

Inflammatory Bowel Diseases

Chiara Viganò

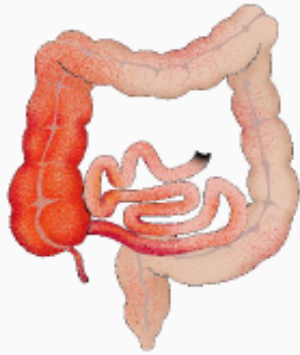
UOC Gastroenterologia H. S Gerardo Monza

**MALATTIE INFIAMMATORIE
INTESTINALI
INFLAMMATORY BOWEL DISEASES
(IBD)**

Inflammatory Bowel Diseases (IBD)

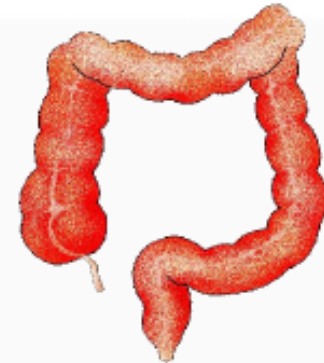
Chronic inflammation of the gastrointestinal tract

Crohn's Disease (CD)



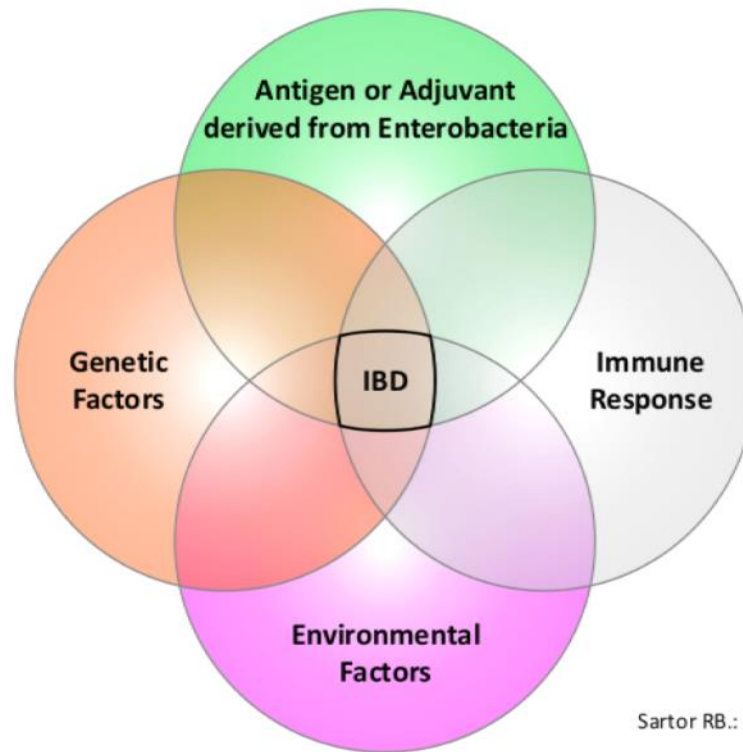
- Segmental inflammation
- Transmural inflammation of any part of GI tract
- Non-Bloody diarrhea
- Weight loss
- Abdominal pain

Ulcerative Colitis (UC)



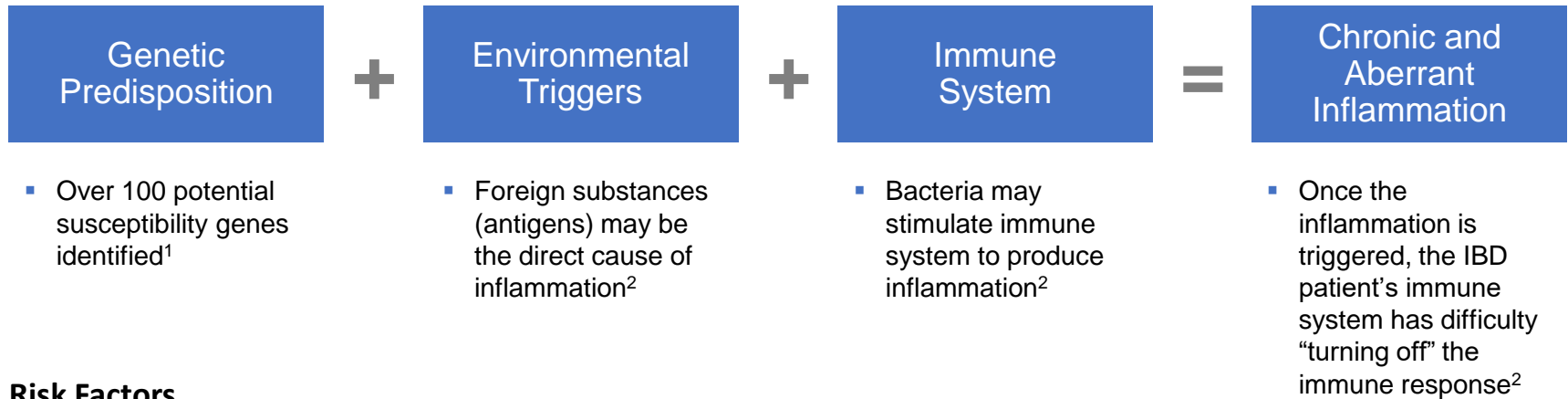
- Diffuse Inflammation
- Limited to colonic mucosa and rectum
- Bloody diarrhea with pus
- Fecal urgency
- Abdominal cramps

Inflammatory bowel disease (IBD) is a multifactorial disease involving environmental and genetic factors



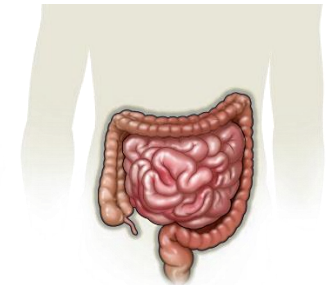
Sartor RB.: Nat Clin Pract Gastroenterol Hepatol 2006;3(7):390-407.

