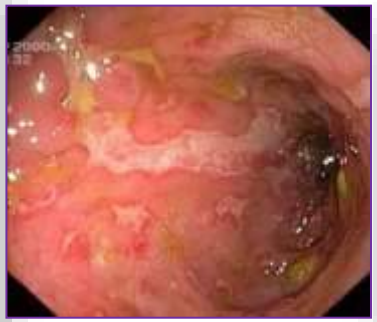


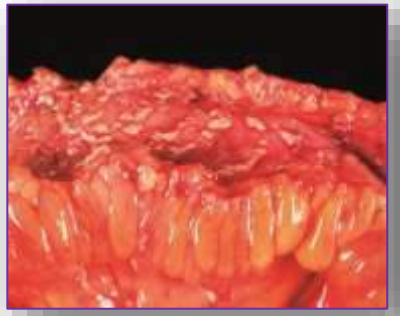
IBD pathology: macroscopic features

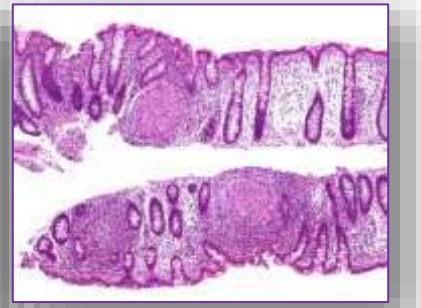
- **UC is a mucosal disease** that usually involves the rectum and extends proximally to involve all or part of the colon. About 40–50% of patients have disease limited to the rectum and rectosigmoid, 30–40% have disease extending beyond the sigmoid but not involving the whole colon, and 20% have a total colitis.
- **CD can affect any part of the gastrointestinal tract from the mouth to the anus.** Some 30–40% of patients have small-bowel disease alone, 40–55% have disease involving both the small and large intestines, and 15–25% have colitis alone. The rectum is often spared in CD

IBDs pathology: CD









- **CD is a transmural process**. Endoscopically, aphthous or small superficial ulcerations characterize mild disease; in more active disease, stellate ulcerations fuse longitudinally and transversely to demarcate islands of mucosa that frequently are histologically normal. This "cobblestone" appearance is characteristic of CD, both endoscopically and by barium radiography. As in UC, pseudopolyps can form in CD.
- Active CD is characterized by focal inflammation and formation of fistula tracts, which resolve by fibrosis and **stricturing of the bowel**. The bowel wall thickens and becomes narrowed and fibrotic, leading to chronic, recurrent bowel obstructions. Projections of thickened mesentery encase the bowel ("**creeping fat"),** and serosal and mesenteric inflammation promotes adhesions and fistula formation.

Crohn's disease

Signs and Symptoms

Although CD usually presents as acute or chronic bowel inflammation, the inflammatory process evolves toward **one of two patterns** of disease:

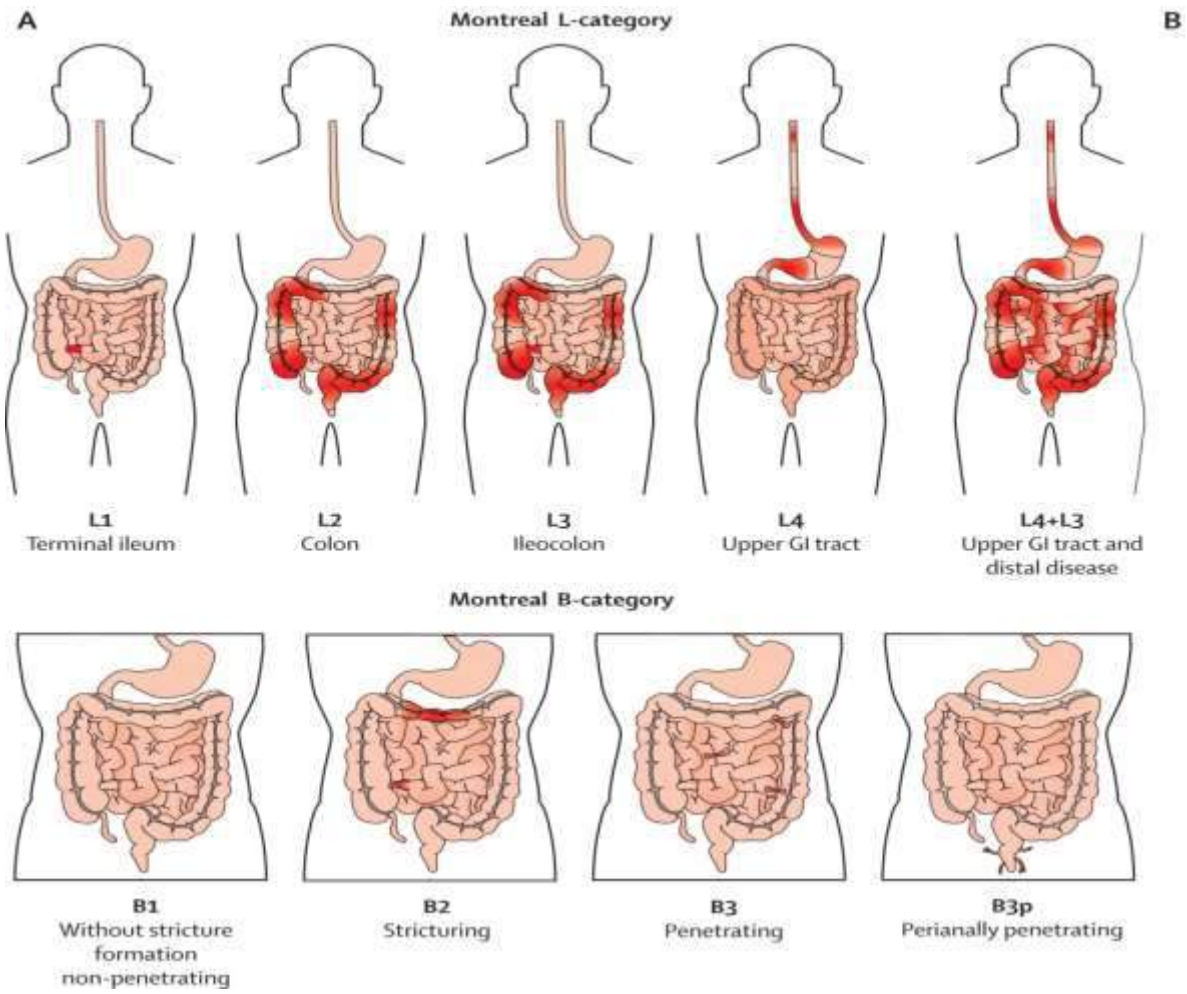
1. **fibrostenotic-obstructing**
2. **penetrating-fistulous**

each with different treatments and prognoses.

The site of disease influences the clinical manifestations.

Crohn's disease: phenotype

Montreal classification



The Lancet 2012 380, 1590-1605DOI: (10.1016/S0140-6736(12)60026-9)

Crohn’s disease

Ileocolitis (L2-L3)

Because the **most common site** of inflammation is the **terminal ileum**, the usual presentation of ileocolitis is a chronic history of recurrent episodes of right lower quadrant pain and diarrhea.

Sometimes the **initial presentation mimics acute appendicitis with pronounced right lower quadrant pain, a palpable mass, fever, and leukocytosis.**

Pain is usually colicky; it precedes and is relieved by defecation. A low-grade fever is usually noted. High-spiking fever suggests intraabdominal abscess formation.

Weight loss is common—typically 10–20% of body weight—and develops as a consequence of diarrhea, anorexia, and fear of eating.

An inflammatory mass may be palpated in the right lower quadrant of the abdomen. The mass is composed of inflamed bowel, adherent and indurated mesentery, and enlarged abdominal lymph nodes.

Crohn's disease

Ileocolite (L2-L3) cont.

Bowel obstruction may take several forms. In the early stages of disease, bowel wall edema and spasm produce intermittent obstructive manifestations and increasing symptoms of postprandial pain.

Over several years, persistent inflammation gradually progresses to fibrostenotic narrowing and stricture.

Diarrhea will decrease and be replaced by chronic bowel obstruction. Acute episodes of obstruction occur as well, precipitated by bowel inflammation and spasm or sometimes

by impaction of undigested food or medication. These episodes usually resolve with intravenous fluids and gastric decompression.

Severe inflammation of the ileocecal region may lead to localized wall thinning, with microperforation and fistula formation to the adjacent bowel, the skin, or the urinary bladder, or to an abscess cavity in the mesentery. Enterovesical, enetrovaginal, enterocutaneous are commons.

Crohn’s disease

Jejunoileitis (L4-L5)

- **Extensive inflammatory disease is associated with a loss of digestive and absorptive surface, resulting in malabsorption and steatorrhea**. Nutritional deficiencies can also result from poor intake and enteric losses of protein and other nutrients.

- **Diarrhea is characteristic of active disease**; its causes include (1) bacterial overgrowth in obstructive stasis or fistulization, (2) bile-acid malabsorption due to a diseased or resected terminal ileum, and (3) intestinal inflammation with decreased water absorption and increased secretion of electrolytes.

Crohn’s disease

Colitis (L2) and Perianal Disease (B3p)

- Patients with colitis present with low-grade fevers, malaise, diarrhea, crampy abdominal pain, and sometimes hematochezia. Gross bleeding is not as common as in UC and appears in about half of patients with exclusively colonic disease. **Only 1–2% bleed massively.** Pain is caused by passage of fecal material through narrowed and inflamed segments of large bowel. Decreased rectal compliance is another cause for diarrhea in Crohn's colitis patients.
- **Stricturing can occur in the colon in 4–16% of patients** and produce symptoms of bowel obstruction.
- **Colonic disease may fistulize** into the stomach or duodenum, causing feculent vomiting, or to the proximal or mid small bowel, causing malabsorption by "short circuiting" and bacterial overgrowth. Ten percent of women with Crohn's colitis will develop a rectovaginal fistula.
- **Perianal disease affects about one-third of patients with Crohn's colitis and is** manifested by incontinence, large hemorrhoidal tags, anal strictures, **anorectal fistulae, and perirectal abscesses.**

Crohn disease activity index (CDAI)

Chart 1.

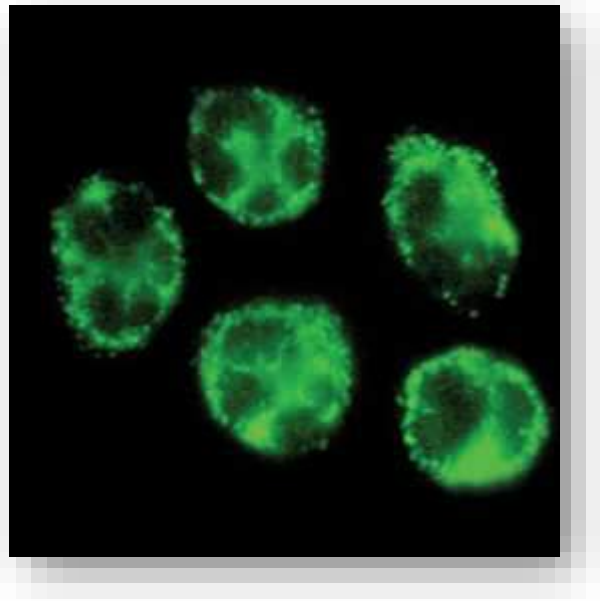
Crohn's Disease Activity Index	
Number of liquid stools (daily for 7 days)	x 2
Abdominal pain (none = 0, mild = 1, moderate = 2, severe = 3)	x 5
Sense of well-being (well = 0, slightly below par = 1, poor = 2, very poor = 4, terrible = 4)	x 7
Number of complications (arthritis/arthralgia, iritis/uveitis, erythema nodosum/pyoderma gangrenosum, aphthous stomatitis, anal fissure/fistula or abscess, fever > 37.8° C)	x 20
Taking diphenoxylate or loperamide (no = 0, yes = 1)	x 30
Abdominal mass (no = 0, questionable = 1, present = 5)	x 10
Hematocrit (males: 47 – HT%, females: 42 – Ht%	x 6
Weight (1 – weight / standard weight x 100). Add or subtract according to the sign	x 1
Total	

Crohn's disease

Laboratory findings:

- Elevated **VES and PCR, fibrinogen, alpha$_1$-glicoprotein, increased platets count and anemia (iron deficiency Bit B12 and folate deficiency**
- Various type of nutritional defects (Ca, Vit D..)

- Two antibodies that can be detected in the serum of IBD patients are perinuclear antineutrophil cytoplasmic antibodies (pANCAs) and anti-Saccharomyces cerevisiae antibodies (ASCAs).
- A distinct set of pANCAs is associated with UC.



pANCA indicates a local vasculitis

IBDs diagnosis

Infectious Disease

- Infections of the small intestines and colon can mimic CD or UC. They may be bacterial, fungal, viral, or protozoal in origin.
- ***Campylobacter* colitis** can mimic the endoscopic appearance of severe UC and can cause a relapse of established UC.
- ***Salmonella*** can cause watery or bloody diarrhea, nausea, and vomiting. **Shigellosis** causes watery diarrhea, abdominal pain, and fever followed by rectal tenesmus and by the passage of blood and mucus per rectum. All three are usually self-limited, but 1% of patients infected with *Salmonella* become asymptomatic carriers.
- ***Yersinia enterocolitica*** infection occurs mainly in the terminal ileum and causes mucosal ulceration, neutrophil invasion, and thickening of the ileal wall.
- ***C. difficile***, which presents with watery diarrhea, tenesmus, nausea, and vomiting;
- ***E. coli,*** three categories: enterohemorrhagic, enteroinvasive, and enteroadherent *E. coli*, all of which can cause bloody diarrhea and abdominal tenderness.
- **Cytomegalovirus**

Crohn’s disease: disease estention

Endoscopy: colonoscopy and enteroscopy and capsule endoscopy

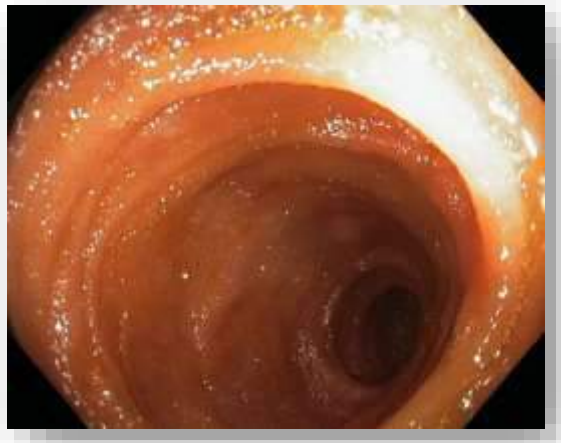
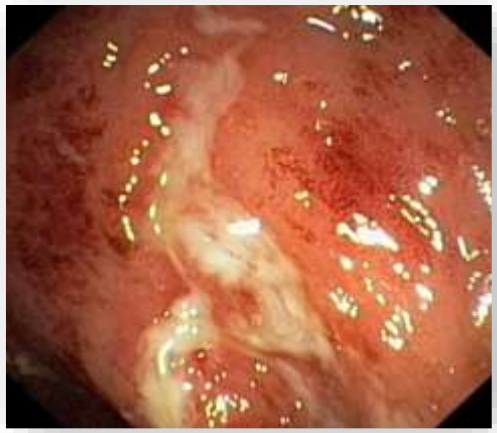
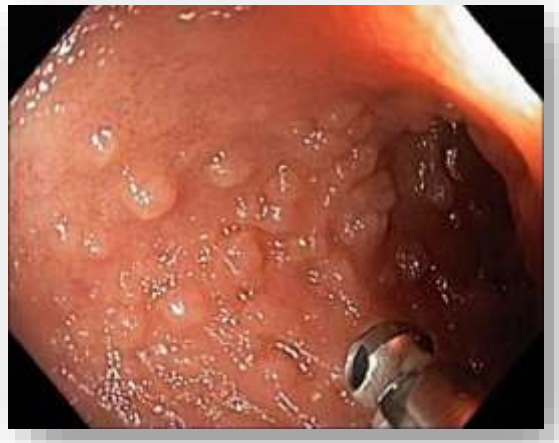
Sonography

Radiology

Conventionl radiology (tenue frazionato)

CT enterography (entero-TC o entero-RM)

Colonoscopy and terminal ileum endoscopy

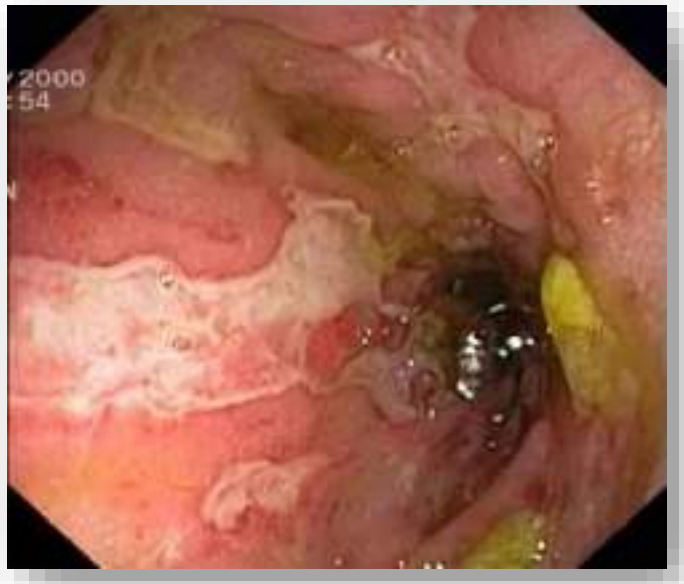




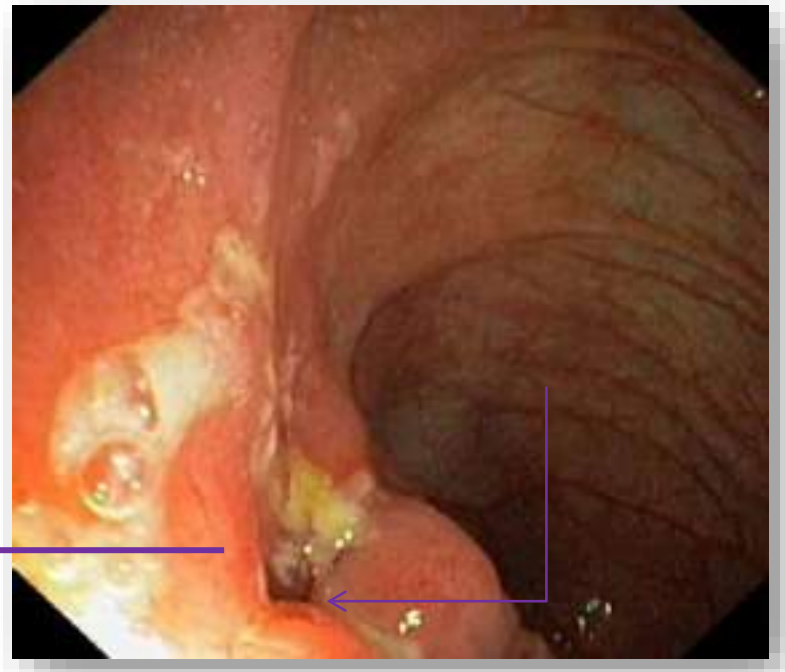
Endoscopic staging of Crohn disease
Ileal: L1

