Update in Pediatric IBD: Diagnosis and disease monitoring

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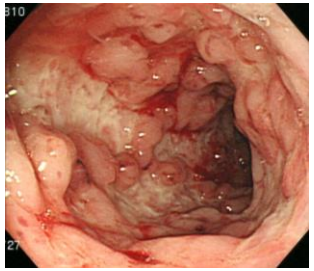
- Introduction
  - Importance of PIBD
- Diagnosis of PIBD
- Monitoring of PIBD

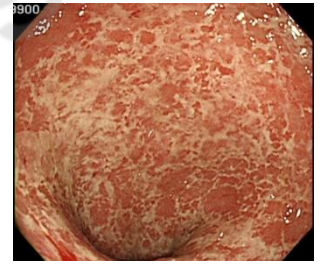
What is IBD?

- **Crohn's disease (CD)**



  - Whole gut
  - Transmural inflammation
  - Skip lesion
  - Abdominal pain, diarrhea, weight loss

- **Ulcerative colitis (UC)**

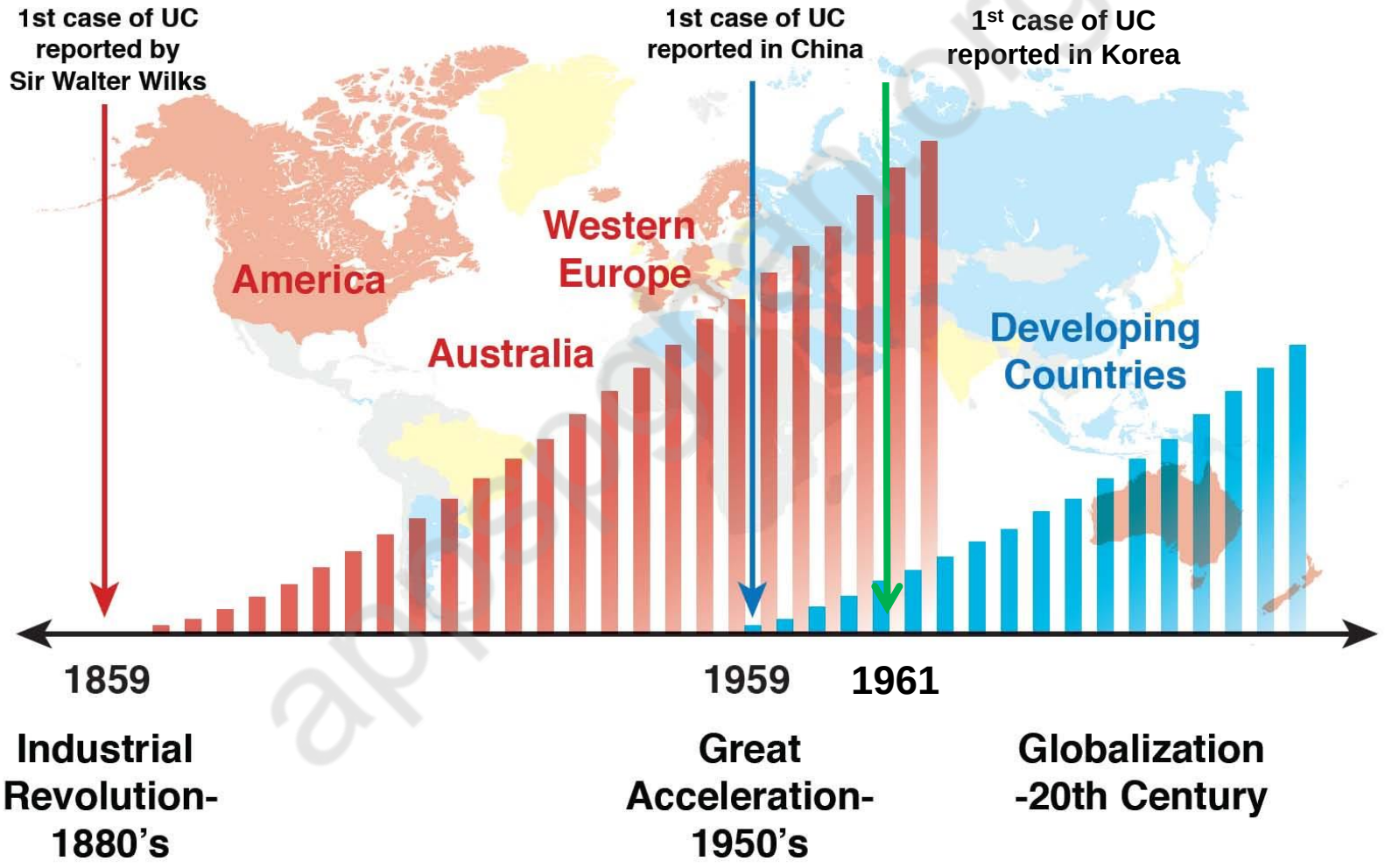


  - Disease of colon
  - Mucosal inflammation
  - Continuous and start in rectum
  - Rectal bleeding

Why PIBD is so important to pediatrician?