While the causes of IBD are unknown, several hypotheses have been suggested

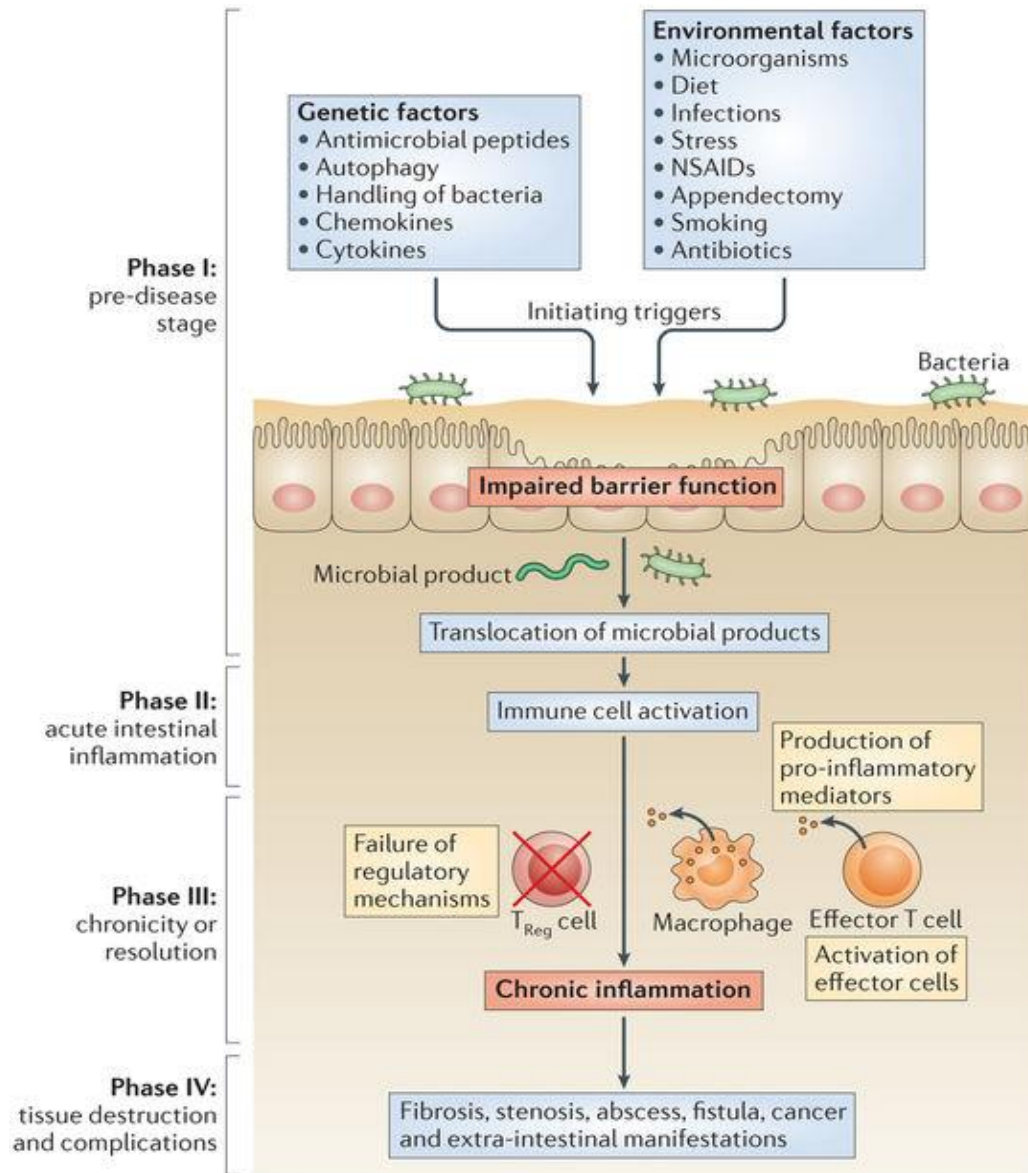


Risk Factors

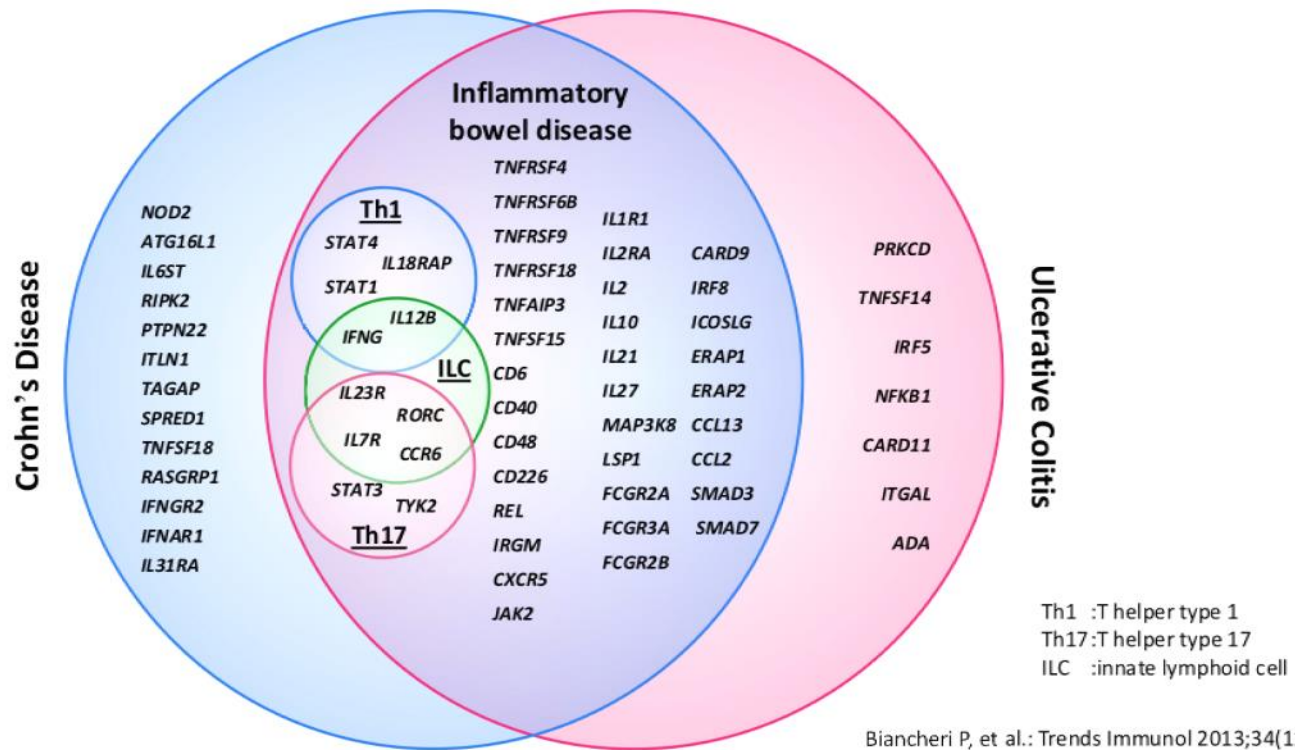
- Age – more likely among younger patients³
- Ethnicity – more likely among Caucasians, in particular Ashkenazi Jews³
- Family history – 10 times greater risk if close relative has disease⁴
- Geography – more common in US and Europe^{5,6}
- Smoking – Active smokers are more than 2 times as likely to develop CD than nonsmokers, but less likely to develop UC³



1. Vermeire S, et al. *Curr Opin Gastroenterol*. 2011;27:32-37. 2. Crohn's and Colitis Foundation of America. About Crohn's disease. 2009. <http://www.cdfa.org/info/about/crohns>. Accessed Sept 9, 2016. 3. Crohn's and Colitis Foundation of America. The facts about inflammatory bowel diseases. 2011. http://www.cdfa.org/media/pdf/PPS_Brochures/ibdfactbook. Accessed Sept 9, 2016. 4. Orholm M, et al. *N Engl J Med*. 1991;324:84-8. 5. Crohn's and Colitis Foundation of America. About the epidemiology of IBD. 2009. <http://www.cdfa.org/about/press/epidemiologyfacts>. Accessed Sept 9, 2016. 6. Kappelman MD, et al. *Clin Gastroenterol Hepatol*. 2007;5:1424-1429.

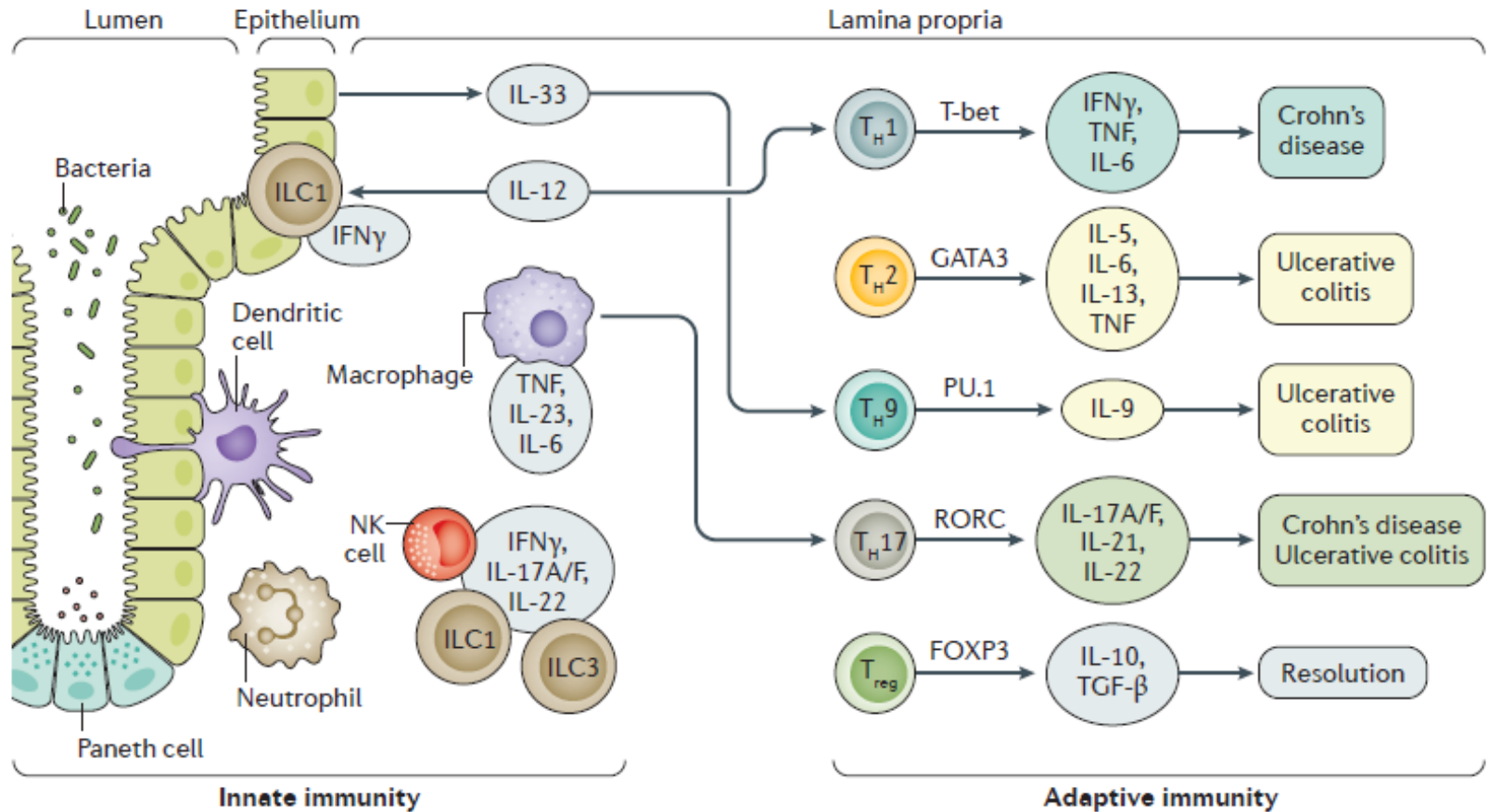


Several genes have been identified that may be associated with inflammatory bowel disease