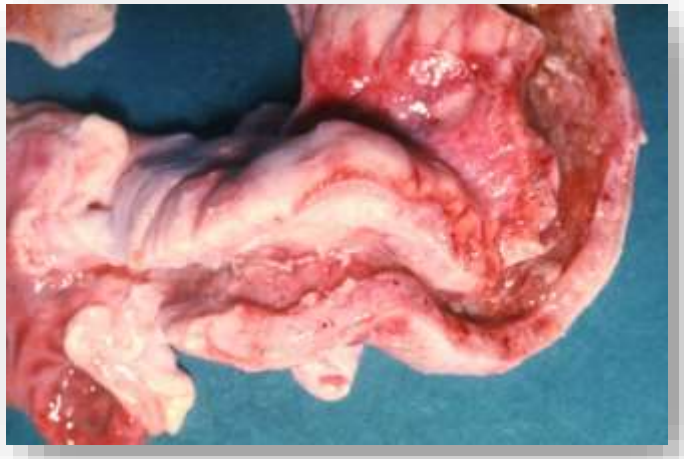
Endoscopic staging of Crohn disease

Ileocolic: L3

Stenosating: B2





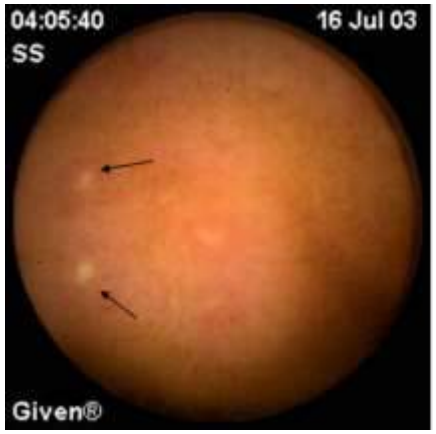


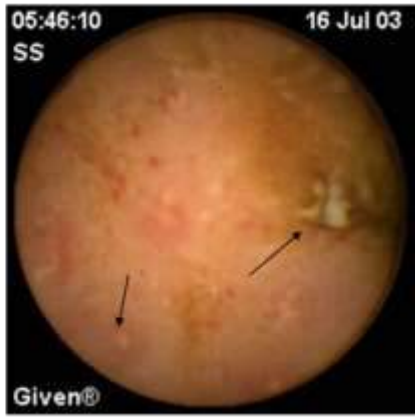
The Simplified Endoscopic Score for Crohn's Disease (SES-CD)

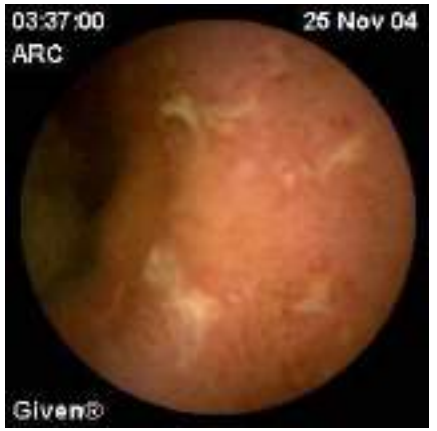
Variable	Score			
	0	1	2	3
Size of ulcers (cm)	None	Aphtous ulcers (0.1-0.5)	Large ulcers (0.5-2)	Very large ulcers (>2)
Ulcerated surface (%)	None	<10%	10-30%	>30%
Affected surface (%)	Unaffected	<50%	50-75%	>75%
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

Daperno M, et al. Gastrointest Endosc 2004; 60(4):505-12

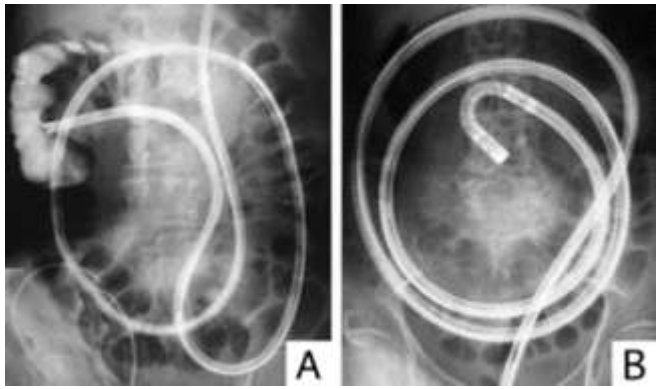
Videocapsule endoscopy

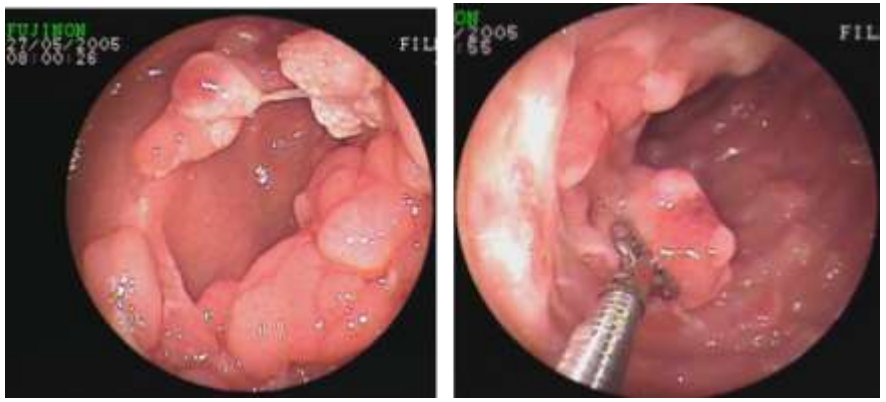




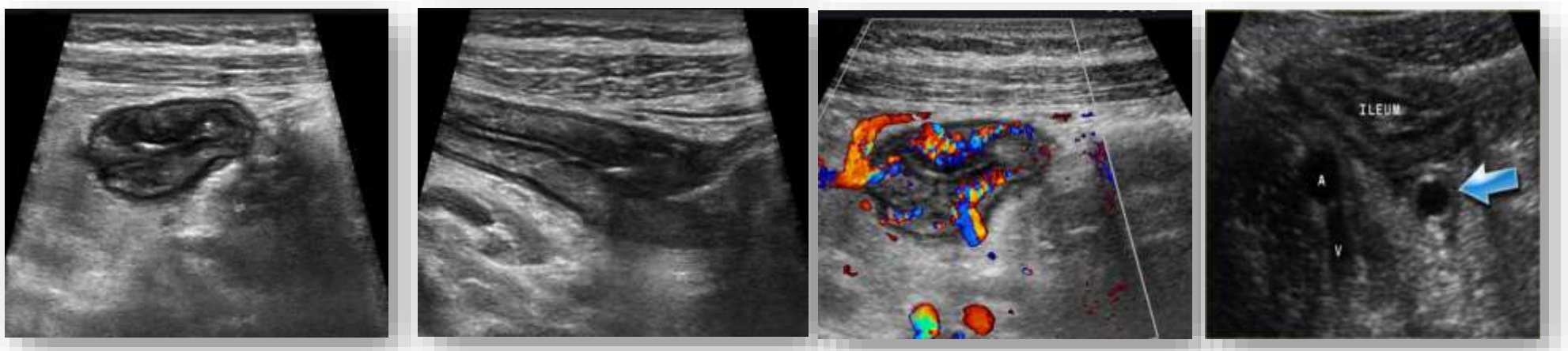


Enteroscopy





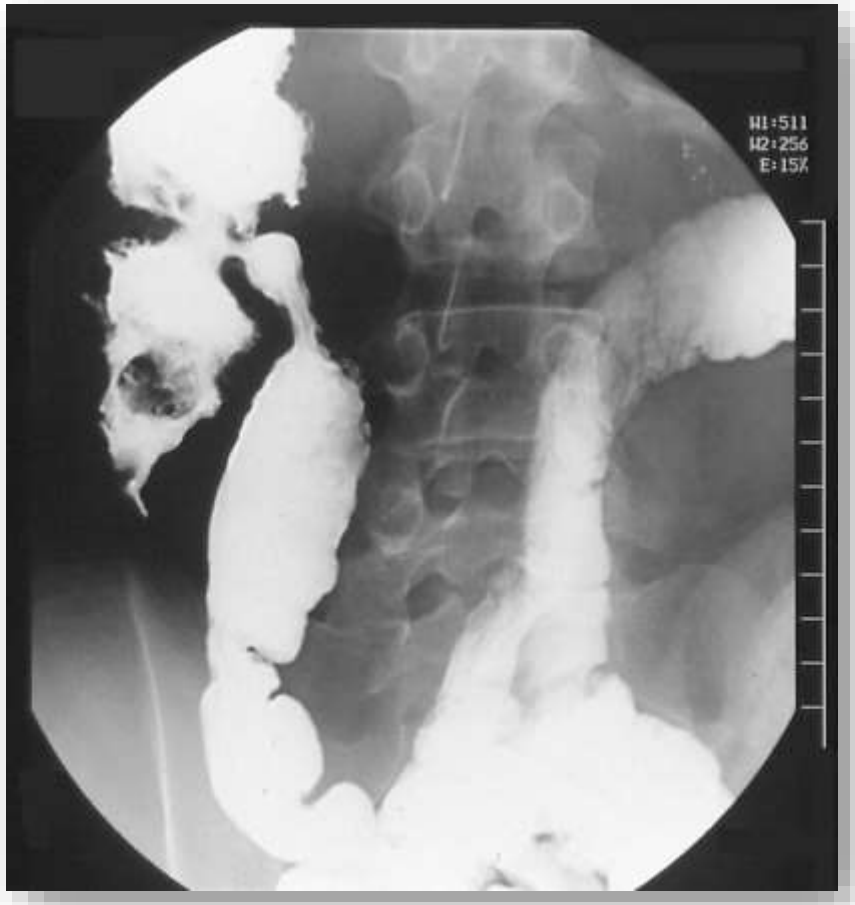
Crohn’s disease: sonography

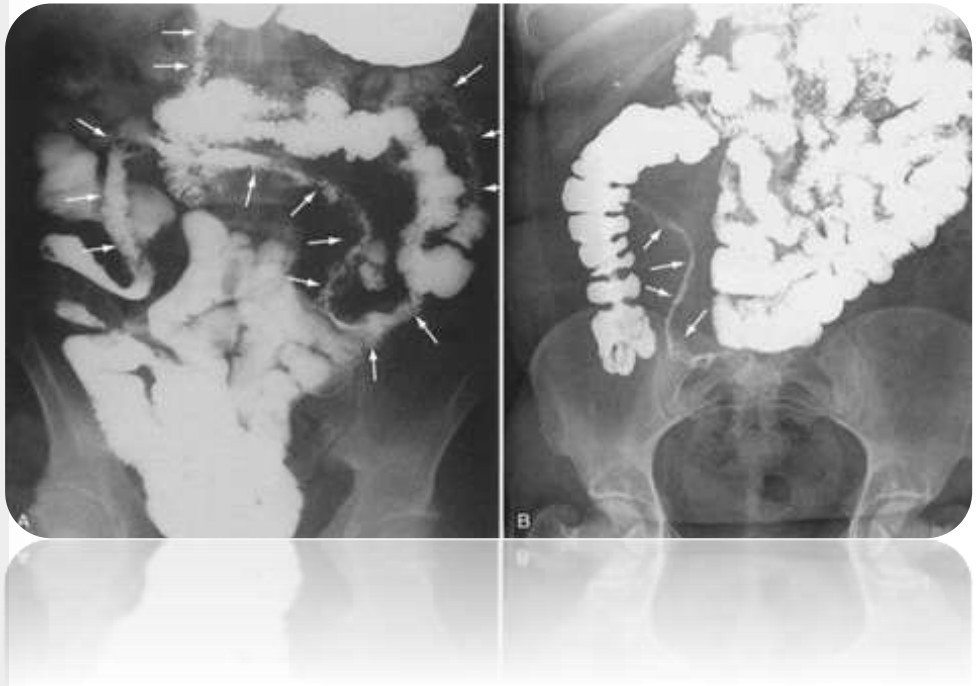


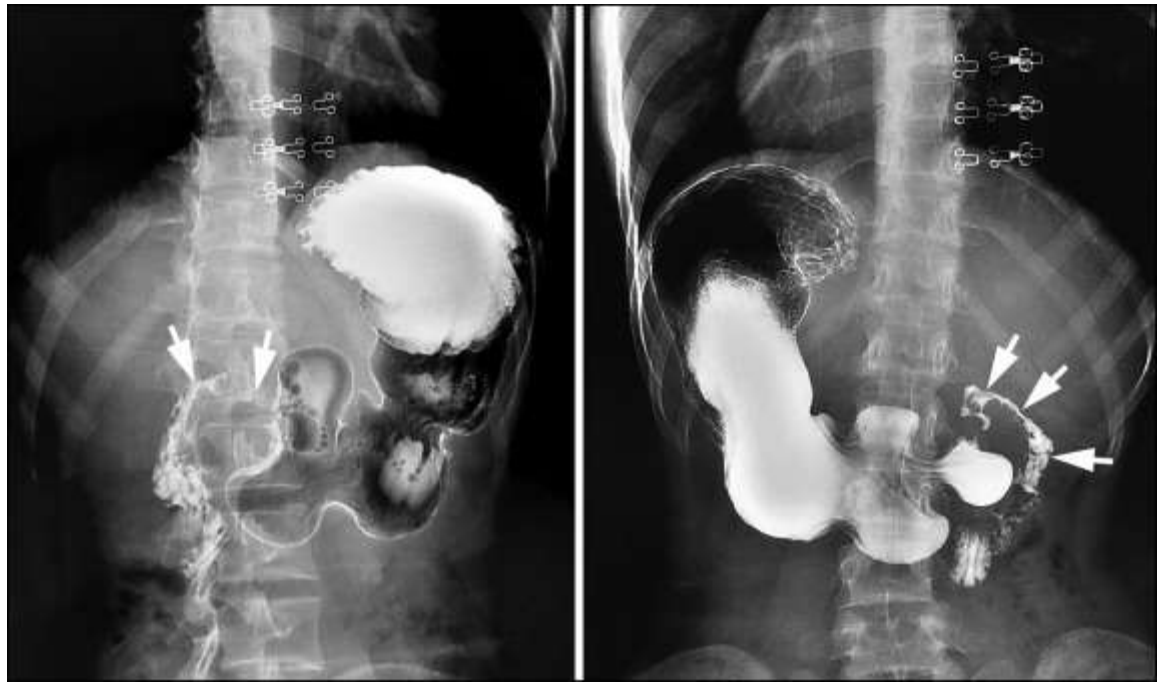
Native and (gas or shell microbubble) contrast-enhanced abdominal ultrasound (figure 4) is a readily available, non-invasive imaging technique with an overall sensitivity and specificity that are much the same as with MRI and CT.9

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

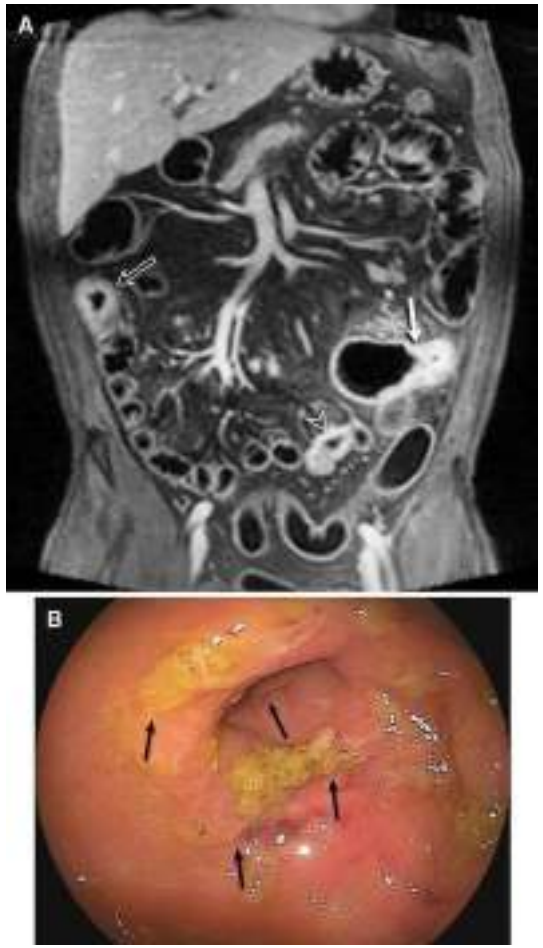
Crohn disease: small bowel series (SBFT)