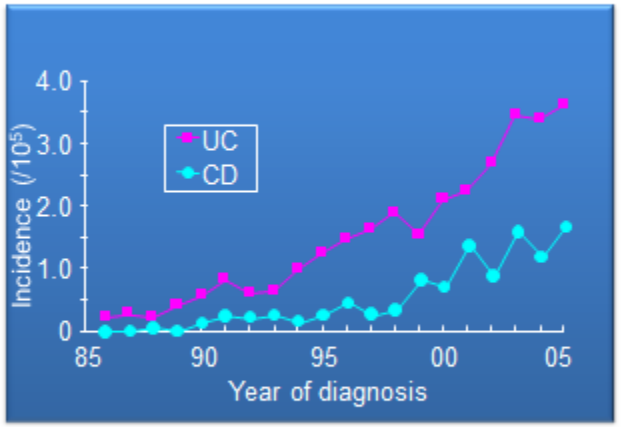
- **Incidence** rising worldwide and ¼ developed <18
- **Growth and puberty** are affected
- **Monogenic IBD** should be considered.

Geographic spreading



Kaplan, *Gastroenterology 2017*

Incidence of IBD in Korean Adults
Population based, Songpa-Kangdong district, Seoul

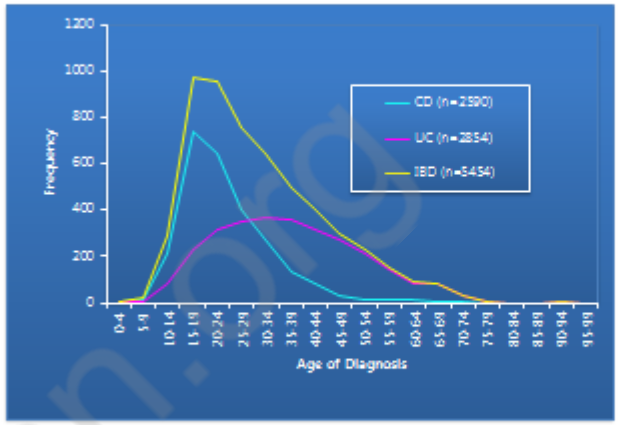


CD
- 86-90 0.05/10⁵/yr
- 01-05 1.34/10⁵/yr

UC
- 86-90 0.34/10⁵/yr
- 01-05 3.08/10⁵/yr

Yang SK, Inflamm Bowel Dis 2008

How Common is IBD in Children ?

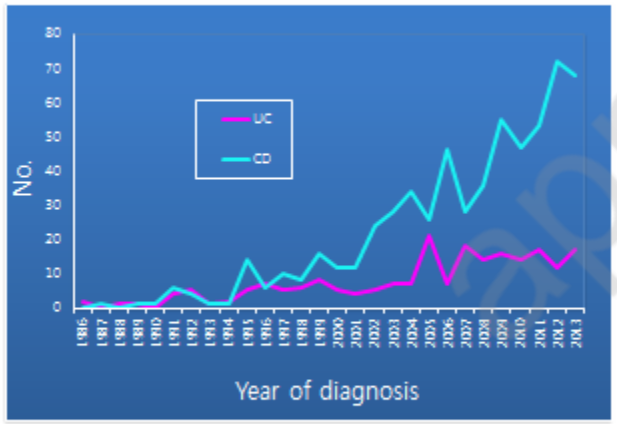


Pediatric age (<18y)
- CD 23.6%
- UC 7.4%
- IBD 15.0%

Peak age
- 15-30y 49.3%

AMC data, unpublished

Incidence of IBD in Korean Children
No population based, No. of registration at AMC



CD = 594
- 86-90 0.6/yr
- 01-05 24.8/yr
- 09-13 66.2/yr

UC = 211
- 86-90 0.8/yr
- 01-05 8.8/yr
- 09-13 15.2/yr

Kim HJ, JCC 2017

Conclusion: PIBD in Korea

- Incidence is **increasing**
- The age distribution is similar to western data
  - **1/4** of CD developed <18y
  - **1/10** of CD developed <18y

Why PIBD diagnosis is a challenge in Asia?