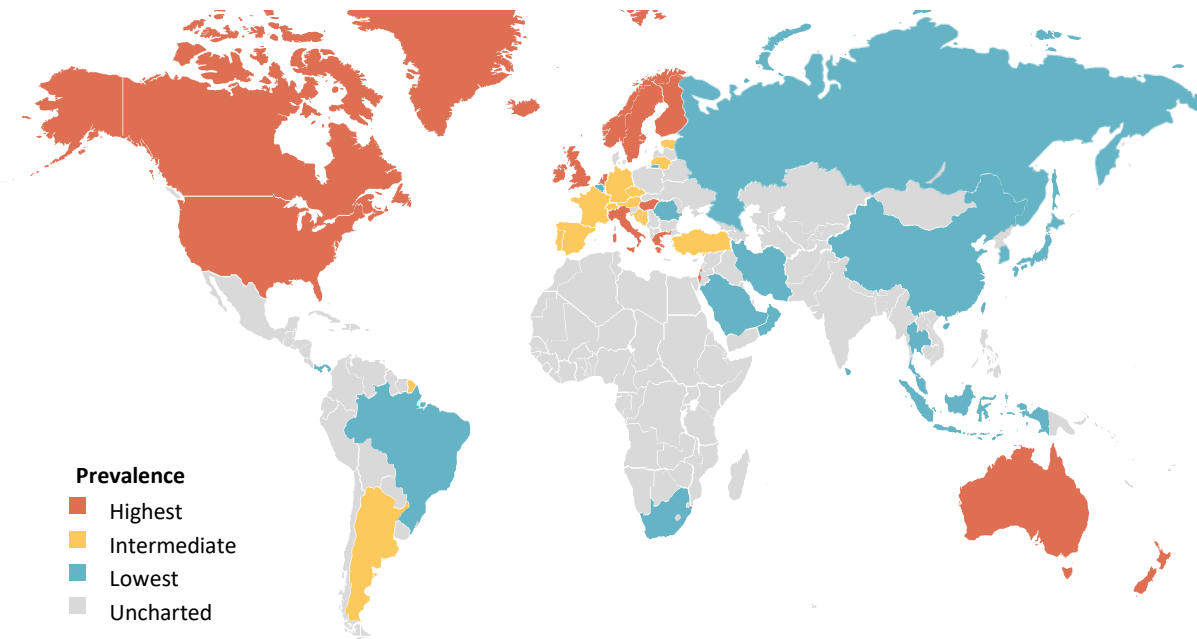
Biancheri P, et al.: Trends Immunol 2013;34(11):564-571.

Immunopathogenesis of IBD



IBD is a global disease with rising prevalence in every continent

The global prevalence of IBD in 2015¹



Prevalence

UC

- **Europe:** up to 505 per 100,000 population²
- **Asia and Middle East:** up to 168 per 100,000 population³
- **North America:** up to 249 per 100,000 population³

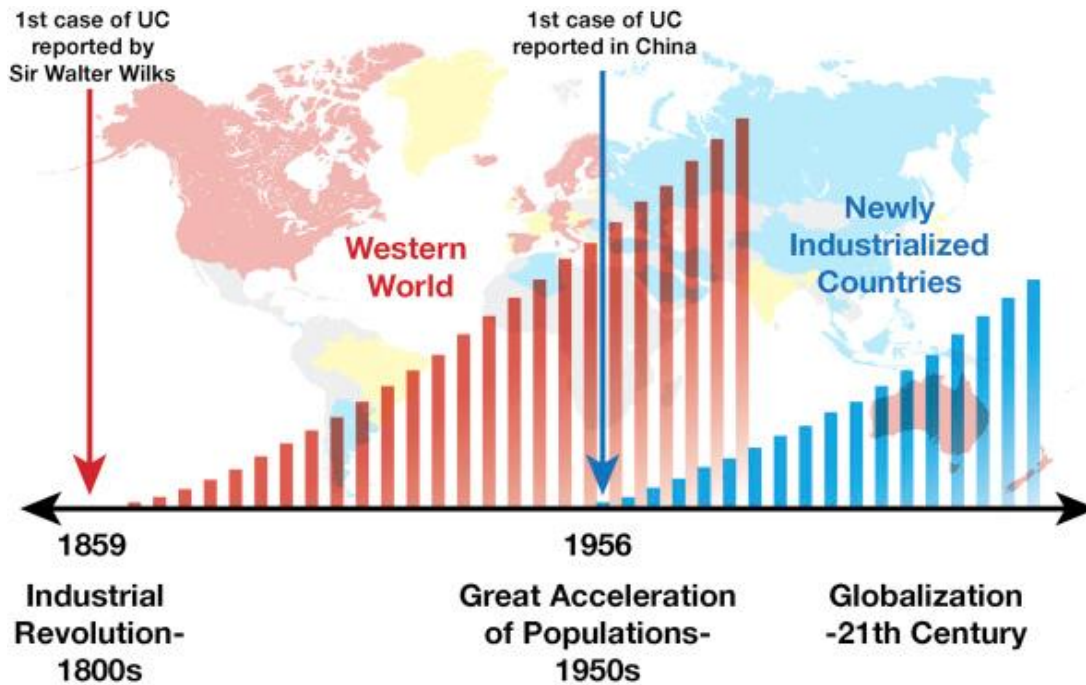
CD

- **Europe:** up to 322 per 100,000 population²
- **Asia and Middle East:** up to 68 per 100,000 population³
- **North America:** up to 319 per 100,000 population³

CD, Crohn's Disease; UC, ulcerative colitis.

1. Kaplan GG. *Nat Rev Gastroenterol Hepatol.* 2015;12:720-7. 2. Molodecky NA. *Gastroenterology.* 2012;142:46-54.e42; 3. M'Koma AE. *Clin Med Insights Gastroenterol.* 2013;6:33-47. Figure adapted from reference 1.

IBD is a global disease with rising prevalence in every continent



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CD

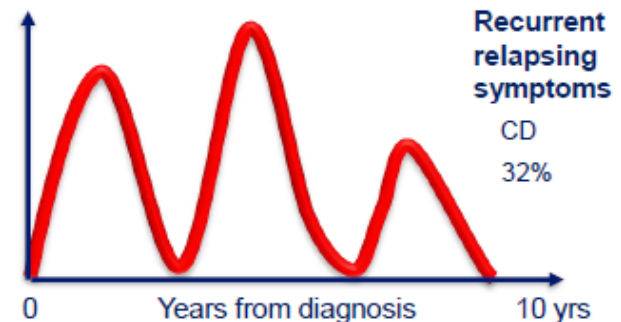
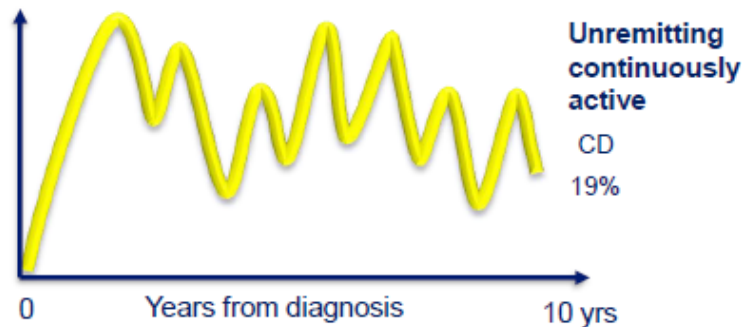
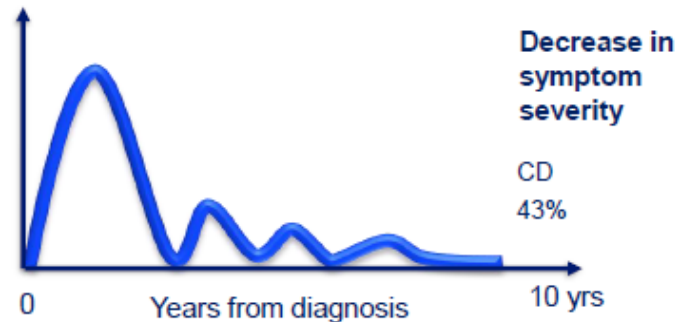
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Variable disease course over first 10 years