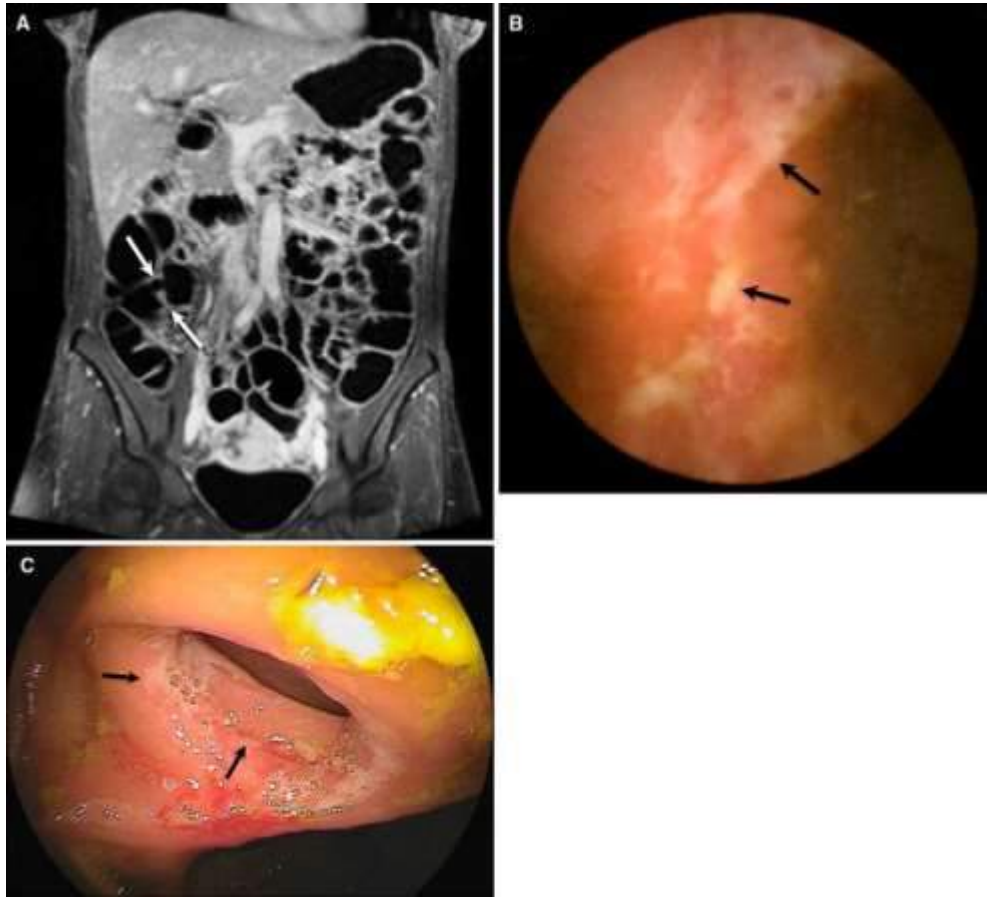




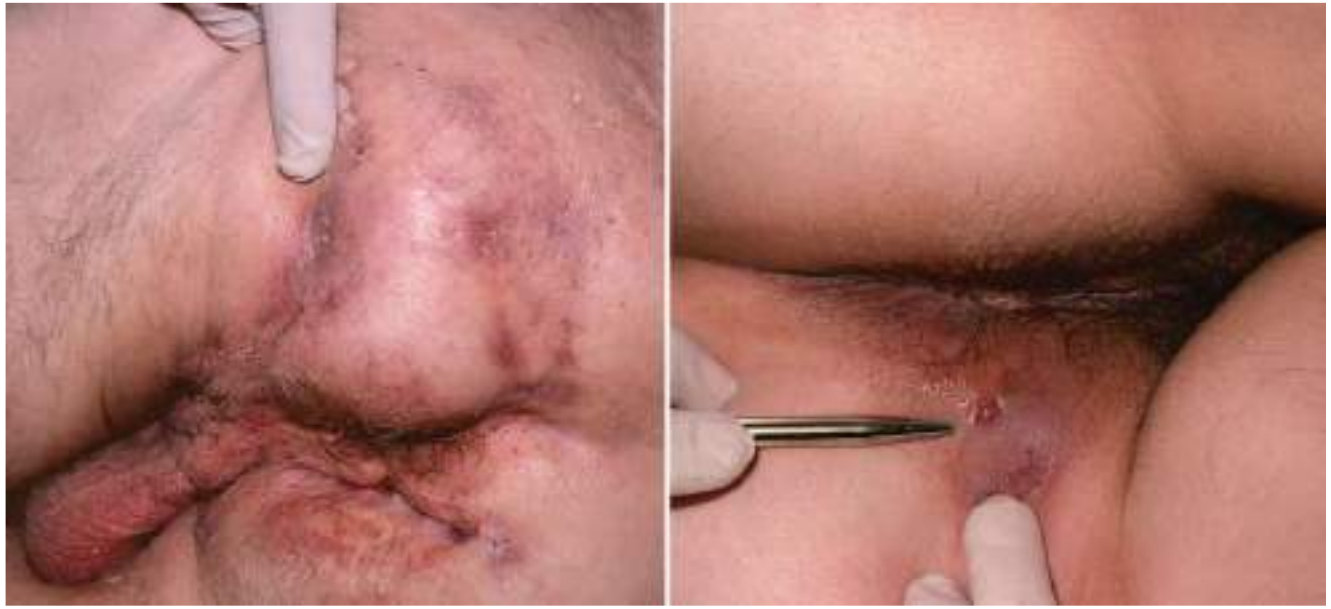


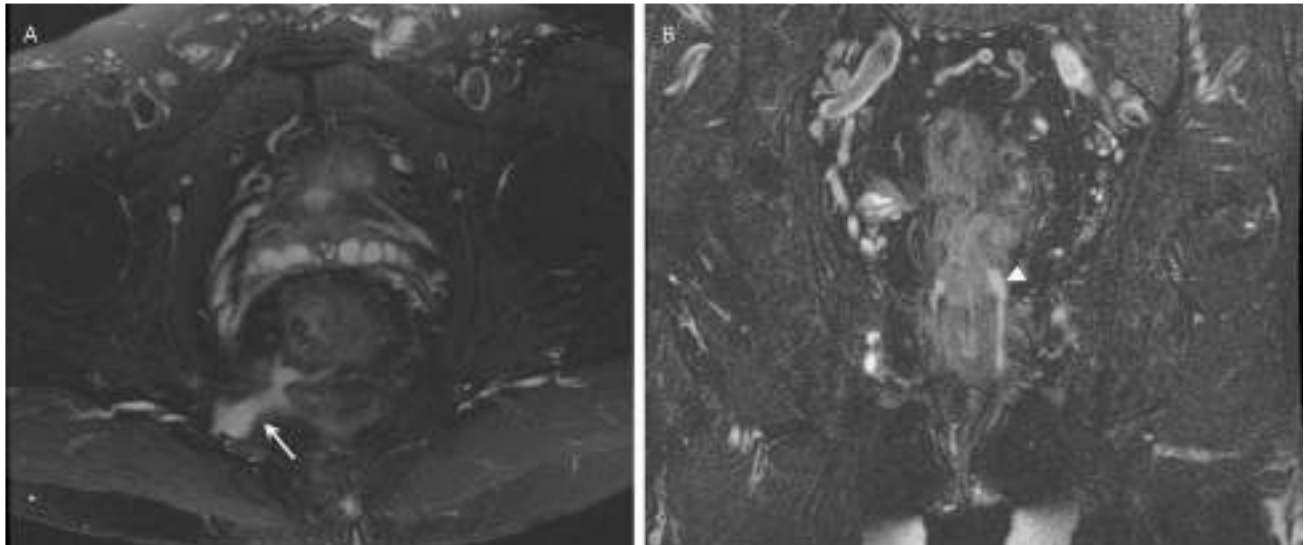
Crohn’s disease CT enterography



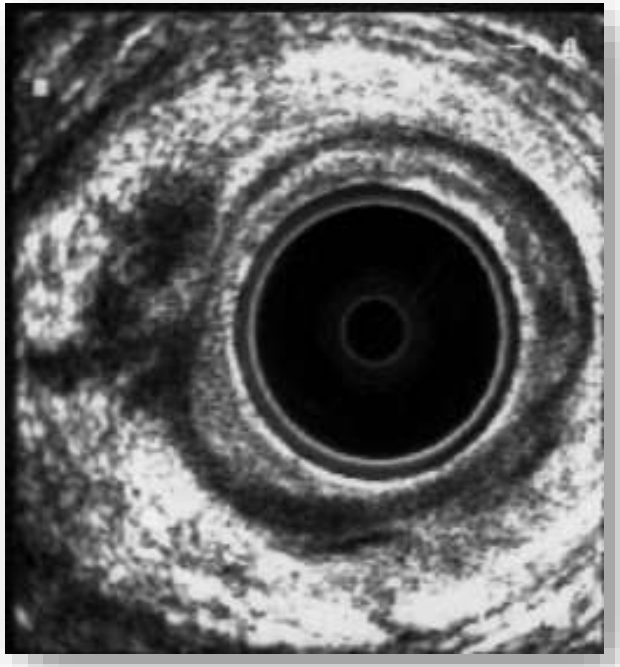


RM is highly effective in detecting pelvis and perianal fistulas

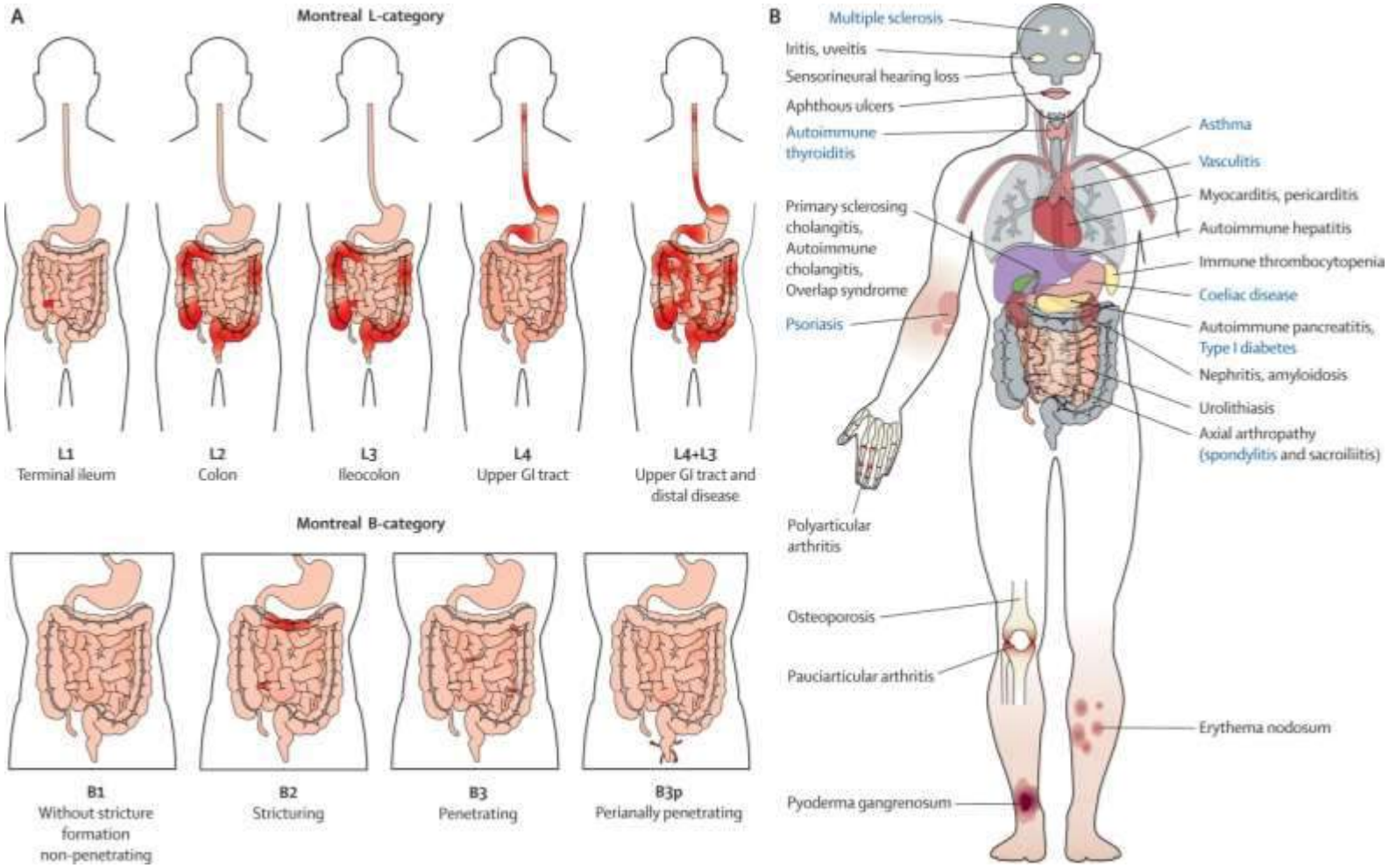




Transanal eco-endoscopy



CD extra intestinal manifestations



The Lancet 2012 380, 1590-1605DOI: (10.1016/S0140-6736(12)60026-9)

Keys factors in Crohn's disease

Crohn's disease

Risk factors: genotype and environment (for example, smoking as a risk factor for aggressive forms of disease)

Onset of disease: usually between 15 and 40 years

Location: **inflammation frequently affects distal ileum and colon**

Pathology: discontinuous, patchy gut inflammation with skip lesions

Histology: transmural inflammation (all layers of the bowel wall)

Symptoms: **diarrhoea, abdominal cramping, fever, anaemia, weight loss and fatigue**

Extra-intestinal inflammatory manifestations: various organs and systems are affected, for example, joints, skin, liver, eye, mouth and blood (coagulation)

Complications: stenosis, abscess formation, fistulas and colon cancer

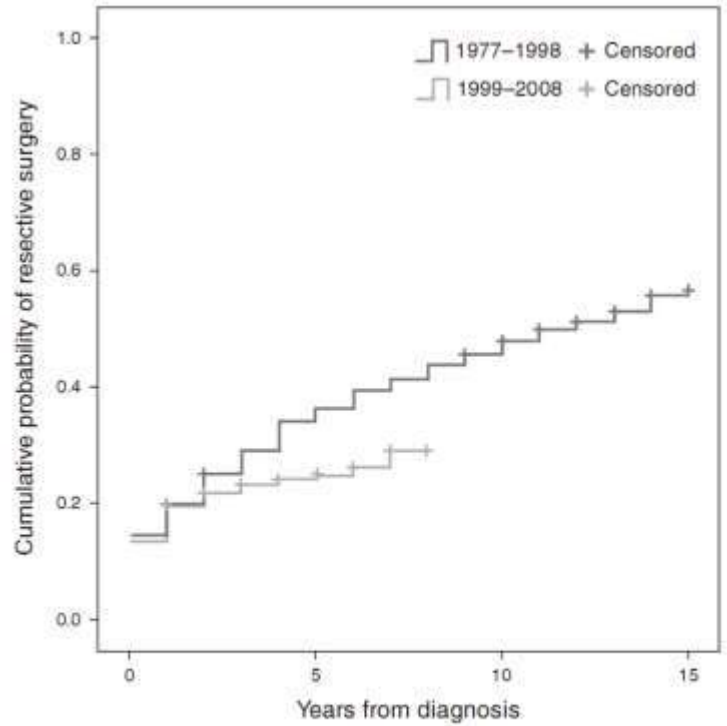


Figure 2. Cumulative probability of resective surgery according to the year of diagnosis. $P_{Logrank}=0.022$, $P_{Breslow}=0.07$.

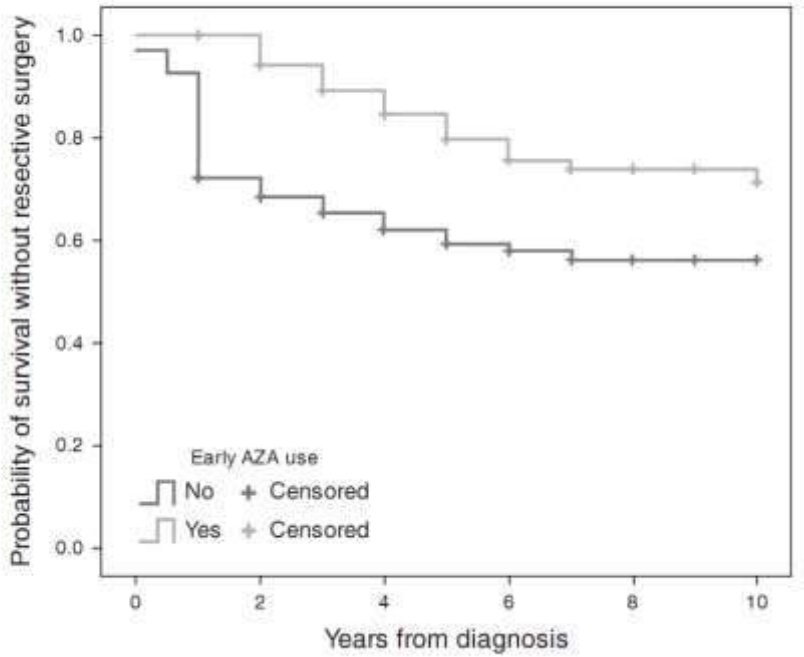
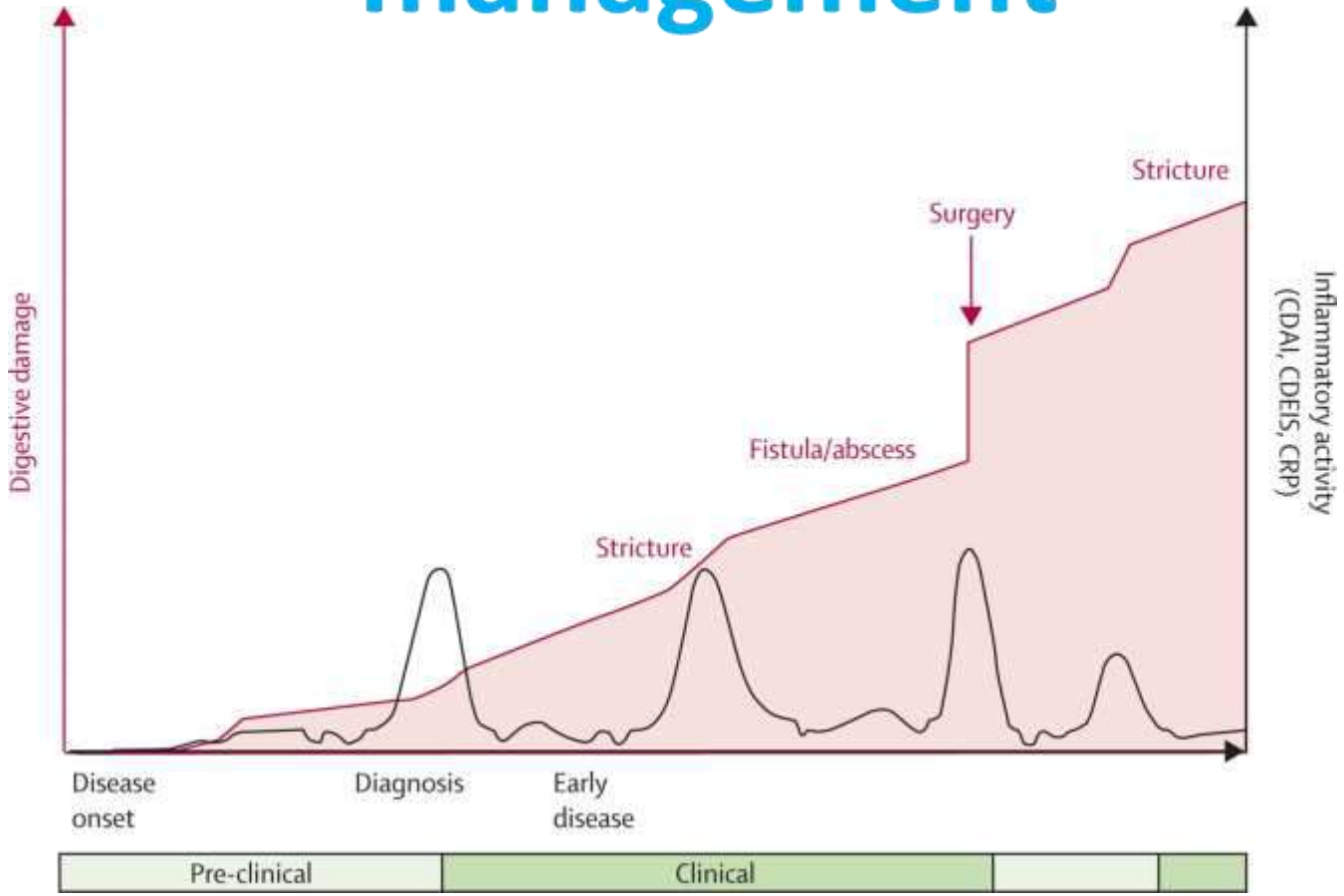


Figure 3. Association between early azathioprine (AZA) use and

- ✓ Medical therapy for Crohn's disease (CD) has changed significantly over the past 20 years with increasing use of immunosuppressive and biological drugs.
- ✓ In contrast, surgery rates are still high in CD (ranging from 25 to 61% at 5 years) and there is little evidence that disease outcomes for CD have changed over the past four decades as a consequence of medical therapy.