- **No surrogate marker** for definite diagnosis
- **Less experience** with low incidence
- **Steadily increasing incidence** in Asia

How to make a better PIBD diagnosis in Asia?

- **Complete and detailed** diagnostic work up because it lasts lifetime.
- **Exact** interpretation of basic tool
  - Endoscopy
  - Histology
- **Standardization**
  - Use of guideline
  - Diagnosis: (revised) Porto criteria
  - Subclass: Paris
  - Activity: PCDAI, PUCAI
  - Endoscopy: SES-CD, Mayo score

JPGN 2005;41:1

Medical Position Paper

Inflammatory Bowel Disease in Children and Adolescents: Recommendations for Diagnosis—The Porto Criteria

IBD Working Group of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)

JPGN 2014;58:795

ESPGHAN Revised Porto Criteria for the Diagnosis of Inflammatory Bowel Disease in Children and Adolescents

*Arie Levine, †Sibylle Koletzko, ‡Dan Turner, §Johanna C. Escher, ||Salvatore Cucchiara, §Lissy de Ridder, ¶Kaija-Leena Kolho, #Gabor Veres, **Richard K. Russell, ††Anders Paerregaard, ‡‡Stephan Buderus, §§Mary-Louise C. Greer, ||||¶¶Jorge A. Dias, ##Gigi Veereman-Wauters, ***Paolo Lionetti, †††Malgorzata Sladek, ‡‡‡Javier Martin de Carpi, §§§Annamaria Staiano, ||||||Frank M. Ruemmele, and ¶¶¶David C. Wilson

Diagnostic Work-Up in PIBD (Porto Criteria)

- History
- Physical examination
- Laboratory work (blood, stool)
- EGD & ileocolonoscopy with histology
- Image of the small bowel

- Exclude enteric infection before endoscopy

Levine A, J Pediatr Gastroenterol Nutr 2014;
J Pediatr Gastroenterol Nutr 2005

Diagnostic pathways in IBD by BSPGHAN

Primary/Secondary Care

- Medical history
- Clinical examination
- Laboratory results:
  - Blood inflammatory markers (ESR/CRP)
  - Full blood count
  - Albumin and liver function
  - if available: faecal calprotectin

> Suspicion of IBD

Specialist Care

- Upper gastrointestinal endoscopy and ileocolonoscopy with histology
- Small bowel imaging (MRE or VCE)
- In selected cases, further laboratory investigations might be required (eg, immune workup)

> Overall assessment consistent with Crohn's Disease

Kammermeier J, Arch Dis Child 2016
Levine A, JPGN 2014

Suspicion: presentations at AMCCH

	CD (n=48) n(%)	UC (n=14) n(%)	p
Abdominal pain	32 (67)	10 (71)	NS
Diarrhea	27 (56)	11 (79)	NS
Weight loss	22 (46)	6 (43)	NS
All triad	37%		
Rectal bleeding	8 (17)	13 (93)	< 0.001
Lethargy	4 (8)	3 (21)	NS
Anorexia	10 (21)	4 (29)	NS
Perianal symptoms	24 (50)	0 (0)	< 0.005
Growth delay	5 (10)	0 (0)	<0.05
Extraintestinal symptoms	12 (25)	2 (14)	NS