IBSEN study: Norwegian cohort (diagnosis 1990 - 1993) (CD, $n=197$ / UC, $n=423$)



- **Complications (structuring or penetrating) = 53%**

Manifestazioni extraintestinali (I)

- Correlate all'attività di malattia:
 - afte orali
 - congiuntivite, episclerite, uveite
 - artropatia pauciarticolare
 - eritema nodoso
 - pioderma gangrenoso



Manifestazioni extraintestinali (II)

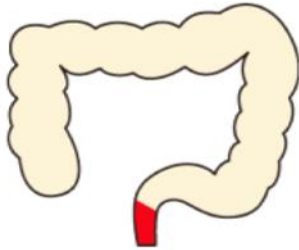
- Non correlate all'attività:
 - calcoli colecistici
 - artropatia assiale:
 - sacro-ileite
 - spondilite anchilosante
 - colangite sclerosante
 - calcoli renali
 - amiloidosi



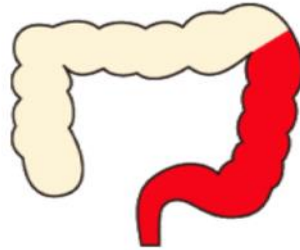
ULCERATIVE COLITIS

The type of Ulcerative Colitis is broadly classified into three groups according to the extent of the inflammatory site

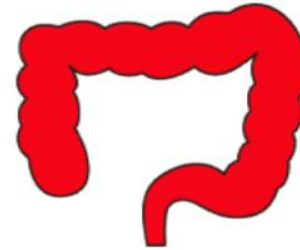
Proctitis type



Left-sided colitis type



Total colitis type



- La lesione è limitata alla mucosa del crasso
- La mucosa si ulcera e sanguina
- La lesione è continua e di estensione variabile (proctite, proctosigmoidite, colite sinistra, colite sostanziale, pancolite)
- Il retto è sempre interessato

RCU: sintomi e segni

- Intestinali:

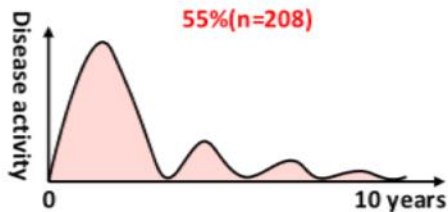
- diarrea ematica con frequenti scariche e stimoli all'evacuazione

- ematochezia

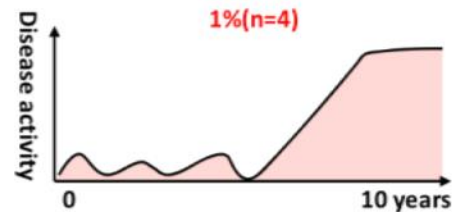
- dolori addominali

- Sistemici: astenia, febbre, calo ponderale, anemia, artrite

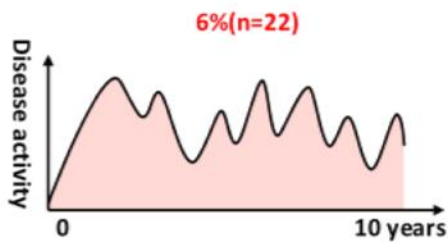
The clinical course of Ulcerative Colitis is often recurrent and remitting



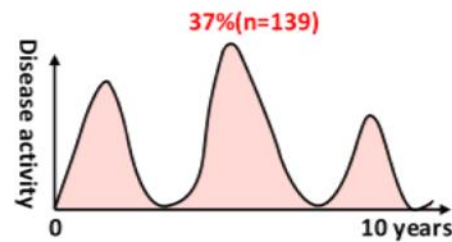
Reduction in the severity of symptoms over time



Symptoms increase over time



Chronic and continuous symptoms



Chronic and intermittent symptoms

Missing: 6 cases

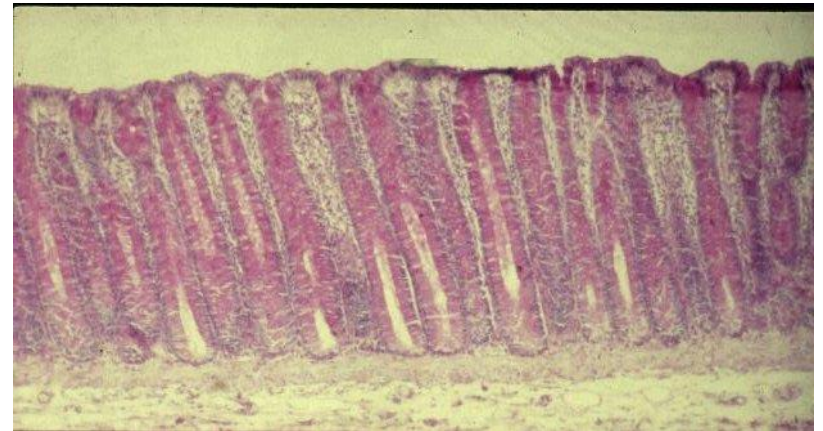
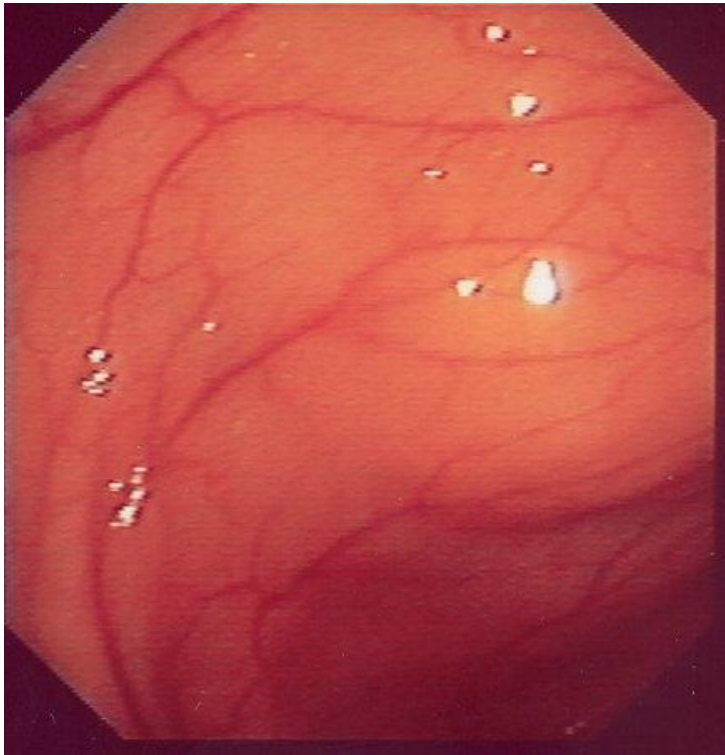
Subjects and Methods : Three hundred seventy-nine patients with unoperated ulcerative colitis who were enrolled in IBSen between January 1, 1990, and December 31, 1993, were followed up at 1, 5, and 10 years post-diagnosis to determine patterns of symptoms (clinical course)

IBSEN : A Cohort-Study of Inflammatory Bowel Diseases in Inflammatory Bowel disease in South-Eastern Norway

Solberg IC, et al.: Scand J Gastroenterol 2009;44(4):431-440.