Crohn's disease: management



The Lancet 2012 380, 1590-1605DOI: (10.1016/S0140-6736(12)60026-9)

Objectives for treatment of CD

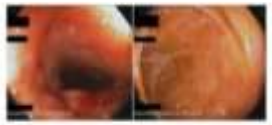
- Rapid induction of remission
- Sustained remission off steroids
- **Mucosal healing**
- Fewer surgeries and hospitalisations
- Effective treatment of fistulae
- Effective treatment of extra-intestinal manifestations
- Improvement of the patient’s quality of life
- Acceptable Benefit / Risk
- At an affordable cost for society

Mucosal healing

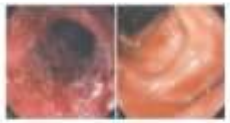
The „ideal" definition of Mucosal Healing (MH) could be ***complete endoscopic healing of all inflammatory and ulcerative lesions of the gut mucosa*** in CD and UC

In CD, an endoscopic response to treatment can be defined as "absence of ulcers" or a significant change of endoscopic disease activity score (CDEIS or SES-CD).

In UC, an endoscopic response to treatment can be defined as a significant change of endoscopic disease activity score (Baron score or Mayo endoscopic subscore).

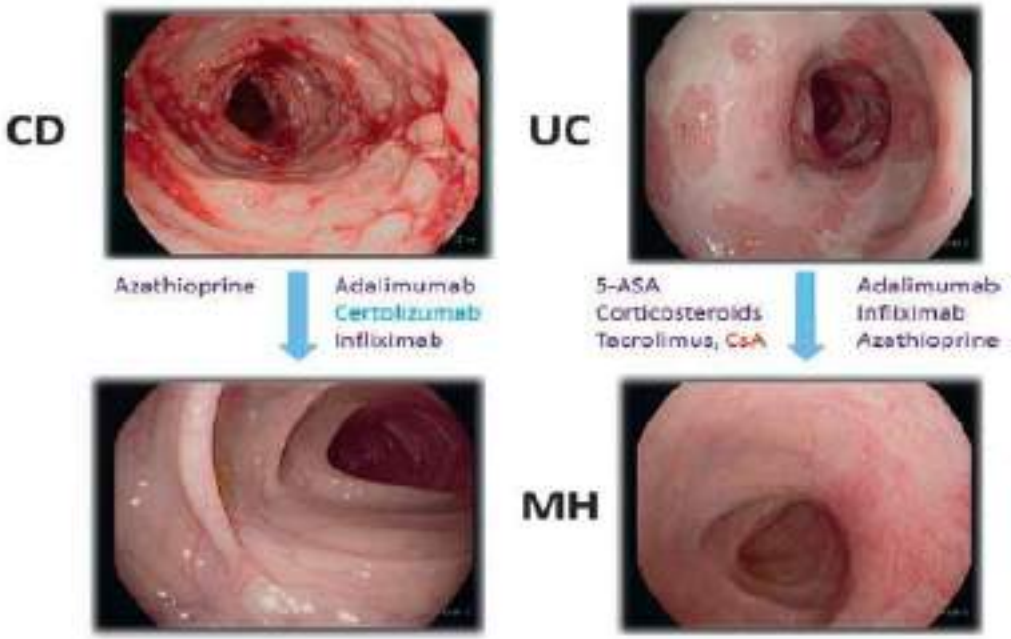


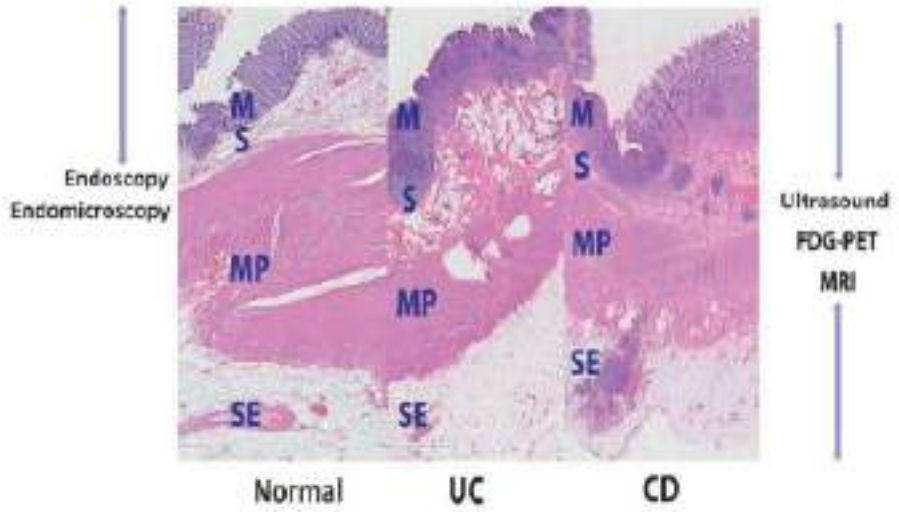
Crohn's disease



Ulcerative colitis

Peyrin-de Chambrun G, et al. Nat Rev Gastroenterol Hepatol 2010.





Crohn disease therapy

- **Oral Aminosalycilates**
- **Antibiotics**
- **Corticosteroids**

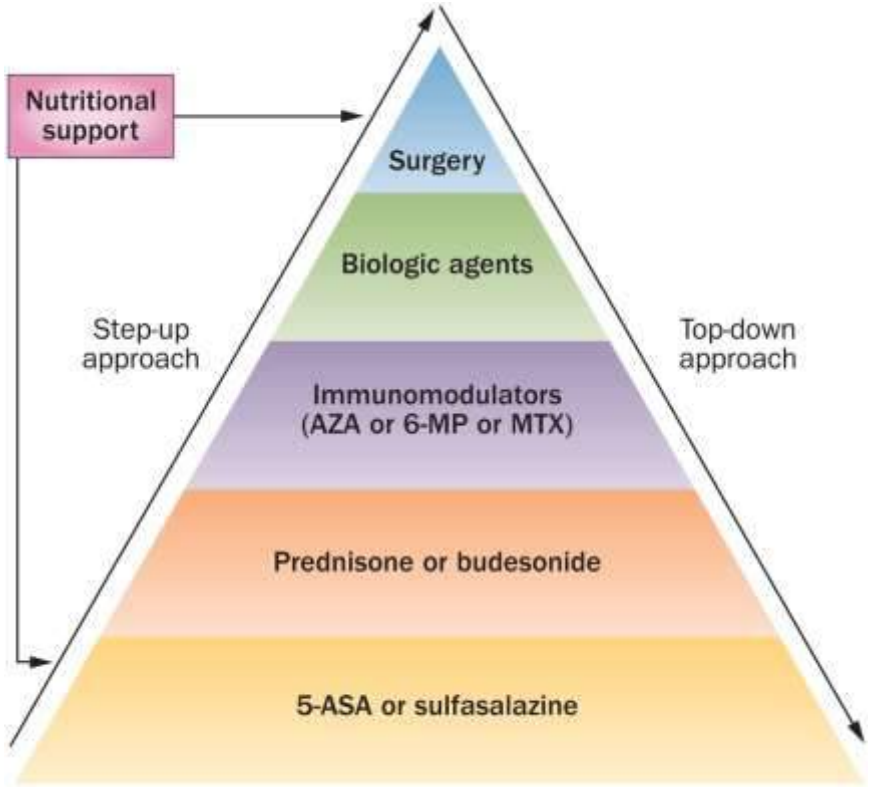
  (Budesonide, prednisolone or metyl-prednisolone)
- **Immune-suppressants**

  (Azathioprine, 6MP, MTX)
- **Biologic: anti-TNFα**

  (infliximab, adalimumab, certolizumab)
- **Biologic: anti integrin**

  (vedolizumab)

Therapeutic pyramid for IBD



Aloi, M. *et al.* (2013) Advances in the medical management of IBD
Nat. Rev. Gastroenterol. Hepatol. doi:10.1038/nrgastro.2013.158

Crohn disease acute onset with abdominal abcess

Medical therapy?
Surgery is an option?

Table 2. Agents and Regimens that May Be Used for the Initial Empiric Treatment of Extra-biliary Complicated Intra-abdominal Infection

		Community-acquired infection in adults	
Regimen	Community-acquired infection in pediatric patients	Mild-to-moderate severity: perforated or abscessed appendicitis and other infections of mild-to-moderate severity	High risk or severity: severe physiologic disturbance, advanced age, or immunocompromised state
Single agent	Ertapenem, meropenem, imipenem-cilastatin, ticarcillin-clavulanate, and piperacillin-tazobactam	Cefoxitin, ertapenem, moxifloxacin, tigecycline, and ticarcillin-clavulanic acid	Imipenem-cilastatin, meropenem, doripenem, and piperacillin-tazobactam
Combination	Ceftriaxone, cefotaxime, cefepime, or ceftazidime, each in combination with metronidazole; gentamicin or tobramycin, each in combination with metronidazole or clindamycin, and with or without ampicillin	Cefazolin, cefuroxime, ceftriaxone, cefotaxime, ciprofloxacin, or levofloxacin, each in combination with metronidazole[a]	Cefepime, ceftazidime, ciprofloxacin, or levofloxacin, each in combination with metronidazole[a]

[a] Because of increasing resistance of *Escherichia coli* to fluoroquinolones, local population susceptibility profiles and, if available, isolate susceptibility should be reviewed.

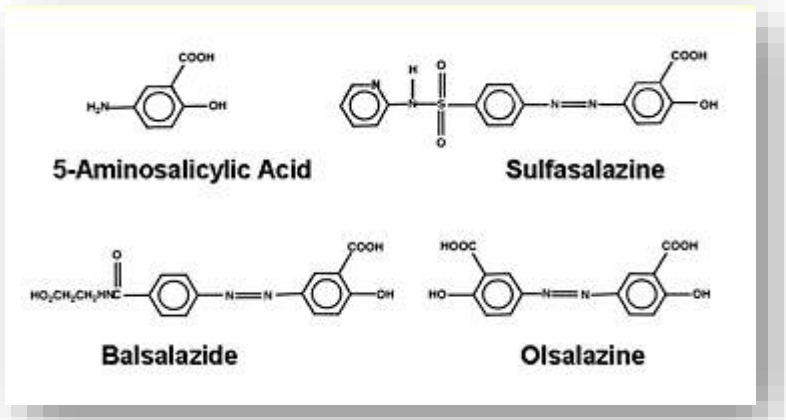
Crohn's disease antibiotic therapy

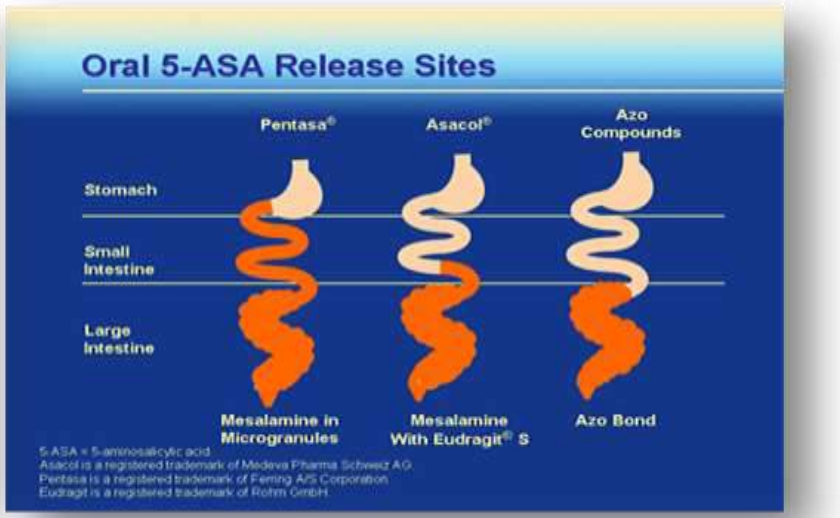
- Metronidazole is effective in active inflammatory, fistulous, and perianal CD and may prevent recurrence after ileal resection. The most effective dose is 250 mg x 4 per day ; it is usually continued for several months. Common side effects include nausea, metallic taste, and disulfiram-like reaction. Peripheral neuropathy can occur with prolonged administration (several months) and on rare occasions is permanent despite discontinuation.
- Ciprofloxacin (500 mg bid) is also beneficial for inflammatory, perianal, and fistulous CD. These two antibiotics should be used as second-line drugs in active CD after 5-ASA agents and as first-line drugs in perianal and fistulous CD. Rifaximin has modest activity in CD.

Middle to moderate active Localized ileal (L1)		**Middle to moderate active Extensive (L2, L3, L4)**		**Refractory ileal (L1)**		**Refractory severe (L2,L3,L4)**		**Perianal (B3p)**	**PS**
Induction Dose	Maintenance	Induction Dose	Maint.	Induction Dose	Maint.	Induction Dose	Maint.		
NR	NR	NR	NR	NR	NR	NR	NR	R	R

NR= non raccomandata R=raccomandata

CD treatment
Oral amoninosalycilates

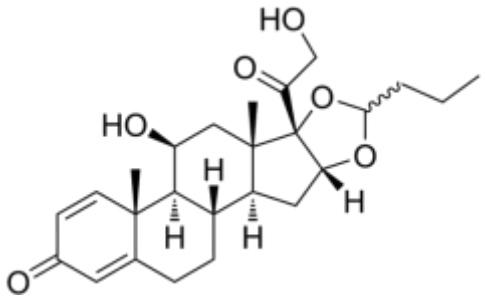




Middle to moderate active Localized ileal (L1)	Middle to moderate active Extensive (L2, L3, L4)	Refractory ileal (L1)	Refractory severe (L2,L3,L4)	Perianal (B3p)	Post surgery
NR	L2-L3 3-6 g/die	NR	NR	NR	NR

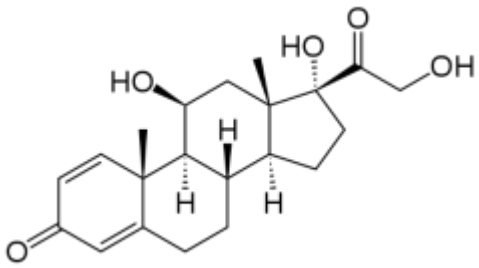
CD treatment
Steroids

Budesonide



3 mg x 3/die

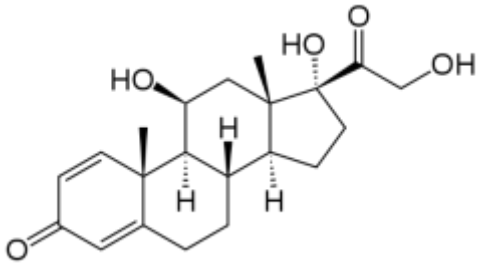
Prednisolone



1 mg/kg /die

CD treatment
Steroids

Prednisone



1 mg/kg/die

Middle to moderate active Localized ileal (L1)			Middle to moderate active Extensive (L2, L3, L4)			Refractory ileal (L1)			Refractory severe (L2,L3,L4)		Perianal (B3p)	PS
Induction	Dose	Maintenance	Induction	Dose	Maint.	Induction	Dose	Maint.	Induction	Dose		
R	40-60 mg/die	NR	R	40-60 mg/die	NR	R	40-60 mg/die	NR	R	R 40-60 mg/die	NR	NR

NR= non raccomandata R=raccomandata

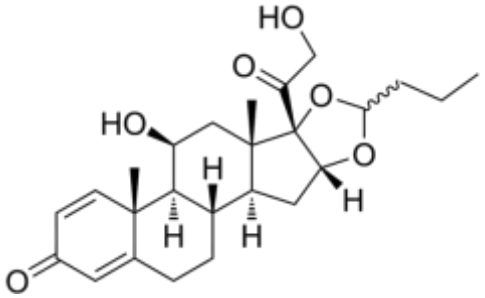
Steroids in Crohn disease

- Glucocorticoids are effective for treatment of moderate-to-severe CD and induce a 60–70% remission rate compared to a 30% placebo response.
- Glucocorticoids play no role in maintenance therapy in either UC or CD. Once clinical remission has been induced, they should be tapered according to the clinical activity, **normally at a rate of no more than 5 mg/week**. sis, are related to the dose and duration of therapy.

- Osteoporosis/osteonecrosis
- Higher risk of infections
- Oedema/Cushing syndrome
- Cataracts/glaucoma
- Growth retardation
- Behavioral changes
- Striae
- Diabetes
- Cardiovascular complications

CD treatment
Steroids

Budesonide



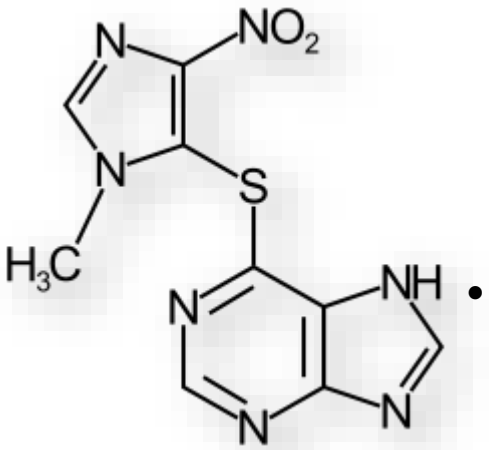
3 mg x 3/die

Middle to moderate active Localized ileal (L1)			Middle to moderate active Extensive (L2, L3, L4)		Refractory ileal (L1)		Refractory severe (L2,L3,L4)		Perianal (B3p)	PS
Induction	Dose	Maintenance	Induction	Dose Maint.	Induction	Dose Maint.	Induction	Dose		
R	9 mg/die	R	NR		NR		NR		NR	

NR= non raccomandata R=raccomandata

Immunomodulators

- Azathioprine



- Azathioprine and 6-mercaptopurine (6-MP) are purine analogues commonly employed in the management of glucocorticoid-dependent IBD. Azathioprine is rapidly absorbed and converted to 6-MP, which is then metabolized to the active end product, thioinosinic acid, an inhibitor of purine ribonucleotide synthesis and cell proliferation. These agents also inhibit the immune response. Efficacy is seen at 3–4 weeks.
- Azathioprine (2.0–3.0 mg/kg per day) or 6-MP (1.0–1.5 mg/kg per day) have been employed successfully as glucocorticoid-sparing agents in up to two-thirds of UC and CD patients previously unable to be weaned from glucocorticoids. The role of these immunomodulators as maintenance therapy in UC and CD and for treating active perianal disease and fistulas in CD appears promising.