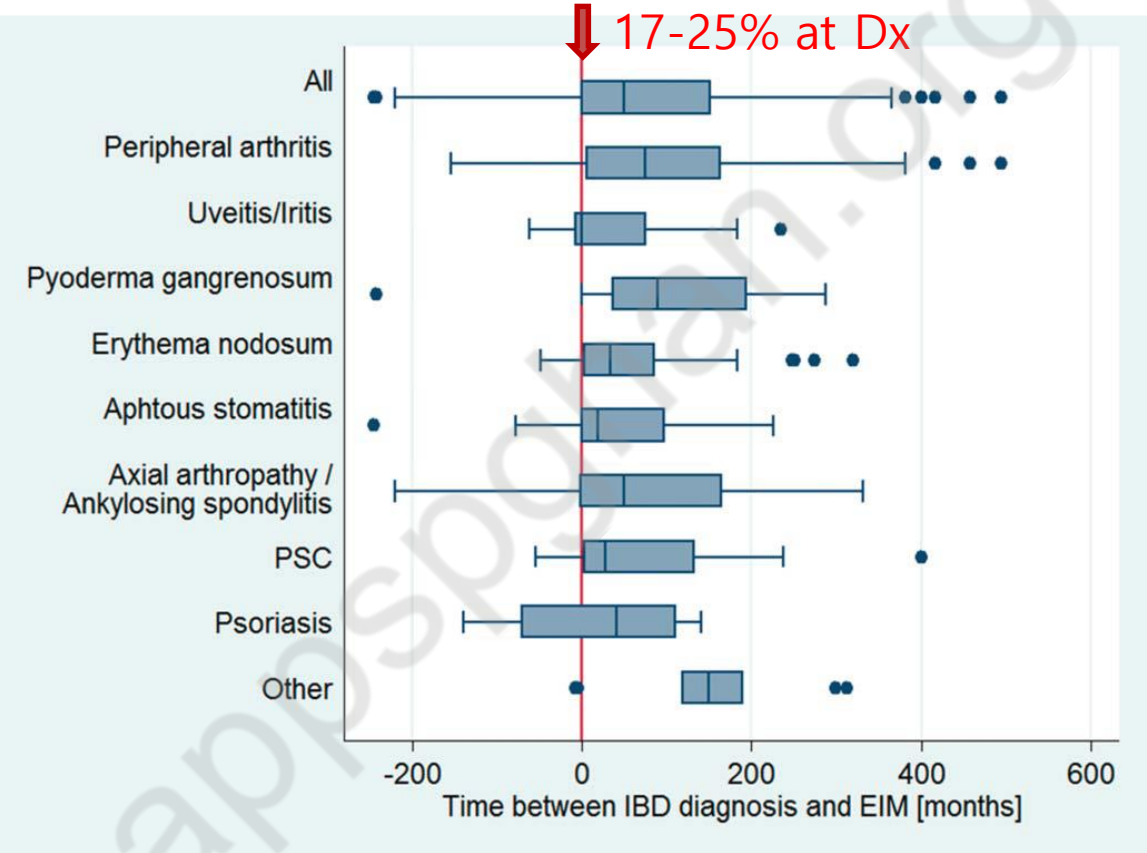
Kim BJ, Dig Dis Sci 2010

Extra-intestinal manifestations

- Oral aphthous ulcer*
- Peripheral arthritis*
- Axial arthritis
- Ankylosing spondylitis more prevalent in subjects with UC
- Osteoporosis (risk is greater in subjects with CD)
- Dermatological : erythema nodosum*, pyoderma gangrenosum
- Eye : episcleritis*, uveitis
- Renal : uric acid stones, oxalate stones
- Arterial and venous thrombosis
- Hepatobiliary complications : granulomatous hepatitis, primary sclerosing cholangitis, amyloid cholesterol gallstones, cholangiocarcinoma
- Lungs?