GASTROENTEROLOGY

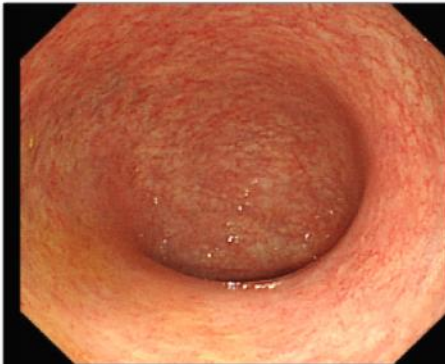
Rettoscopia normale



UC Mayo Endoscopic Score

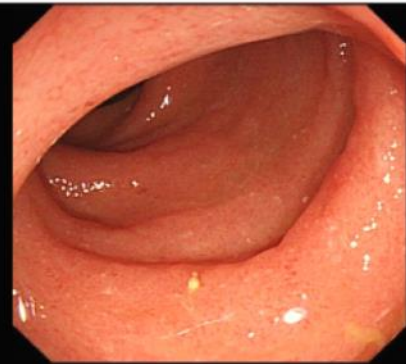
0

Normal/no activity



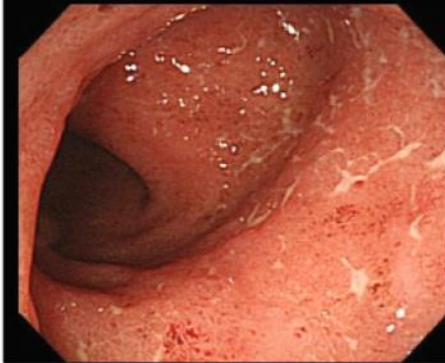
1

The mucosa becomes red and the vessels that were visible in the normal mucosa become invisible



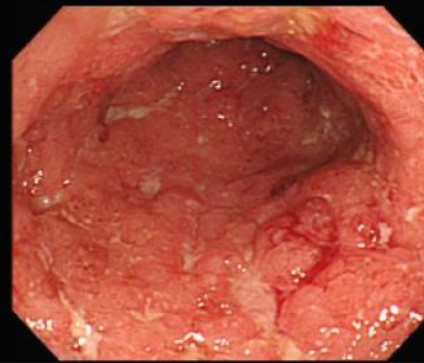
2

The mucosa erodes (erosions) and the vessels that were visible in the normal mucosa become invisible

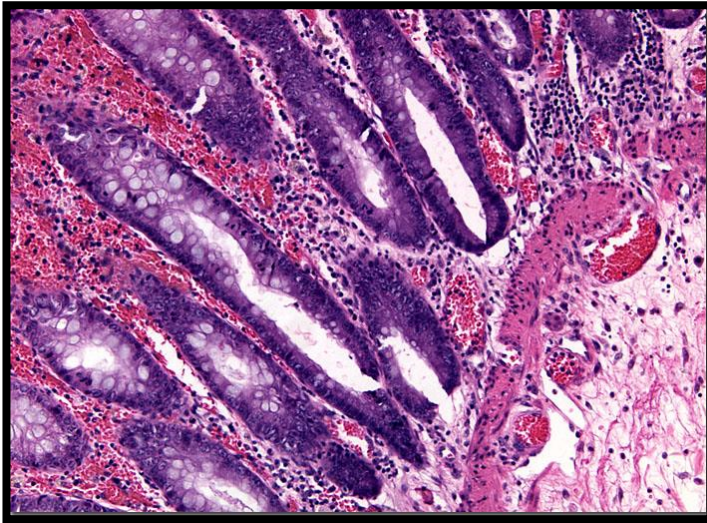


3

Deep mucosal injury (ulcer) and bleeding are visible



Istopatologia



- Inflammatione limitata alla mucosa
- Criptite e ascessi criptici
- Infiltrato infiammatorio acuto e cronico
- Distorsione delle cripte
- Deplezione delle cellule mucipare

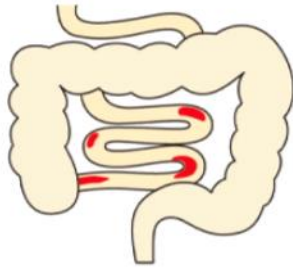
RCU: diagnosi differenziale

- Coliti infettive
 - C. Difficile, Salmonella, Shigella, C. Jejuni, E. Coli 0157, Yersinia, Ameba, Schistosoma
 - CMV, Erpetica, M avium, (HIV)
- Colite di Crohn/ ischemica/ da raggi/ da farmaci/ vasculitica/ Bechet
- Microscopica (linfocitaria/ collagenosica)
- Ulcera solitaria del retto, carcinoma
- Da farmaci

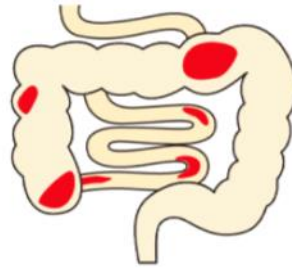
CROHN'S DISEASE

Many lesions in Crohn's disease are noncontiguous.
Broadly classified into three groups according to the site of the lesion

Small intestinal type



Small intestine/
Large intestine type

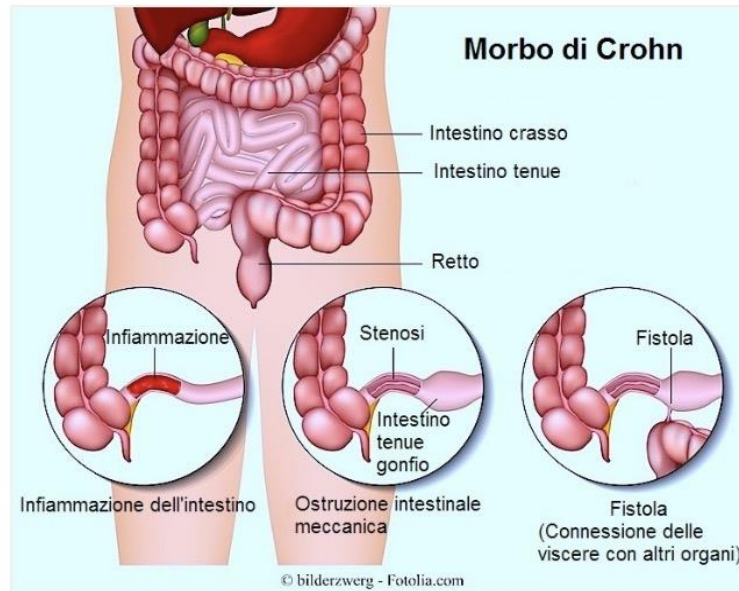


Large intestine type



- Le lesioni possono interessare tutto il canale alimentare dalla bocca all'ano, più frequentemente ileocolica
- Le lesioni sono discontinue
- La parete intestinale è interessata a tutto spessore
- Può dare manifestazioni perianali

Presentazione clinica fenotipo MC

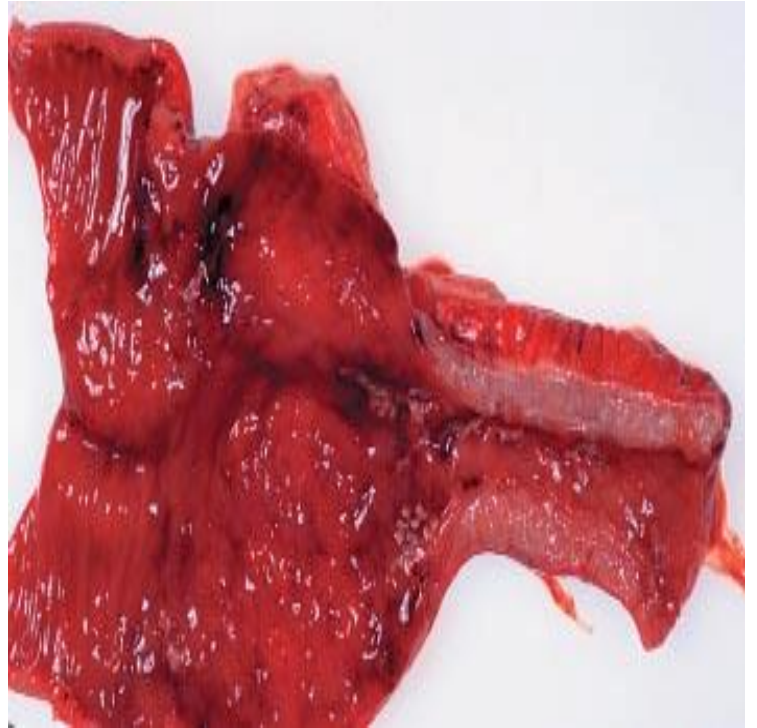
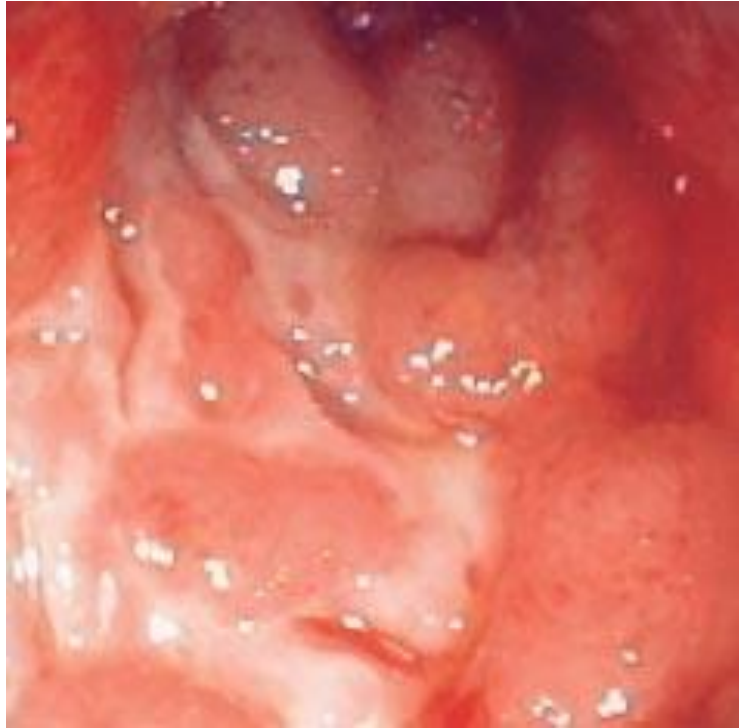