Middle to moderate active Localized ileal (L1)			**Middle to moderate active Extensive (L2, L3, L4)**			**Refractory ileal (L1)**			**Refractory severe (L2,L3,L4)**			**Perianal (B3p)**	**PS**
Induction	Dose	Maintenance	Induction	Dose	Maint.	Induction	Dose	Maint.	Induction	Dose	Maint.		
NR		R 2 mg/Kg/die	NR	2 mg/Kg/die	R	NR					R	R	R

NR= non raccomandata R=raccomandata

Farmaci biologici approvati per il trattamento d

- **Anti-TNFα**

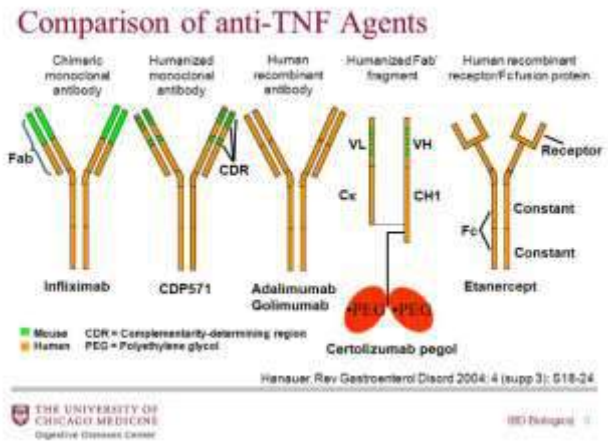
Infliximab (RCU-MC)

Adalimubab (CRU-MC)

Golimumab (RCU)

Certolizumab

Bruce Beutler (Noble Prize 2011)



- **Anti-Integrine (α4β7)**

Vedolizumab

Anti-TNFα

Infliximab (5 mg/kg at 0, 2 and 6 week) IV

Middle to moderate active Localized ileal (L1)			Middle to moderate active Extensive (L2, L3, L4)		Refractory ileal (L1)		Refractory severe (L2,L3,L4)		Perianal (B3p)	PS
Induction	Dose	Maintenance	Induction	Dose Maint.	Induction	Dose Maint.	Induction	Dose Maint.		
R		R	R	R	R	R	R	R	R	R

Adalimumab

Induction 160/80mg/kg at 0

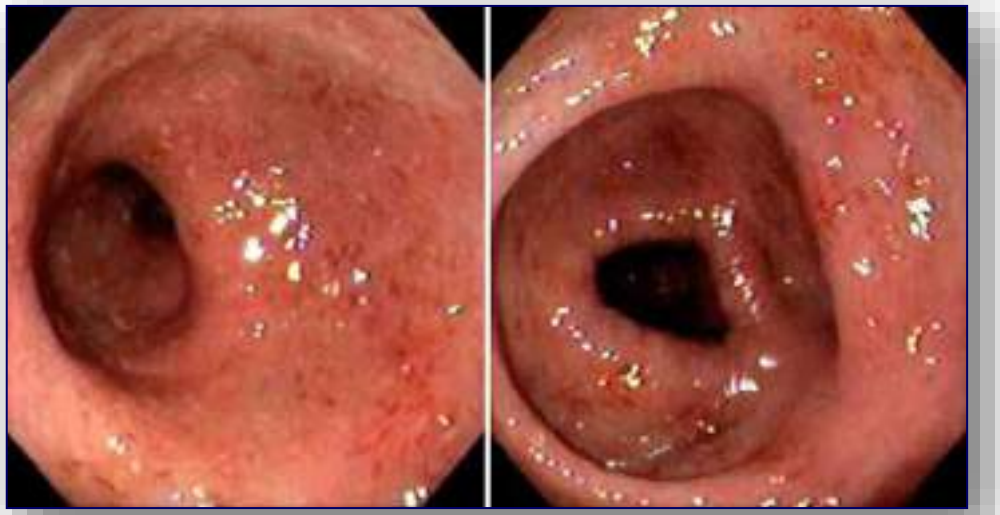
Maintenance 40 mg/ every 2 weeks

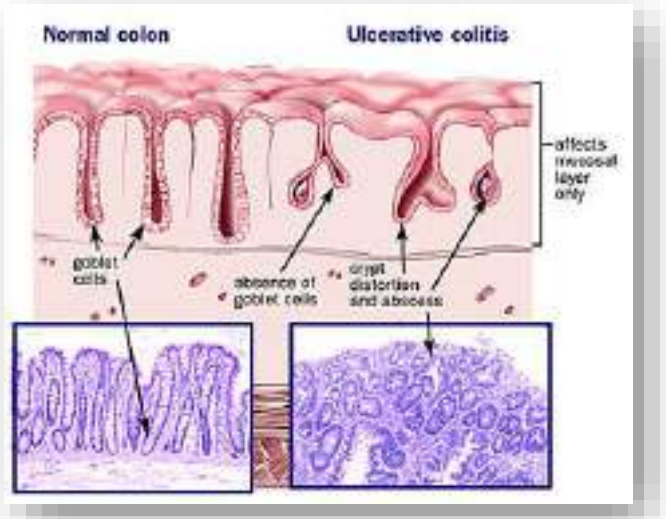
Middle to moderate active Localized ileal (L1)			Middle to moderate active Extensive (L2, L3, L4)		Refractory ileal (L1)		Refractory severe (L2,L3,L4)		Perianal (B3p)	PS
Induction	Dose	Maintenance	Induction	Dose Maint.	Induction	Dose Maint.	Induction	Dose Maint.		
R		R	R	R	R	R	R	R	R	R*

* Few data

Ulcerative colitis

IBDs pathology: UC

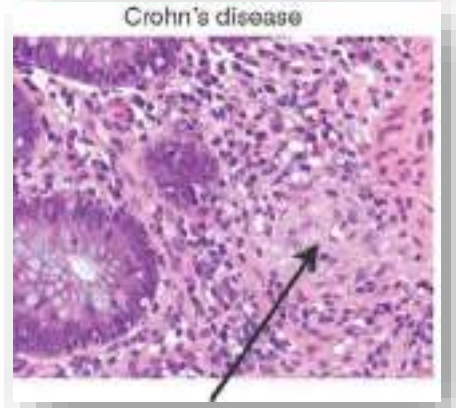


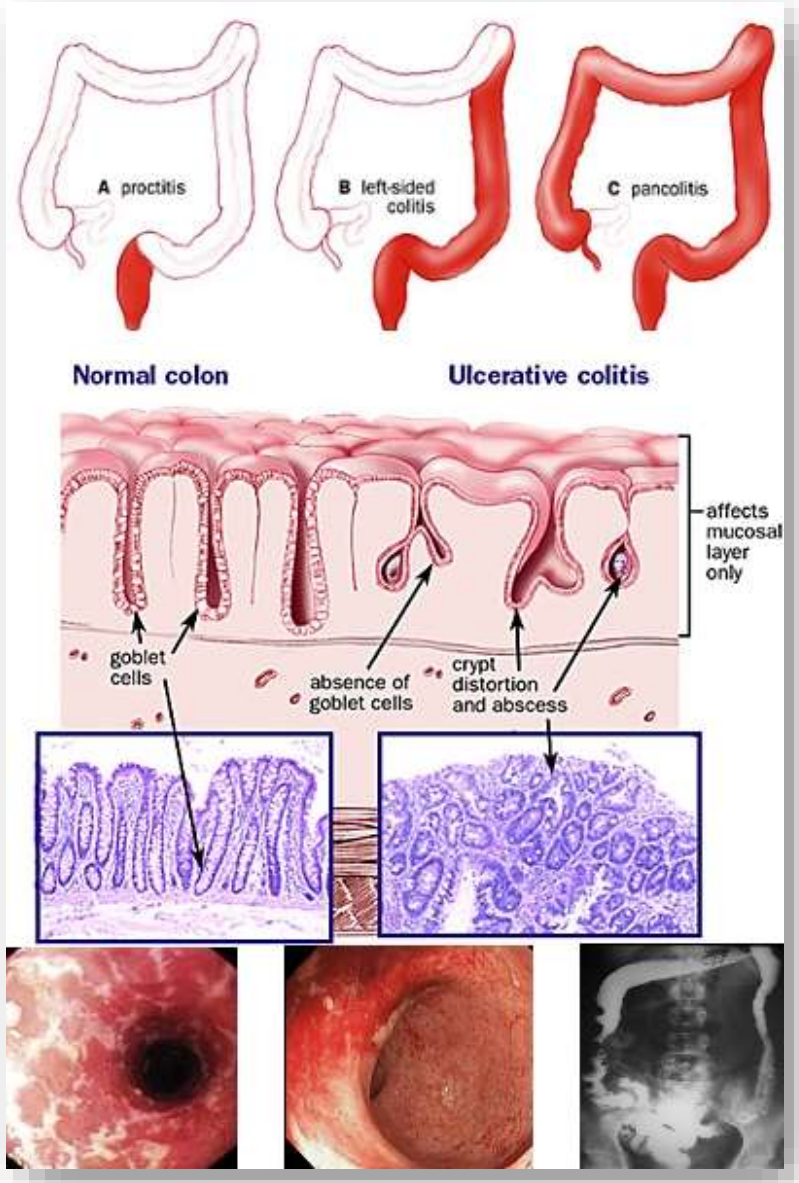


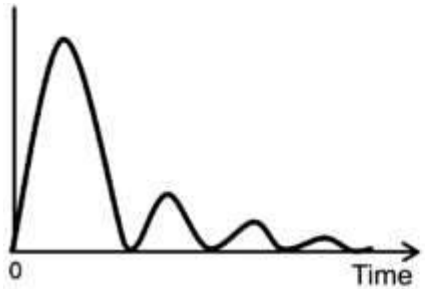
In the UC the process is limited to **the mucosa and superficial submucosa**, with deeper layers unaffected except in fulminant disease. In UC, two major histologic features suggest chronicity and help distinguish it from infectious or acute self-limited colitis. **First, the crypt architecture of the colon is distorted;** crypts may be bifid and reduced in number, often with a gap between the crypt bases and the muscularis mucosae. Second, some patients have basal plasma cells and multiple basal lymphoid aggregates. Mucosal vascular congestion, with edema and focal hemorrhage, and an inflammatory cell infiltrate of neutrophils, lymphocytes, plasma cells, and macrophages may be present. The neutrophils invade the epithelium, usually in the crypts, giving rise to cryptitis and, ultimately, to crypt abscesses

IBDs: pathology

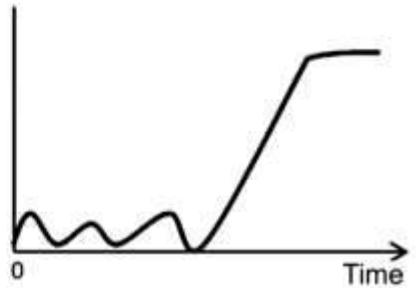
Crohn's	Features	Ulcerative colitis
Normal	Goblet cells	Depleted
Scanty	Crypt abcesses	Common
Preserved	Glandular architecture	Distorted atrophic
Patchy, heavy in places	Lymphocytic infiltrate	Uniformly heavy
Present	Granulomas	Absent
Normal	Muscularis mucosae	Thickened
Disproportionately heavy	Submucosal inflammation	Little





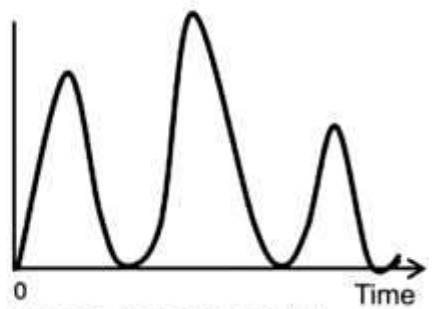


Curve 1: Remission or mild severity of intestinal symptoms after initial high activity



Curve 2: Increase in the severity of intestinal symptoms after initial low activity

Curve 3: Chronic continuous symptoms



Curve 4: Chronic intermittent symptoms

UC: clinical by topography

Ulcerative proctitis. In this form of ulcerative colitis, inflammation is confined to the area closest to the anus (rectum), rectal bleeding may be the only sign of the disease. Rectal pain, a feeling of urgency or frequent, small bowel movements. This form of ulcerative colitis tends to be the mildest.

Left-sided colitis. As the name suggests, inflammation extends from the rectum up through the sigmoid and descending colon. Signs and symptoms include bloody diarrhea, abdominal cramping and pain on the left side, and unintended weight loss.

Pancolitis. Affecting more than the left colon and often the entire colon, pancolitis causes bouts of bloody diarrhea that may be severe, abdominal cramps and pain, fatigue, and significant weight loss.

Table 1.2 Distribution of ulcerative colitis (from[16]).

Term	Distribution	Description
E1	Proctitis	involvement limited to the rectum (ie proximal extent of inflammation is distal to the rectosigmoid junction)
E2	Left-sided	involvement limited to the proportion of the colon distal to the splenic flexure (analogous to 'distal' colitis)
E3	Extensive	involvement extends proximal to the splenic flexure, including pancolitis

UC clinical by severity
Disease activity in UC

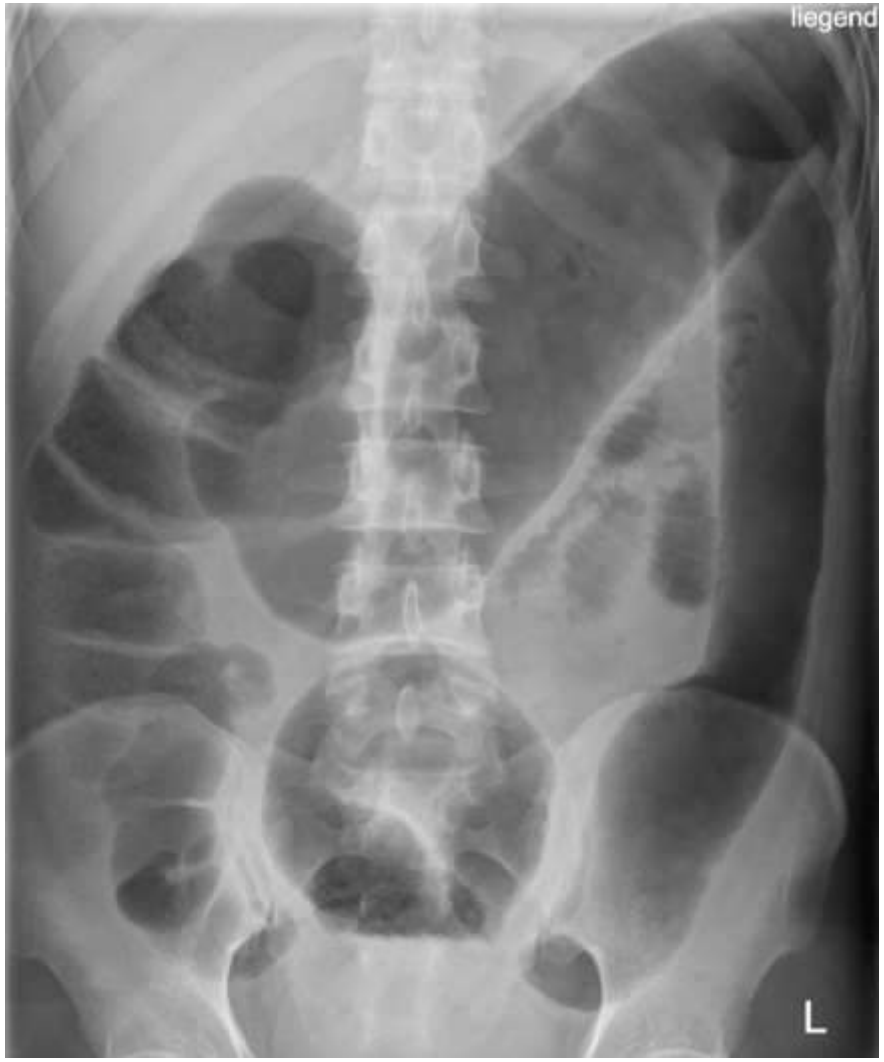
Table 1.5 Montréal classification of disease activity in ulcerative colitis.[16]

	S0 Remission	S1 Mild	S2 Moderate	S3 Severe
Stools/day	Asymptomatic	≤4	>4	≥6 *and*
Blood		May be present	Present	Present
Pulse		All	minimal, or no signs	>90 bpm *or*
Temperature		Normal	of systemic toxicity	>37.5 °C *or*
Haemoglobin				<10.5 g/dL *or*
ESR				>30 mm/h

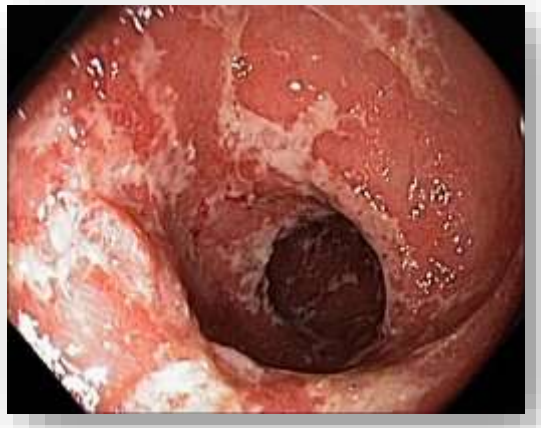
Fulminat colitis

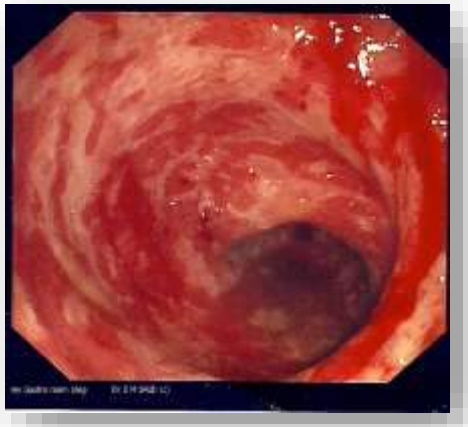
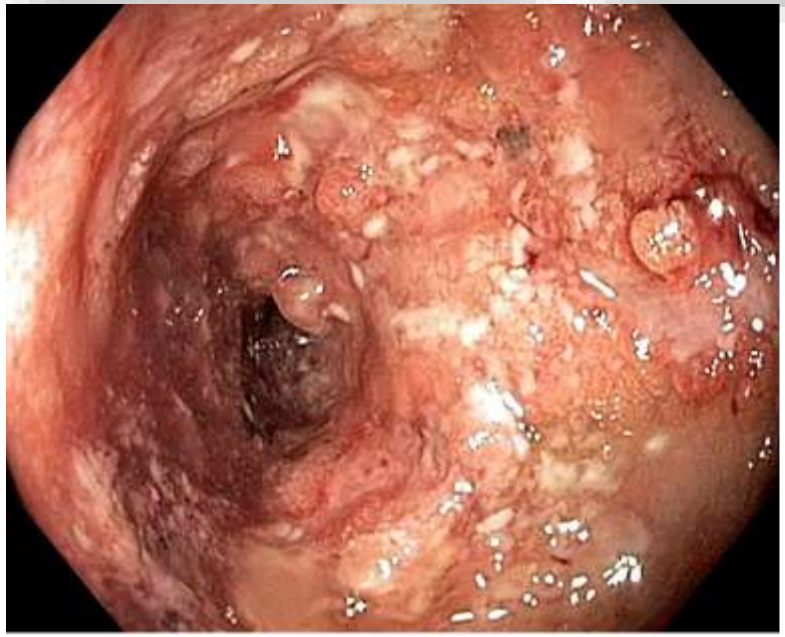
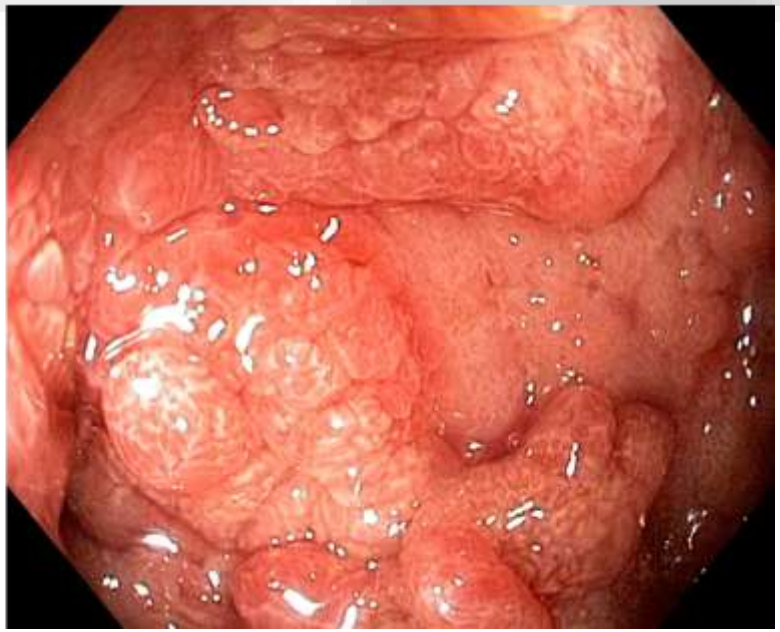
This rare, life-threatening form of colitis affects the entire colon and causes severe pain, profuse diarrhea and, sometimes, dehydration and shock.