Inflammatorio
Flogosi attiva senza stenosi
o fistole

Stenosante
Esito in fibrosi delle lesioni
con stenosi di lume

Penetrante o
fistolizzante
Flogosi
transmurale,
ulcerazioni
profonde,
interessamento
sieroso, adesione
a strutture vicine,
fistole e ascessi

	Montreal (2005)	Parigi (2009)
Malattia di Crohn		
Età alla diagnosi	A1: <17 anni A2: 17-40 anni A3: >40 anni	A1a: 0-<10 anni A1b: 10-<17 anni A2: 17-40 anni A3: >40 anni
Localizzazione	L1: limitata all'ileo terminale ± cieco L2: colon L3: ileocolon L4: isolata delle alte vie digestive	L1: 1/3 ileo distale ± limitata malattia cecale L2: colon L3: ileocolon L4a: malattia delle alte vie digestive prossimale al Treitz L4b: malattia delle alte vie digestive distale al Treitz e prossimale al 1/3 distale dell'ileo
Caratteristiche	B1: non stenosante, non penetrante B2: stenosante B3: penetrante P: malattia perianale	B1: non stenosante, non penetrante B2: stenosante B3: penetrante B2B3: penetrante e stenosante, allo stesso tempo o in tempi diversi P: malattia perianale
Crescita	//	G ₀ : nessun ritardo di crescita G ₁ : ritardo di crescita



Malattia di Crohn

Sintomi :

- Diarrea (ematica se localizzazione colica),
- dolori addominali,
- Vomito e distensione addominale (localizzazione ileale stenosante)
- astenia, febbre, calo ponderale
- fistole perianali

Malattia di Crohn

Sintomi:

- Da manifestazioni extraintestinali: articolari, cutanee, oculari, epatiche
- Da sedi atipiche: bocca, esofago, stomaco, duodeno
- Da complicanze: nausea, vomito, drenaggio di fistole

Diagnosi

- Un singolo gold standard per la diagnosi non è disponibile
- La diagnosi si basa su una non strettamente definita combinazione di dati clinici, endoscopici, ecografici, radiologici e istologici...da verificare nel tempo

Malattia colica: diagnosi differenziale

- Coliti infettive
 - C. Difficile, Salmonella, Shigella, C. Jejuni, E. Coli 0157, Yersinia, Ameba, Schistosoma
 - CMV, Erpetica, M avium, (HIV)
- RCU/ ischemica/ da raggi/ da farmaci/ vasculitica/ Bechet
- Microscopica (linfocitaria/ collagenosica)
- Ulcera solitaria del retto, carcinoma
- Da farmaci

Malattia ileale: diagnosi differenziale

- Appendicite acuta
- Anomalie tubo-ovariche (tumore, cisti, endometriosi)
- Neoplasie (carcinoide, linfoma, carcinomi)
- Malattie vascolari (contraccettivi orali, vasculiti sistemiche, Behcet, da raggi)
- Infezioni (tubercolosi, amebiasi, Yersinia)
- Digiuno ileite ulcerativa, gastroenterite eosinofila, amiloidosi, FANS

Valutazione clinica

- Anamnesi: familiarità, fumo, farmaci, appendicectomia, manifestazioni extraintestinali / perianali
- Esame obiettivo: febbre, BMI, massa in FID, lesioni perianali

Laboratorio

- Emocromo (GB, Hb, VGM, piastrine), PCR, Ferritina
- Coprocoltura per C Difficile
- Parassiti e anticorpi anti-ameba in casi selezionati
- Ricerca TB (esame diretto/colturale/NAAT) in casi selezionati

La calprotectina

Calprotectina

(Foell D et al – Gut 2009;58:859-68)

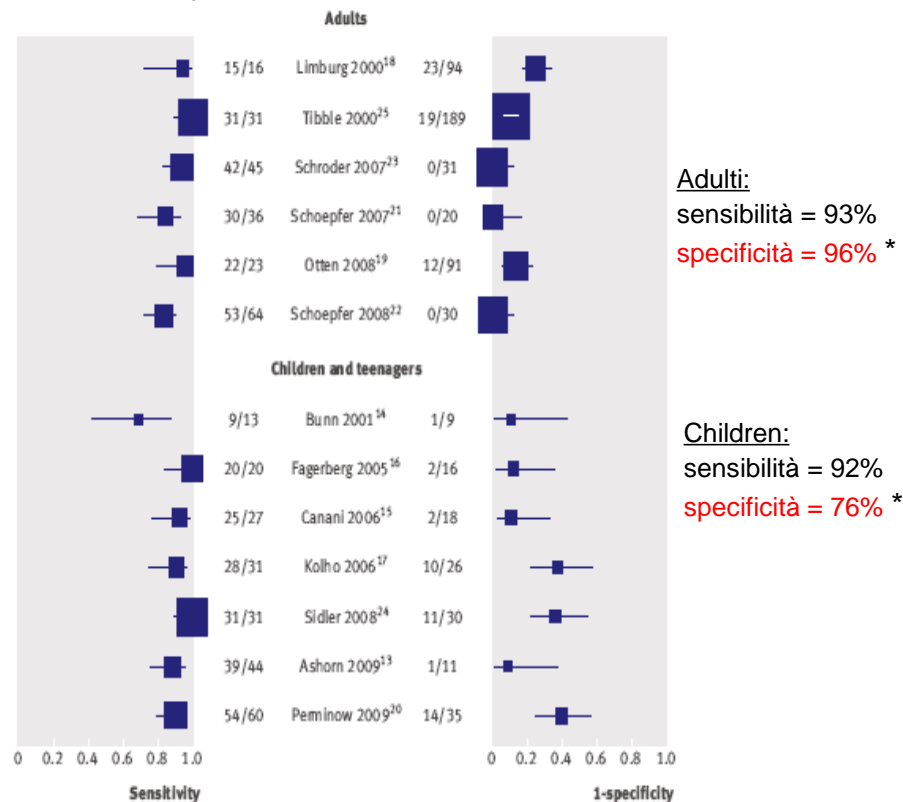
- Proteine S100 : famiglia di oltre 20 proteine leganti il calcio, con un pattern di espressione tessuto-specifico
- 3 di queste sono coinvolte nell'immunità innata:
 - S100A8 (*calgranulina A*) and S100A9 (*calgranulina B*) presenti in granulociti, monociti, macrofagi giovani (e nelle cellule epiteliali in corso di infiammazione)
 - S100A12 (*calgranulina C*) limitata ai granulociti
- Esistono varie isoforme di S100A9 associate con S100A8 a formare diversi dimeri e tetrameri, raggruppati sotto al termine "**calprotectina**"
- Stabile nelle feci per oltre 7 giorni a temperatura ambiente

La calprotectina

Calprotectina fecale come screening per sospetta IBD: meta-analisi

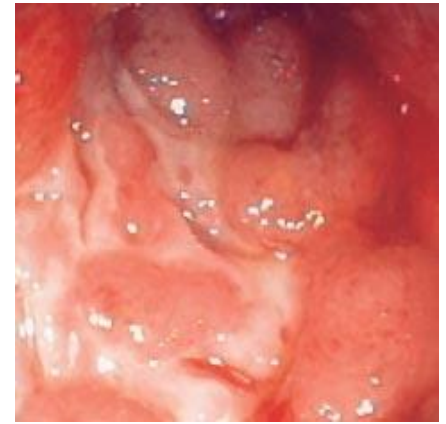
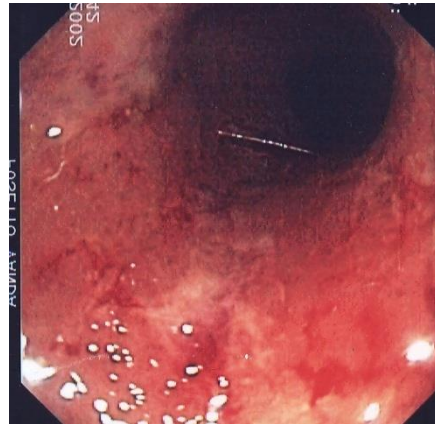
(van Rheenen PF et al – BMJ 2010;341:c3369)

Lavori identificati = 179 ⇒ lavori inclusi = 13 ⇒
 pazienti pediatrici = 7 (371 casi sospettati ⇒ 61% IBD
 confermata)

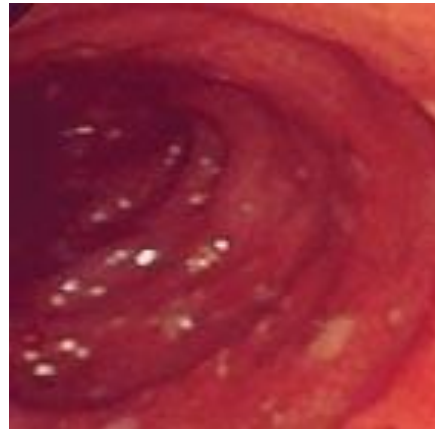
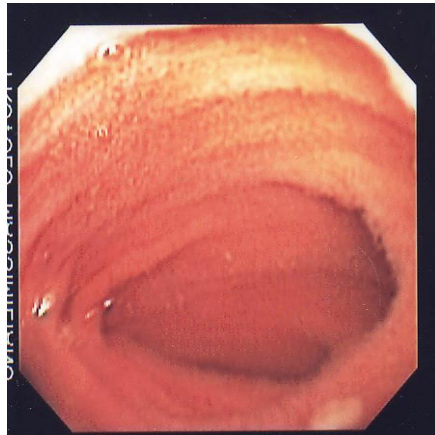


Colonscopia

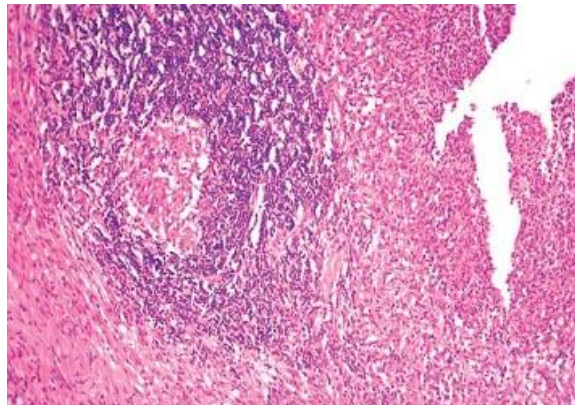
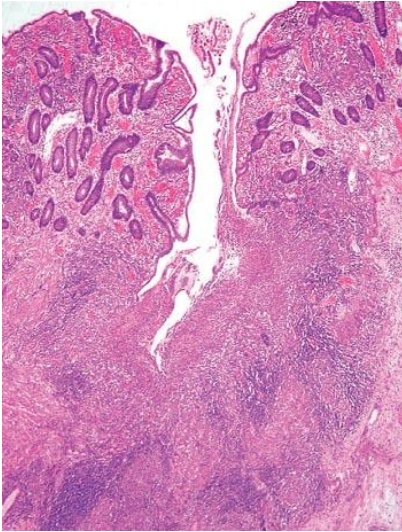
Colon



Ileo



Istologia

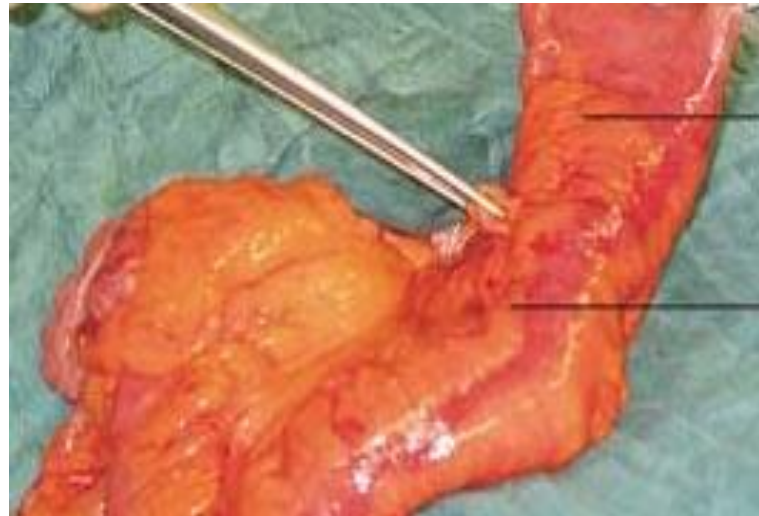


- Infiltrato cronico infiammatorio focale
- Irregolarità focale delle cripte
- Granulomi
- Lesione transmurale

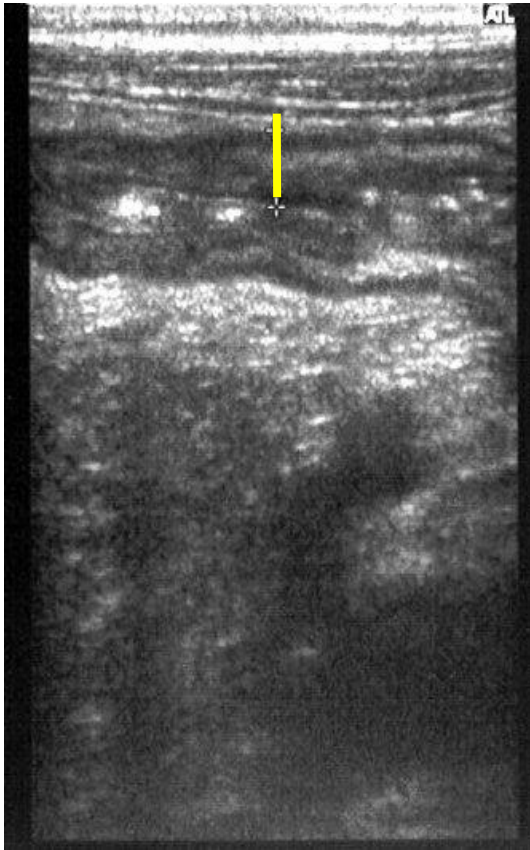
Diagnosi intra-operatoria



- Ispessimento della parete intestinale
- Grasso mesenterico ipertrofico

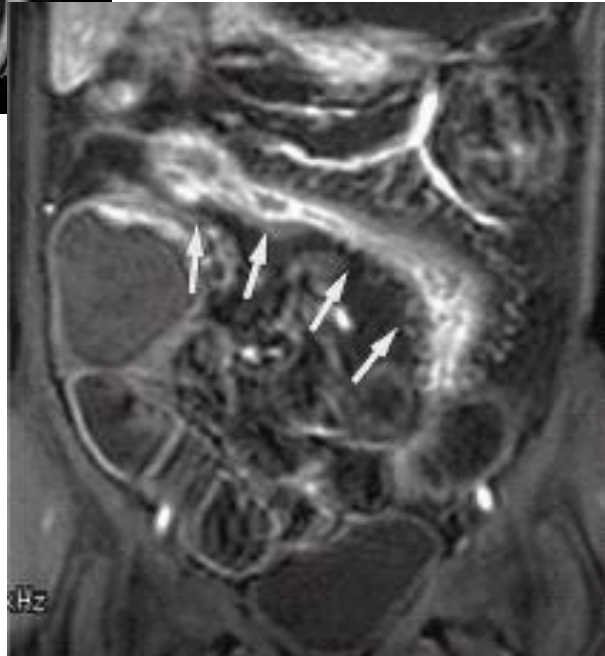


Ecografia delle anse intestinali



- Ispessimento parietale (>3-4mm)
- Ipertrofia del grasso mesenterico
- Linfadenopatie
- Versamento liquido tra le anse
- Retrodilatazione