People with fulminant colitis are at risk of serious complications, including colon rupture and toxic megacolon, a condition that causes the colon to rapidly expand.



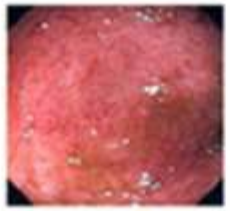
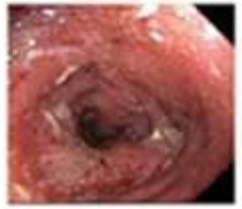
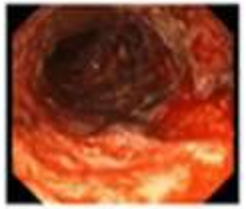
Ulcerative colitis



UC endoscopy: staging

Endoscopic Severity of Disease

0 = NORMAL	1 = MILD	2 = MODERATE	3 = SEVERE
			
• No friability or granularity • Intact vascular pattern	• Erythema • Decreased vascular pattern • Mild friability	• Marked erythema • Absent vascular pattern • Friability • Erosions	• Marked erythema • Absent vascular markings • Granularity • Friability • Spontaneous bleeding • Ulcerations

de Chambrun GP, et al. *Nat Rev Gastroenterol Hepatol.* 2010;7:15-29.

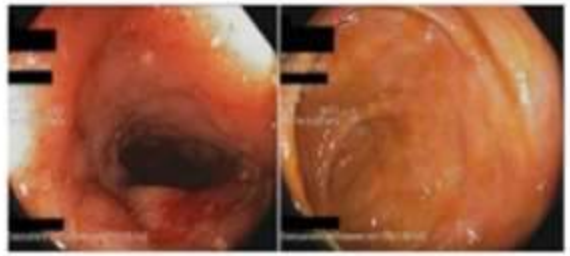
UC and mucosal healing

There is no validated definition of MH in IBD

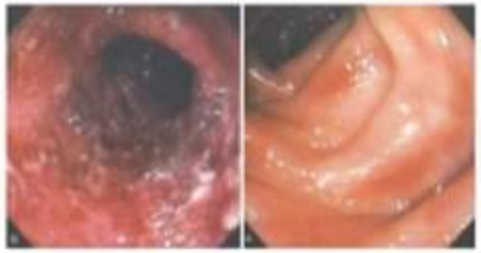
The „ideal“ definition of Mucosal Healing (MH) could be ***complete endoscopic healing of all inflammatory and ulcerative lesions of the gut mucosa*** in CD and UC

In CD, an endoscopic response to treatment can be defined as “absence of ulcers” or a significant change of endoscopic disease activity score (CDEIS or SES-CD).

In UC, an endoscopic response to treatment can be defined as a significant change of endoscopic disease activity score (Baron score or Mayo endoscopic subscore).



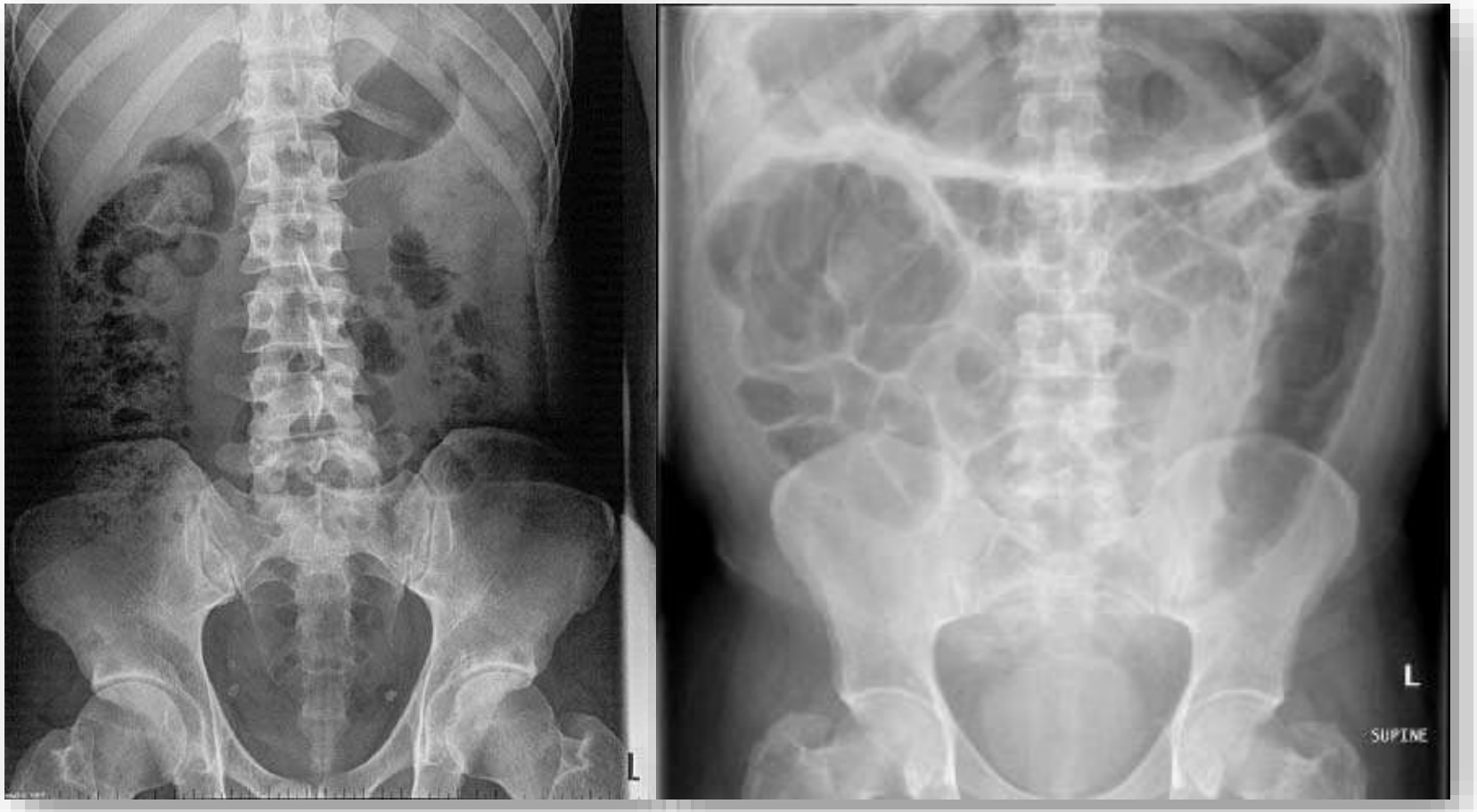
Crohn’s disease



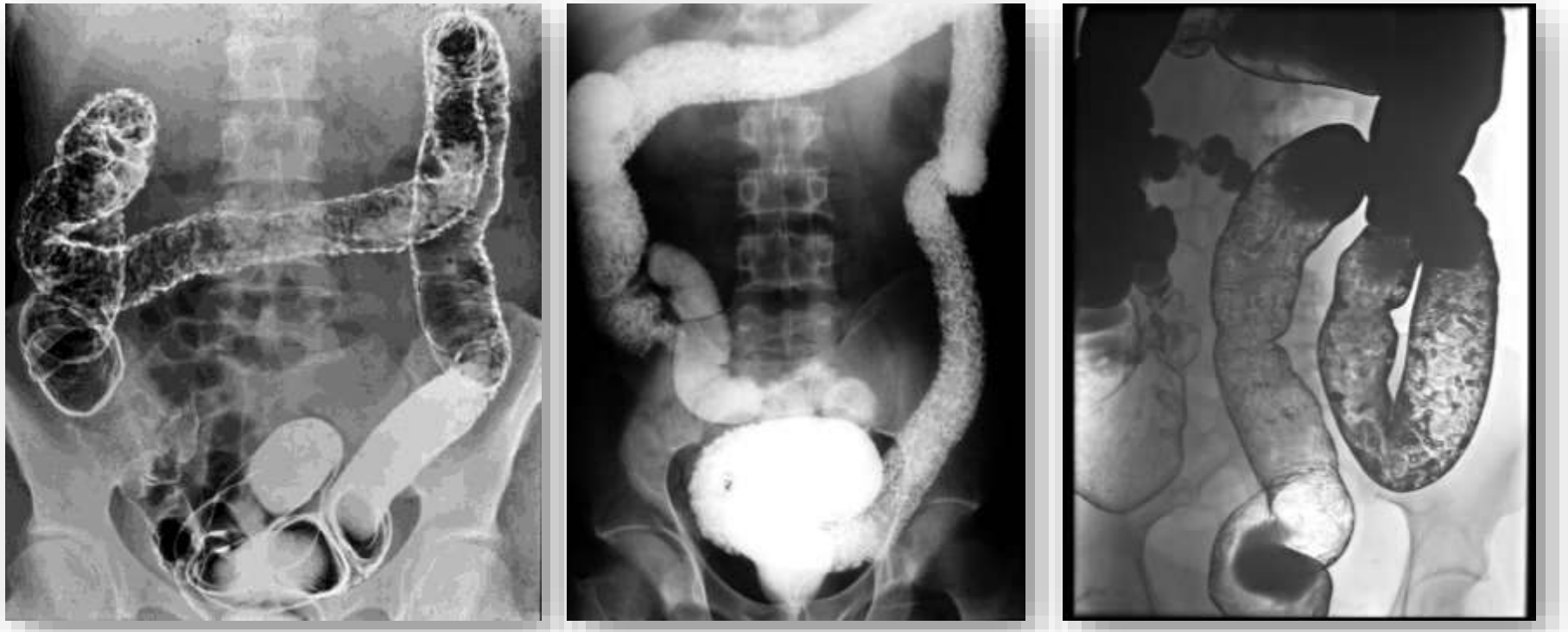
Ulcerative colitis

Pineton de Chambrun G, et al. Nat Rev Gastroenterol Hepatol 2010.

Ulcerative colitis: Rx



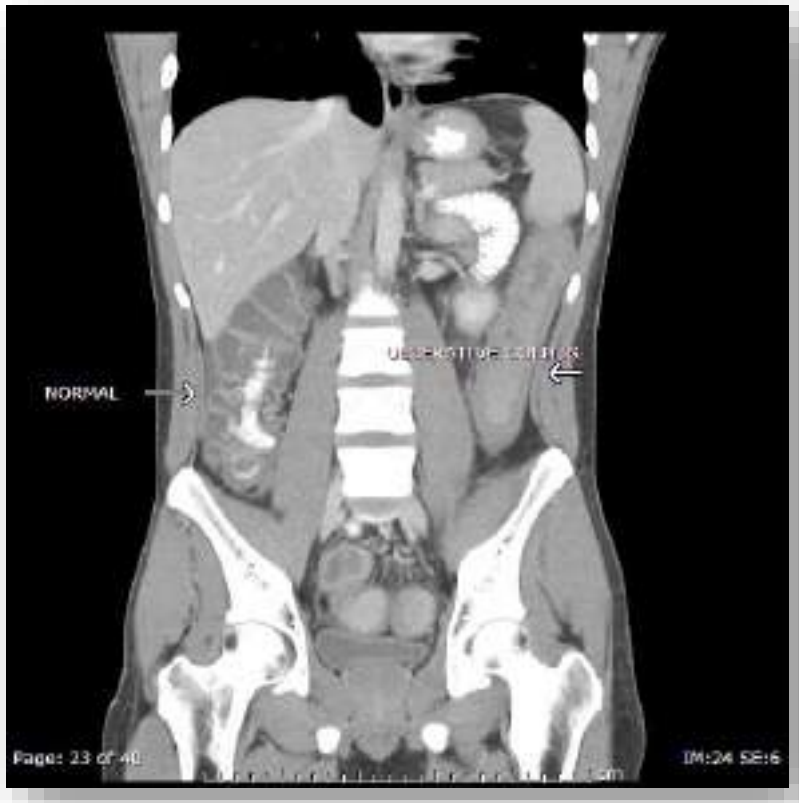
Ulcerative colitis: barium enema

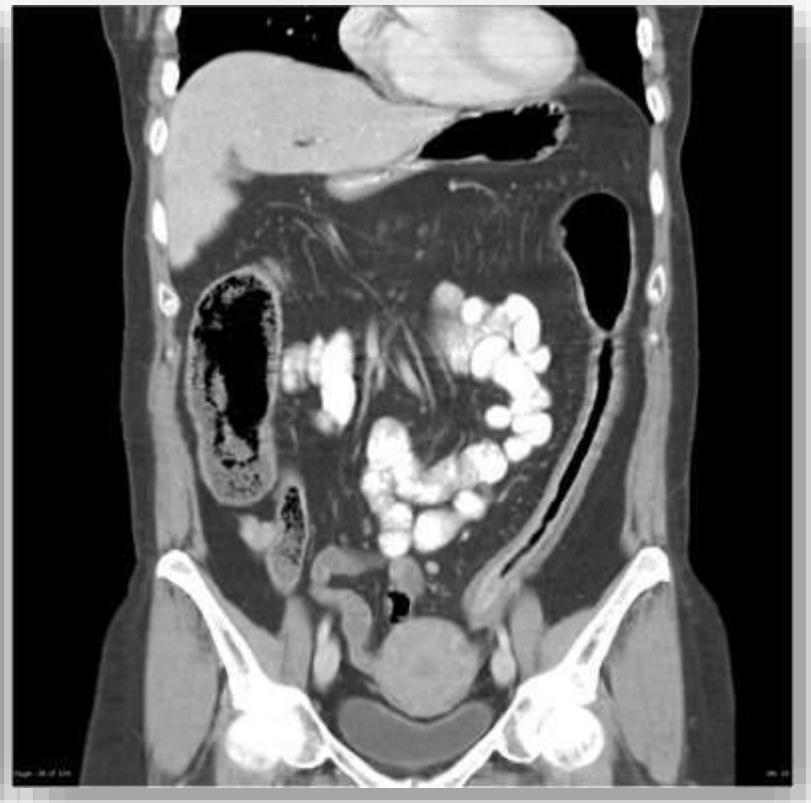


Double-contrast barium enema

- This examination method can be used to assess the extent and severity of IBD and to differentiate UC from CD.
- Precise data on sensitivity and specificity for diagnosis and for determining the extent and severity of colonic IBD are lacking. In the modern colonoscopy era, DCBE is rarely used in IBD patients.