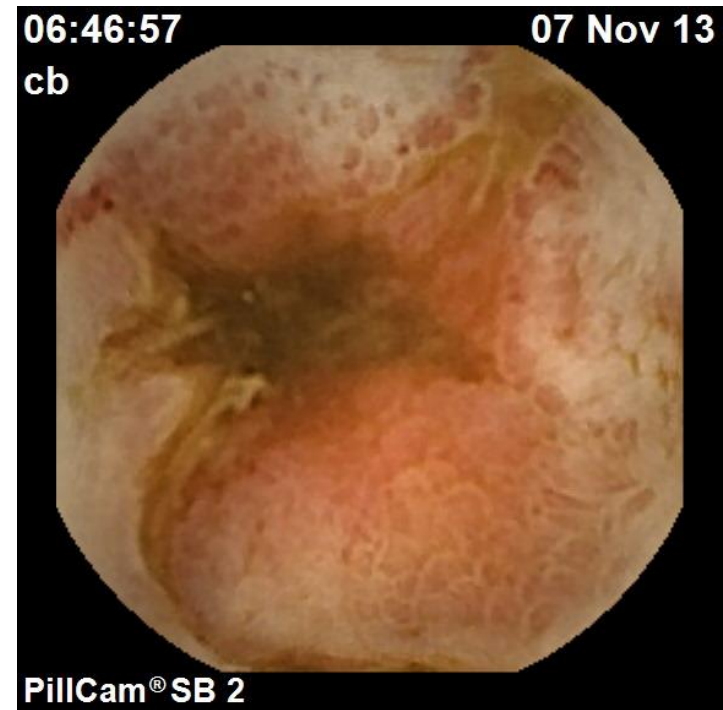
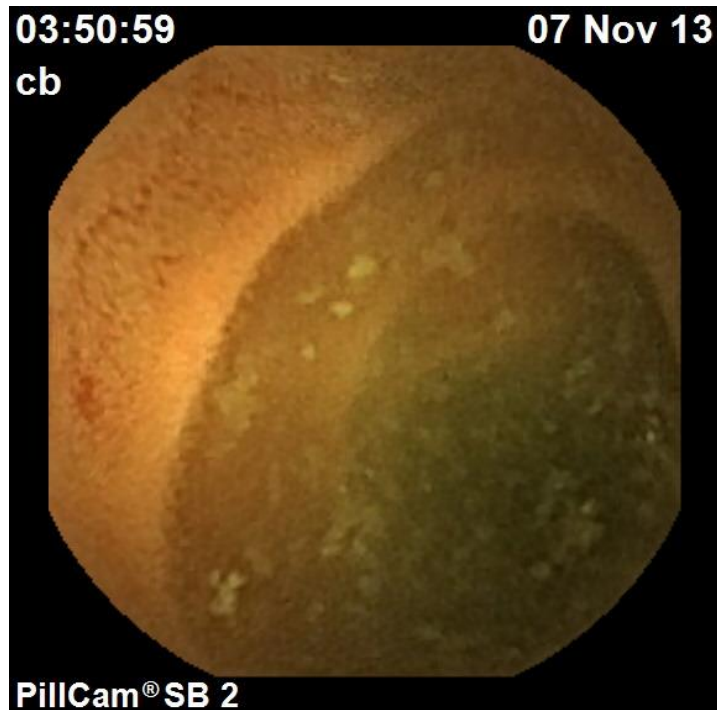
Entero-TC o Entero MRI



- Tratto intestinale:
 - Ispessito
 - Infiammato
 - Iperenhancement di mdc
- Strutture extra parietali:
 - Aumentata densità del grasso mesenterico
 - Ipervascularizzazione (Segno del pettine, comb sign)

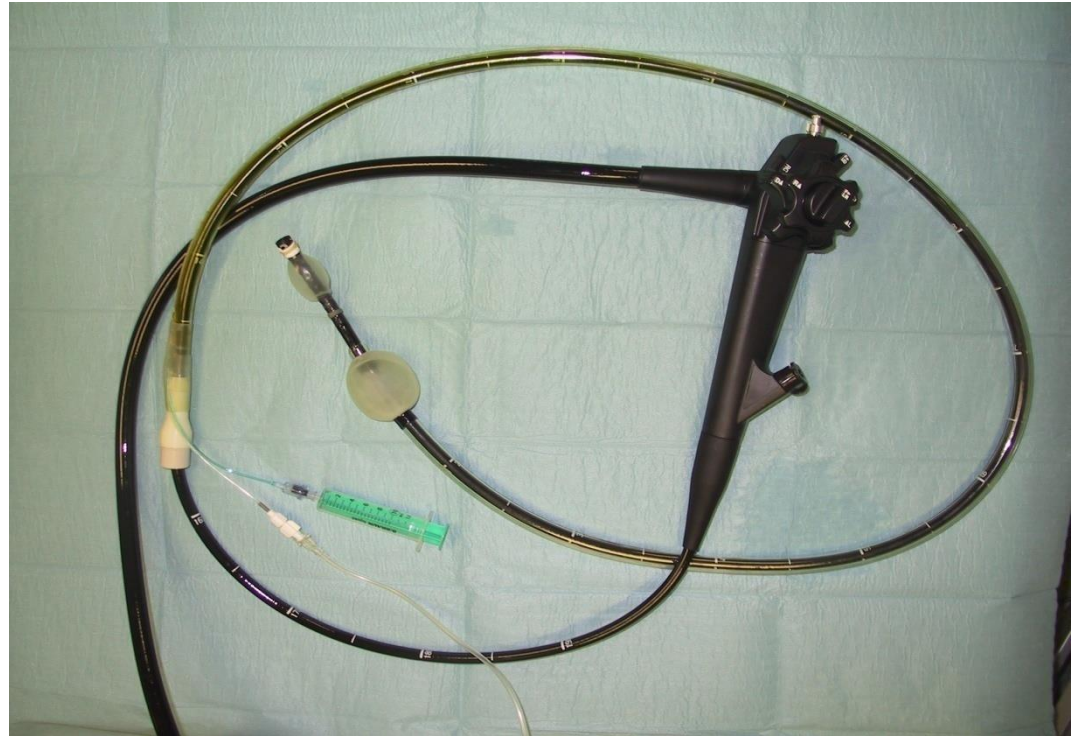
Capsula endoscopica

- La specificità è sconosciuta:
 - lesioni mucose in 10-21% dei normali
 - enteropatia da FANS
- Rischio di ostruzione: 2%



Enteroscopia a doppio pallone

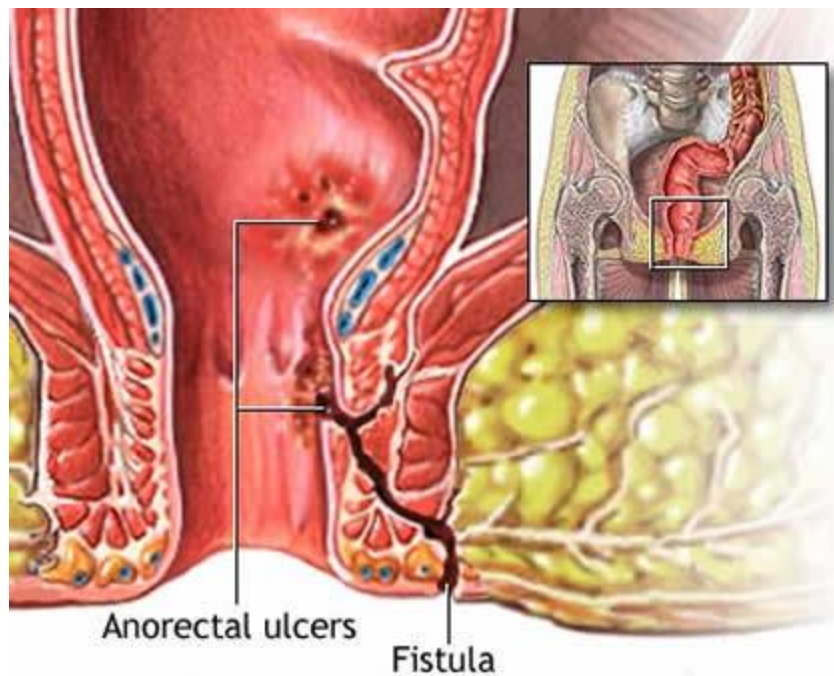
- Consente di esplorare per via anterograda e retrograda tutto (o quasi) il tenue
- Consente di fare biopsie
- Lunga ed indaginosa



Perianal Fistulas

A “tunnel or tract” of pus and/or granulation tissue between two sections of the intestines or between the intestines and other organs, including the skin.

Occurrence in about 30% of CD patients over disease course



Ecografia transanale e RM perianale