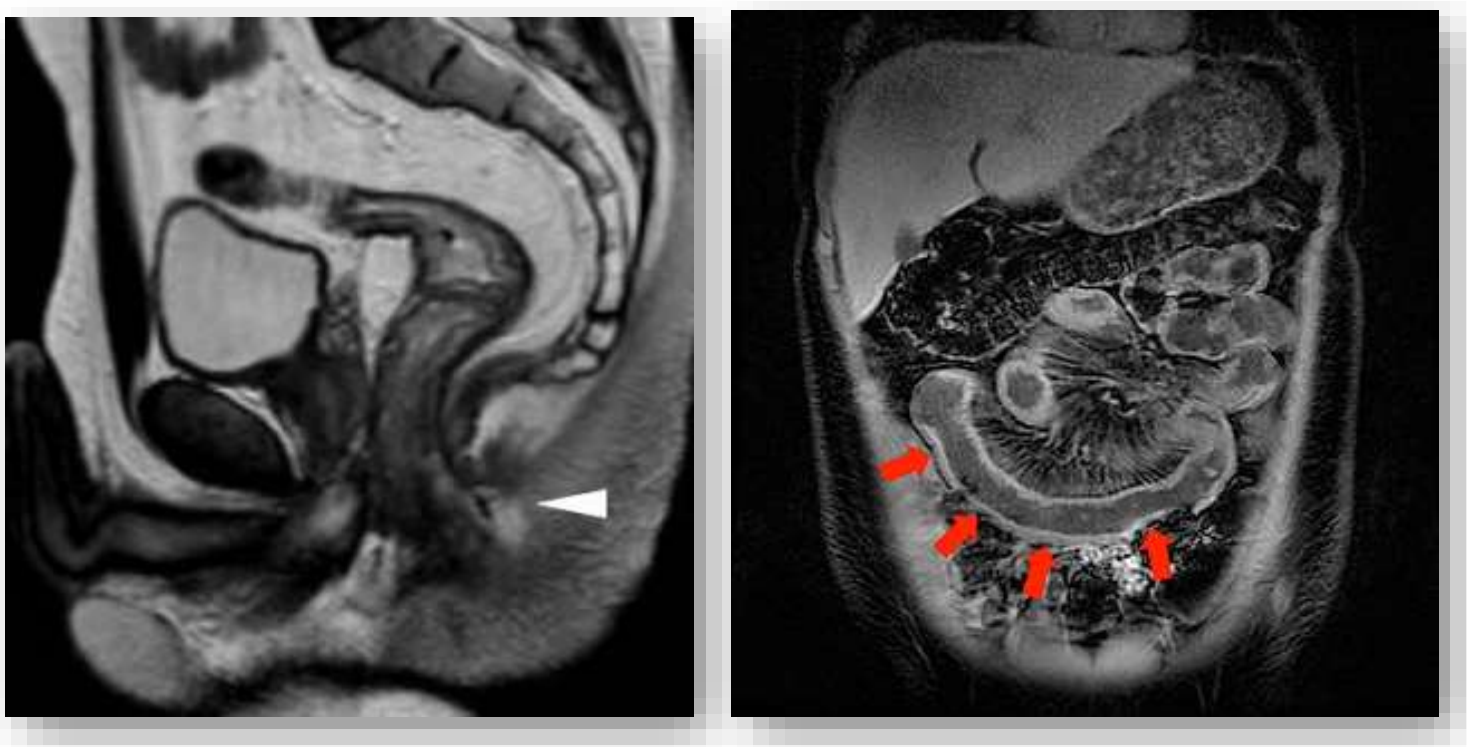
Ulcerative colitis. CT



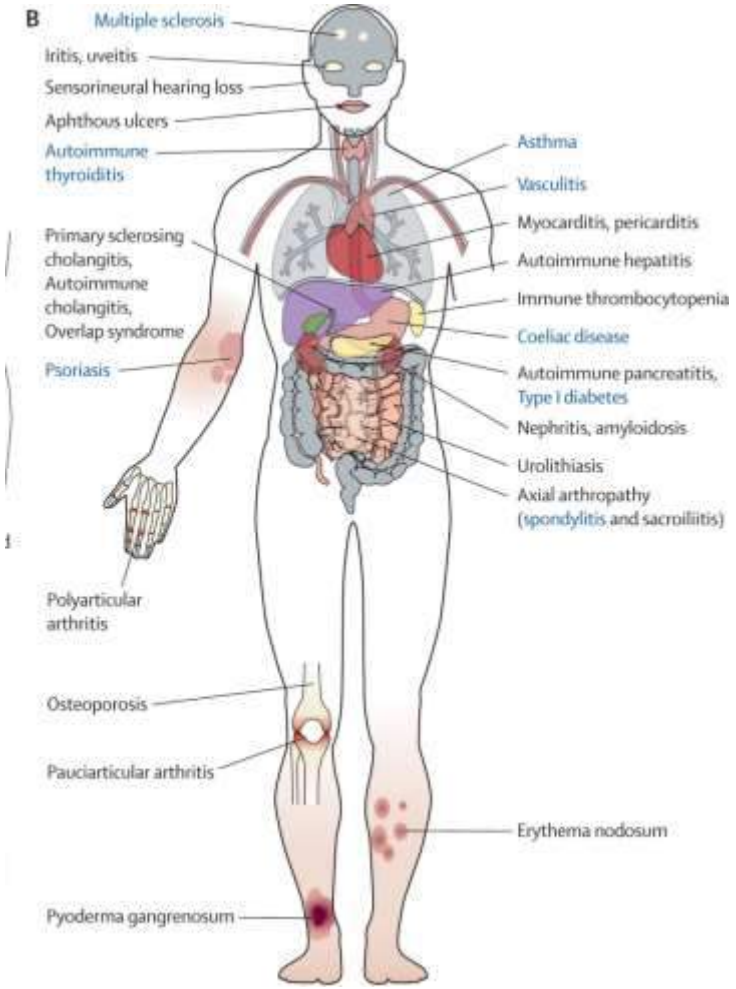


Only a few studies have compared CT results with the results of other imaging methods for evaluation of IBD. CT sensitivity for colonic IBD changes has been reported to be 69% to 84%. [18] An emerging technique is CT colonography

Ulcerative colitis: MR



Ulcerative colitis : systemic disease



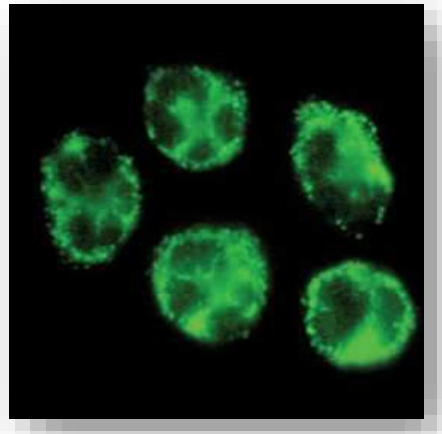
The Lancet 2012 380, 1590-1605DOI: (10.1016/S0140-6736(12)60026-9)

UC's disease

Laboratory findings:

- Elevated **VES and PCR, fibrinogen, alpha$_1$-glicoprotein, increased platets count and anemia (iron deficiency**

- Two antibodies that can be detected in the serum of IBD patients are perinuclear antineutrophil cytoplasmic antibodies (pANCAs) and anti-Saccharomyces cerevisiae antibodies (ASCAs).
- A distinct set of pANCAs is associated with UC.
- **pANCA in CD is associated with colonic disease that resembles UC.**

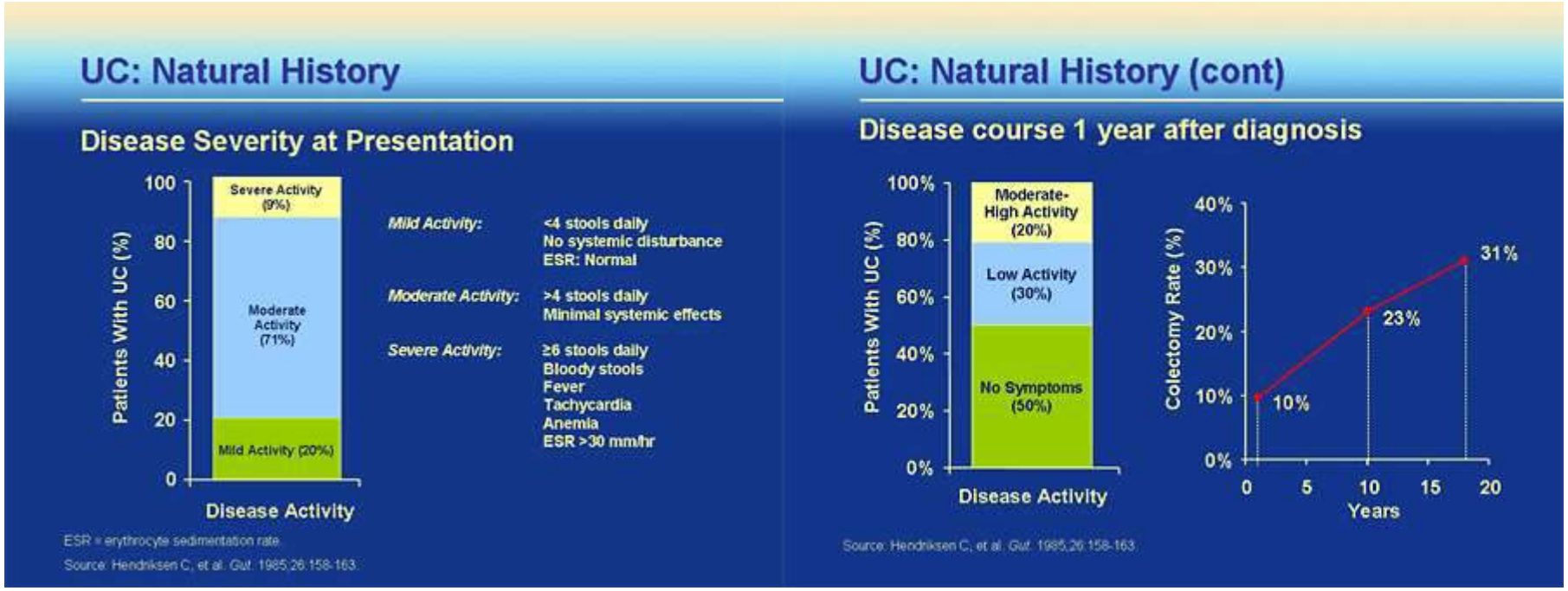


pANCA indicates a local vasculitis

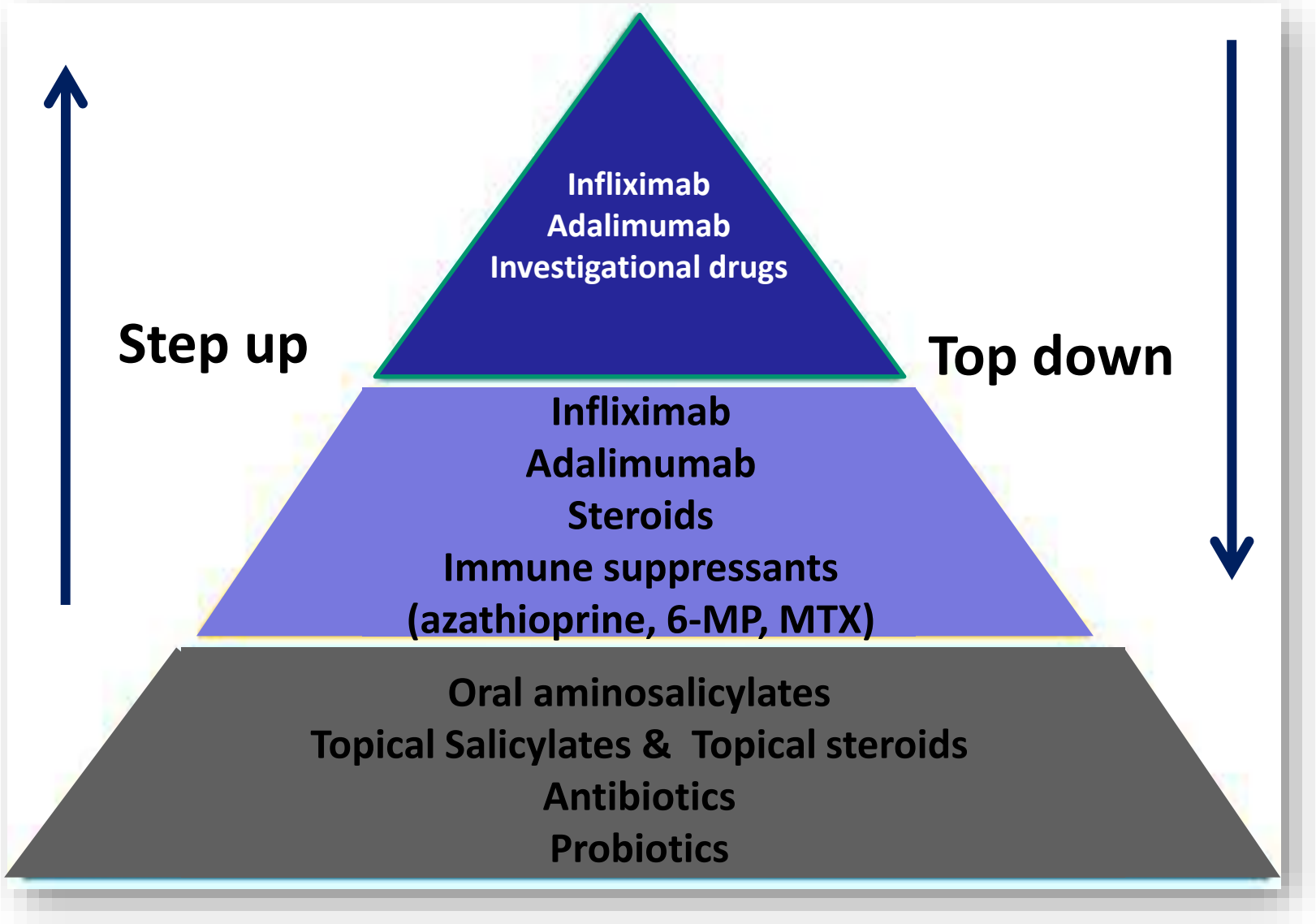
Keys factors in Ulcerative colitis

- Risk factors: genotype and environment (smoking and appendectomy are protective factors)
- Onset of disease: usually between 15 and 40 years
- Location: inflammation affects the colon only (distal colitis or proctitis (55%), left-sided colitis (25%) and pancolitis (20%))
- Pathology: continuous inflammation from the rectum to proximal parts of the colon
- Histology: superficial inflammation (mucosa and submucosa)
- Symptoms: diarrhoea (bloody), abdominal cramping, anaemia, weight loss and fatigue
- Extra-intestinal inflammatory manifestations: various organs and systems are affected, for example, joints, skin, liver, eye, mouth and blood (coagulation)
- Complications: severe bleeding, toxic megacolon, rupture of the bowel and colon cancer

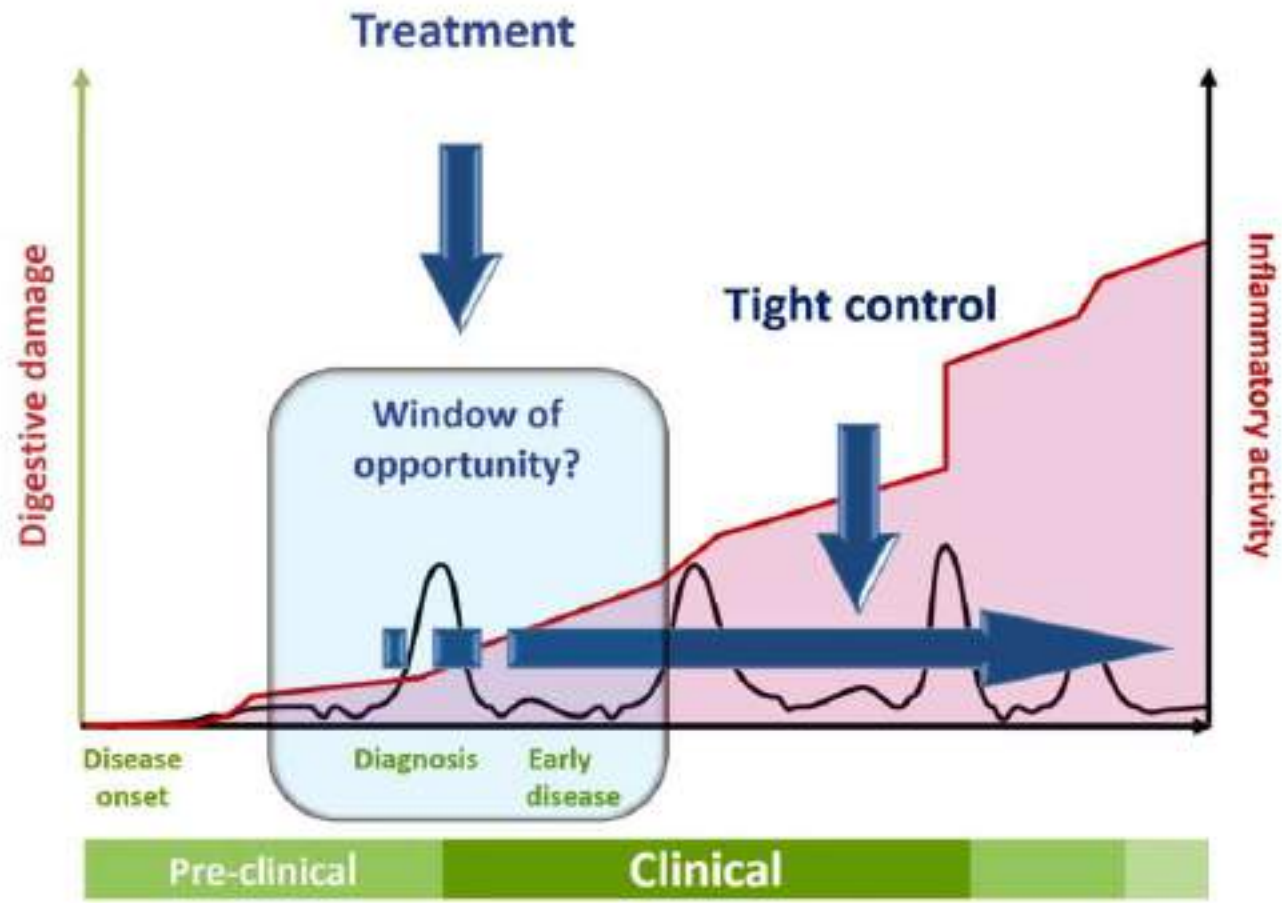
Ulcerative colitis: natural history



Therapeutic strategies in IBD



“window of opportunity” in IBD



Ulcerative colitis: therapy

Induction of remission

Ulcerative colitis: therapy

Proctitis

A mesalazine 1 g suppository or enema once daily is the preferred initial treatment for mild or moderately active proctitis.

Mesalazine foam enemas are an alternative (4 gr)
Suppositories may deliver drug more effectively to the rectum and are better tolerated than enemas.

Combining topical mesalazine with oral mesalazine or topical steroid is more effective than either alone and should be considered for escalation of treatment.

Oral mesalazine alone is less effective.

Refractory proctitis may require treatment with immunosuppressants and/or biologics

Ulcerative colitis: therapy

Left side

Left-sided active ulcerative colitis of **mild–moderate severity** should initially be treated with an **aminosalicylate enema 1 g/day combined with oral mesalazine 2 g/day**

Topical therapy with steroids or aminosalicylates alone as well as mono-therapy with oral aminosalicylates is less effective than oral plus topical 5ASA therapy.

Topical mesalazine is more effective than topical steroid.

Once daily dosing with 5ASA is as effective as divided doses.
Systemic corticosteroids are appropriate if symptoms of active colitis do not respond to mesalazine

Severe left-sided colitis is usually an indication for hospital admission for intensive treatment with systemic therapy

Ulcerative colitis: therapy
Pancolitis

Extensive ulcerative colitis of mild–moderate severity should initially be treated with oral 5-ASA 2 g/day which should be combined with topical mesalazine to increase remission rates if tolerated.

Once daily dosing with 5ASA is as effective as divided doses

Systemic corticosteroids are appropriate if symptoms of active colitis do not respond to mesalazine.

Severe extensive colitis is an indication for hospital admission for intensive treatment including IV steroids

Patients with bloody diarrhoea ≥6/day and any signs of systemic toxicity (tachycardia 90 bpm, fever 37.8 °C, Hb b10.5 g/dL, or an ESR 30 mm/h)

Ulcerative colitis: therapy

Pancolitis

The response to **intravenous steroids (1 mg/kg)** is best assessed objectively around the third day

Treatment options **including colectomy** should be discussed with patients with severely active UC not responding to intravenous steroids.

Second line therapy with either ciclosporin or infliximab or tacrolimus may be appropriate.

If there is no improvement within 4–7 days of salvage therapy, colectomy is recommended

Patients with bloody diarrhoea ≥6/day and any signs of systemic toxicity (tachycardia 90 bpm, fever 37.8 °C, Hb b10.5 g/dL, or an ESR 30 mm/h)

Ulcerative colitis: therapy

Maintenance

The goal of maintenance therapy in UC is to maintain steroid-free remission without clinical and endoscopic signs

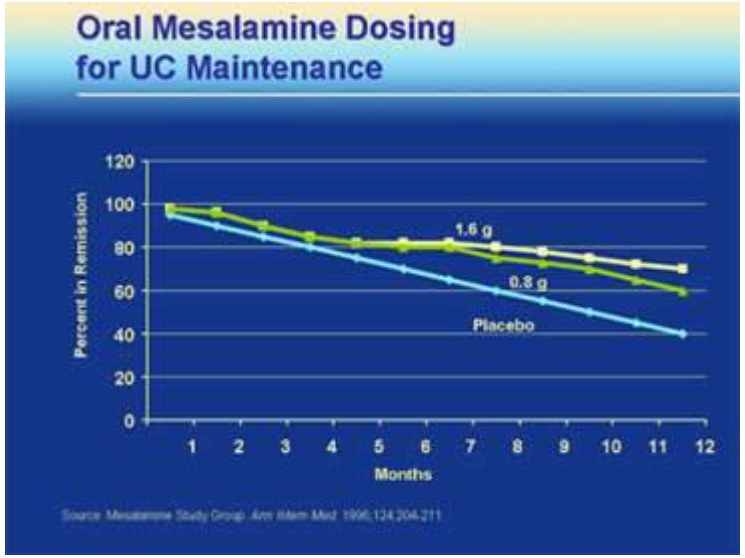
Maintenance treatment is recommended for all patients

Intermittent therapy is acceptable in a few patients with disease of limited extent

Oral 5-aminosalicylate (5-ASA) containing compounds are the first line maintenance treatment in patients responding to 5-ASA or steroids (oral or rectal).
A combination of oral and rectal 5-ASA can be used as a second line maintenance treatment

Ulcerative colitis: therapy

5-ASA maintenance



The minimum effective dose of oral 5-ASA is 1.2 g per day

For rectal treatment 3 g/week in divided doses is sufficient to maintain remission.

There is no robust evidence to support the choice of any specific 5-ASA preparation for maintenance

Ulcerative colitis: therapy

Azathioprine/Anti-TNF maintenance

Azathioprine/mercaptopurine is recommended for patients with mild to moderate disease activity who have experienced early or frequent relapse whilst taking 5-ASA at optimal dose or who are intolerant to 5-ASA patients that are steroid-dependent] and for patients responding to ciclosporin (or tacrolimus) for induction of remission.

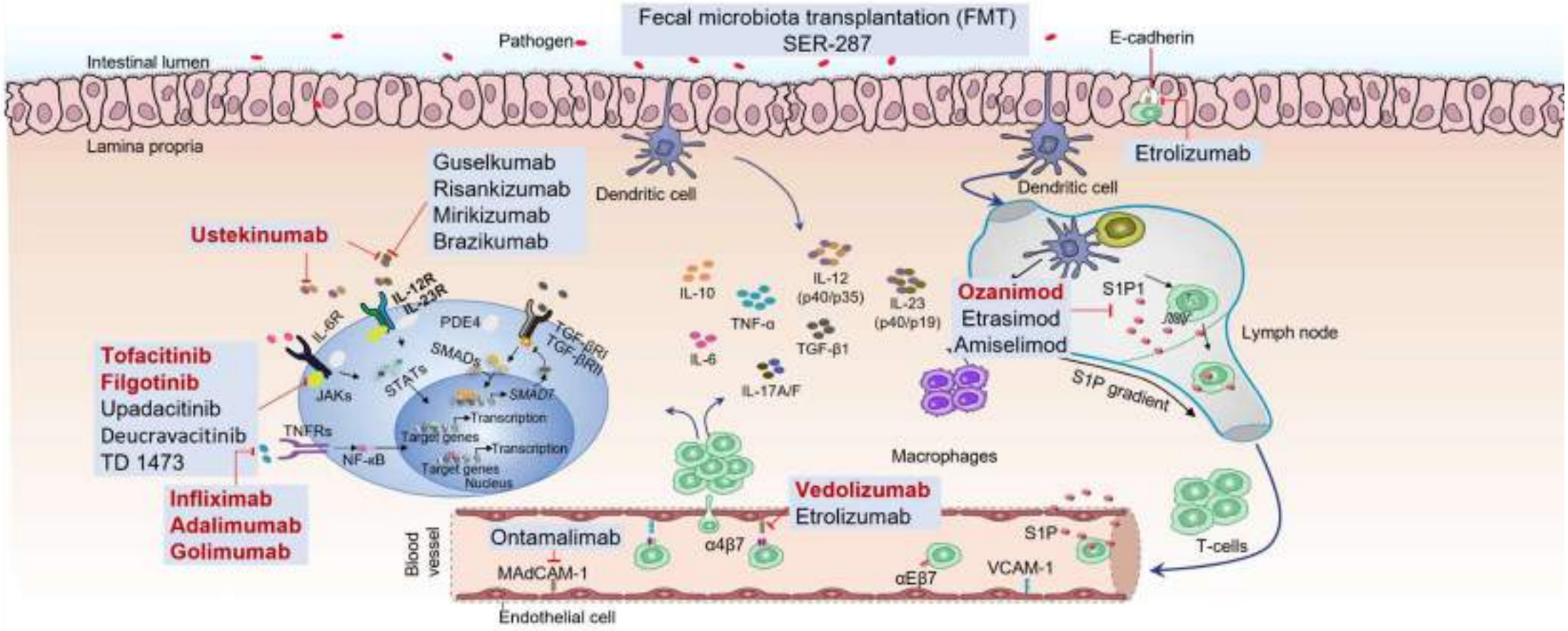
In patients responding to anti-TNF agents, both maintaining remission with azathioprine/mercaptopurine and continuing anti-TNF therapy with or without thiopurines are appropriate.

In patients with severe colitis responding to intravenous steroids, intravenous ciclosporin or infliximab, **azathioprine/ mercaptopurine should be considered to maintain remission**

However, in patients responding to **infliximab continuing infliximab** is also appropriate

The prior failure of thiopurines favours maintenance with anti-TNF therapy

The evolving IBD treatment landscape



Adapted from Nielsen OH, et al. Expert Opin Investig Drugs ,2016;25:709-18; Coskún M, et al. Trends Pharm Sci. 2017;38:127-42; Torres J, et al. Lancet 2017;389:1741-55; Ungaro R, et al. Lancet. 2017;389:1756-70; Privitera G, et al. Therap Adv Gastroenterol. 2021 Apr 27;14:17562848211006669. doi: 10.1177/17562848211006669.

Which options (2022) after "conventional" treatment's failure?

Mechanism of action	Drug name	Crohn's disease	Ulcerative colitis
Anti-TNF (MAb)	Infliximab Infliximab biosimilar	✓	✓
	Certolizumab pegol	✓ Not approved in EU	NA
	Adalimumab Adalimumab biosimilar	✓	✓
	Golimumab	NA	✓
Anti-adhesion (MAb)	Natalizumab	✓ Not approved in EU	NA
	Vedolizumab	✓	✓
S1P receptor modulator	Ozanimod	X	✓
Anti-IL12/23 (MAb)	Ustekinumab	✓	✓
eASC (MSC)	Darvadstrocel	✓ Perianal CD	NA
Anti-JAK (SM)	Tofacitinib (JAK 1-3) Filgotinib (JAK 1)	X	✓

Ulcerative Colitis complications colorectal cancer

- Patients with long-standing UC are at increased risk for developing colonic epithelial dysplasia and carcinoma

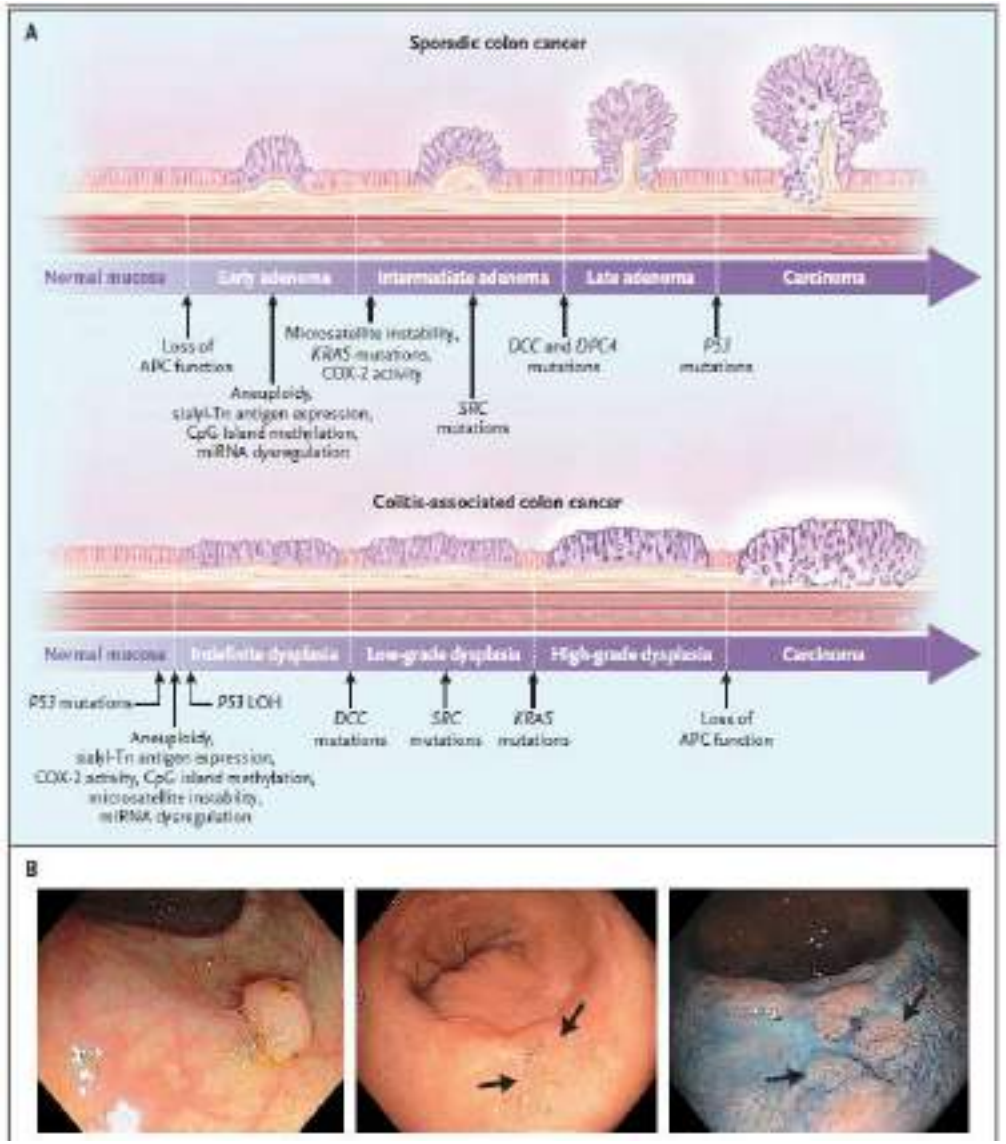
- The risk of neoplasia in chronic UC increases with duration and extent of disease. **The risk of cancer rises 0.5–1% per year after 8–10 years of disease in patients with pancolitis. The only prospective surveillance study reported a lower rate of cancer; 2.5% at 20 years of disease, 7.6% at 30 years of disease, and 10.8% at 40 years. The rates of colon cancer are higher than in the general population, and colonoscopic surveillance is the standard of care.**

- Annual or biennial colonoscopy with multiple biopsies is recommended for patients **with >8–10 years of pancolitis or 12–15 years** of left-sided colitis and has been widely employed to screen and survey for subsequent dysplasia and carcinoma. Risk factors for cancer in UC include long-duration disease, extensive disease, family history of colon cancer, PSC, a colon stricture, and the presence of postinflammatory pseudopolyps on colonoscopy.

IBD and colon cancer

Colon Cancer and IBD

- Equal risk for UC and CD with colitis
- Depends on extent of colitis and duration
- Risk increases after 8-10 years
- Need to screen for flat lesions
- 2.5% risk after 20 years
- 7.6% risk after 30 years



N Engl J Med 2015;372:1441-52.
DOI: 10.1056/NEJMra1403718

Table 1. Risk Factors for Colorectal Cancer in Patients with Inflammatory Bowel Disease.

Risk factors established in the general population
Increasing age*
Male sex*
History of colorectal cancer in first-degree relatives*
Increased body-mass index†
Low level of physical activity†
Cigarette smoking†
High consumption of red meat†
Consumption of alcohol†
Risk factors specific to patients with inflammatory bowel disease
Coexisting primary sclerosing cholangitis
Increasing cumulative extent of colonic inflammatory lesions‡
Increasing duration of inflammatory bowel disease§
Active chronic endoscopically assessed inflammation
Active chronic histologically assessed inflammation
Anatomical abnormalities
Foreshortened colon
Strictures
Pseudopolyps
Personal history of flat dysplasia

N Engl J Med 2015;372:1441-52.
DOI: 10.1056/NEJMra1403718

Surgery in UC

BOX 116-9 Indications for Surgery in Patients with UC

Colonic dysplasia or carcinoma
Colonic perforation
Growth retardation
Intolerable or unacceptable side effects of medical therapy
Medically refractory disease
Systemic complications that are recurrent or unmanageable
Toxic megacolon
Uncontrollable colonic hemorrhage

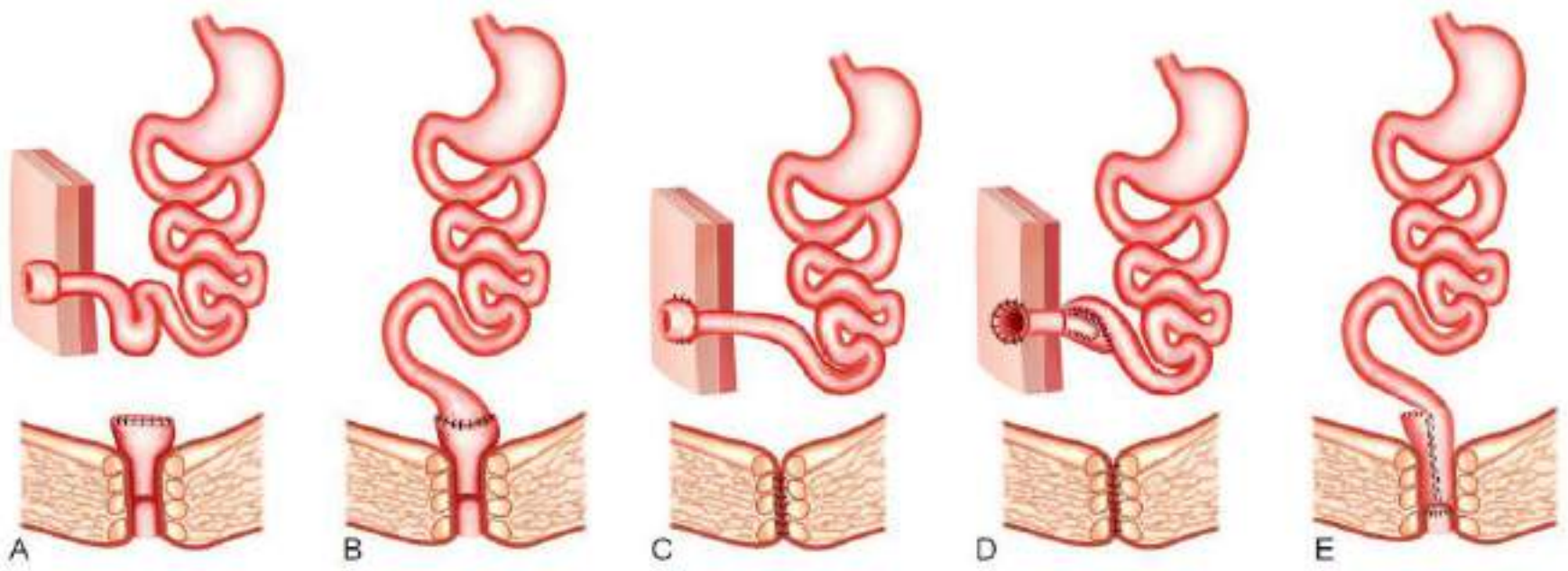
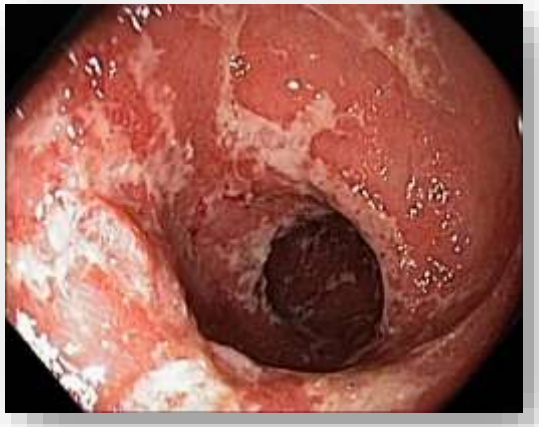


FIGURE 116-16. Schematic diagrams of various surgical options for the management of UC. *A*, Conventional (Brooke) ileostomy with a subtotal colectomy and a Hartman pouch. *B*, Subtotal colectomy with ileorectal anastomosis. *C*, Conventional (Brooke) ileostomy with a total proctocolectomy. *D*, Continent ileostomy (Koch pouch) with total proctocolectomy. *E*, Restorative proctocolectomy with ileal pouch-anal anastomosis (see Chapter 117). *(A-E, Adapted from Blumberg D, Beck DE. Surgery for ulcerative colitis. Gastroenterol Clin North Am 2002; 31:219-35.)*

Ulcerative colitis



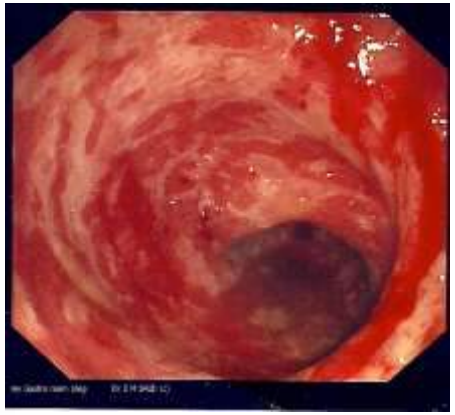


Table 3.2 Ulcerative colitis Endoscopic Index of Severity (UCEIS)[184]

Descriptor (score most severe lesions)	Likert scale anchor points	Definition
Vascular pattern	Normal (0)	Normal vascular pattern with arborisation of capillaries clearly defined, or with blurring or patchy loss of capillary margins
	Patchy obliteration (1)	Patchy obliteration of vascular pattern
	Obliterated (2)	Complete obliteration of vascular pattern
Bleeding	None (0)	No visible blood
	Mucosal (1)	Some spots or streaks of coagulated blood on the surface of the mucosa ahead of the scope, which can be washed away
	Luminal mild (2)	Some free liquid blood in the lumen
	Luminal moderate or severe (3)	Frank blood in the lumen ahead of endoscope or visible oozing from mucosa after washing intra-luminal blood, or visible oozing from a haemorrhagic mucosa
Erosions & Ulcers	None (0)	Normal mucosa, no visible erosions or ulcers
	Erosions (1)	Tiny (≤ 5 mm) defects in the mucosa, of a white or yellow colour with a flat edge
	Superficial ulcer (2)	Larger (>5 mm) defects in the mucosa, which are discrete fibrin-covered ulcers when compared to erosions, but remain superficial
	Deep ulcer (3)	Deeper excavated defects in the mucosa, with a slightly raised edge