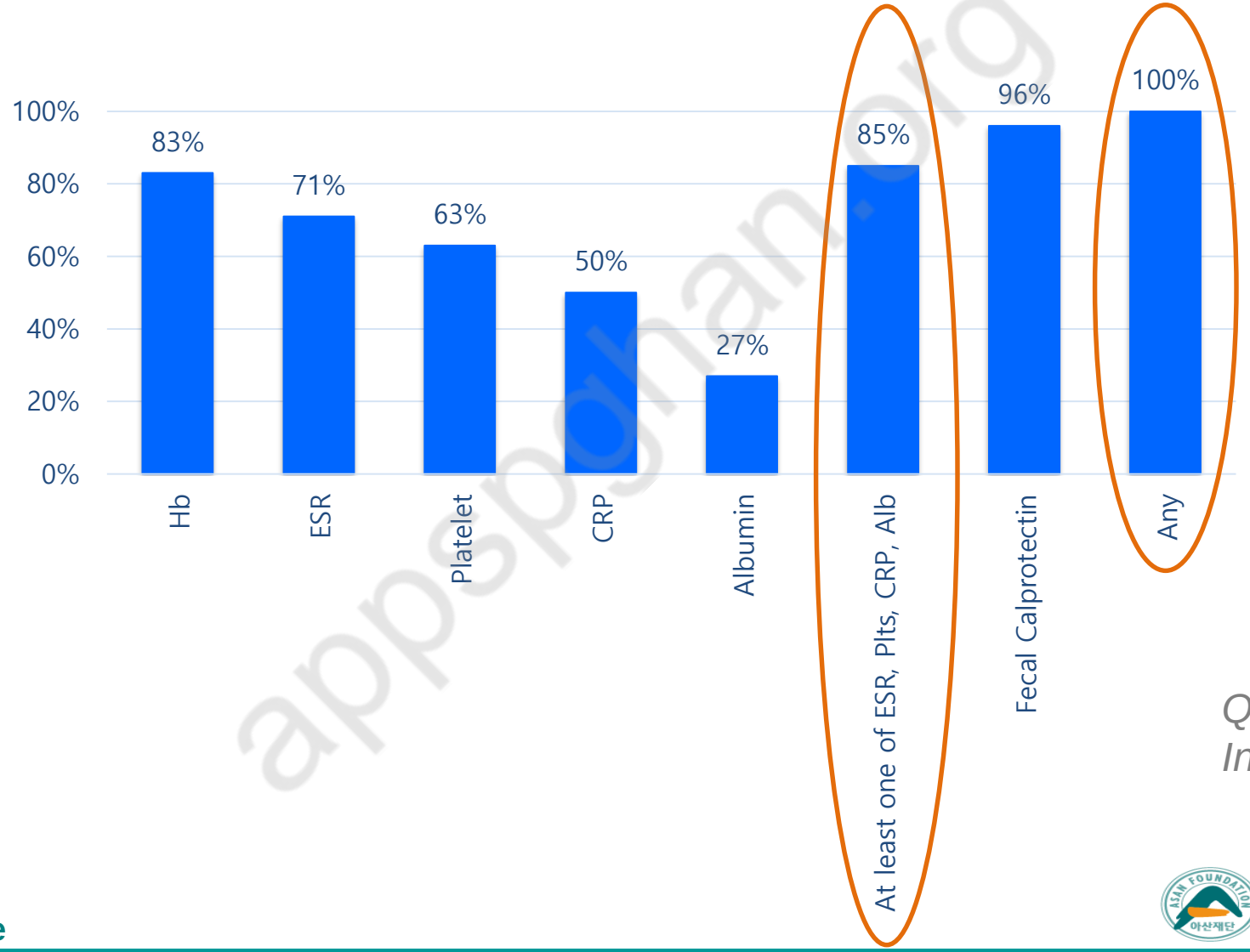
* In parallel with IBD symptoms

Chronological Order of Appearance of EIM



Vavricka SR, Inflamm Bowel Dis 2015
Dotson JL, J Pediatr Gastroenterol Nutr 2010

Comparison of positive individual and combination investigations at diagnosis of IBD



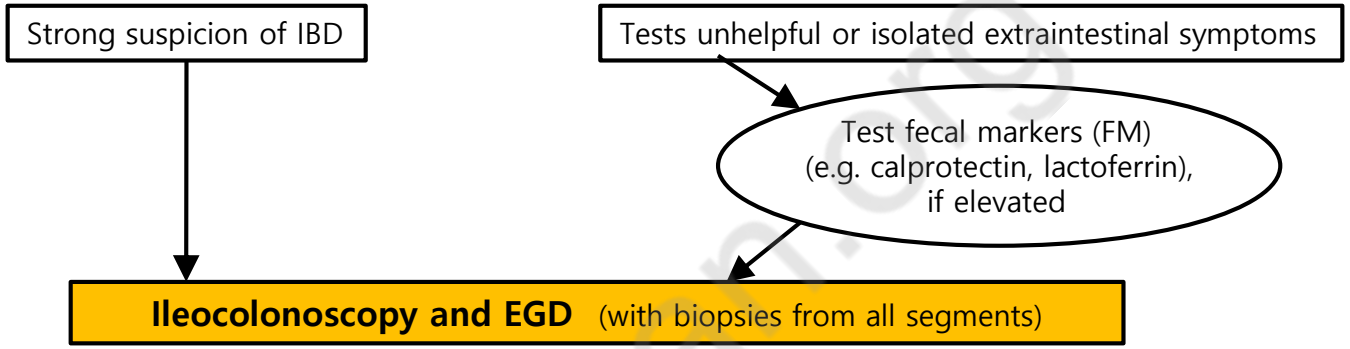
Quail MA,
Inflamm Bowel Dis 2009

Afflux of activated leukocytes containing fecal calprotectin during intestinal inflammation

- Normal < 50 mg/g
- Elevation with intestinal inflammation
- Minor elevation is common
- > 5y (Inadequate <5y)
- IBD (even with normal lab)
  - >250 mg/g suggestive of IBD
  - 96% of IBD patients
- Complementary to clinical findings
- Enteric infection and juvenile polyps

Nancey S, Hepato Gastro 2015;22:477-87
Hansen R, Arch Dis Child 2015

ESPGHAN revised Porto criteria for diagnosis of PIBD



Levin A, JPGN 2014

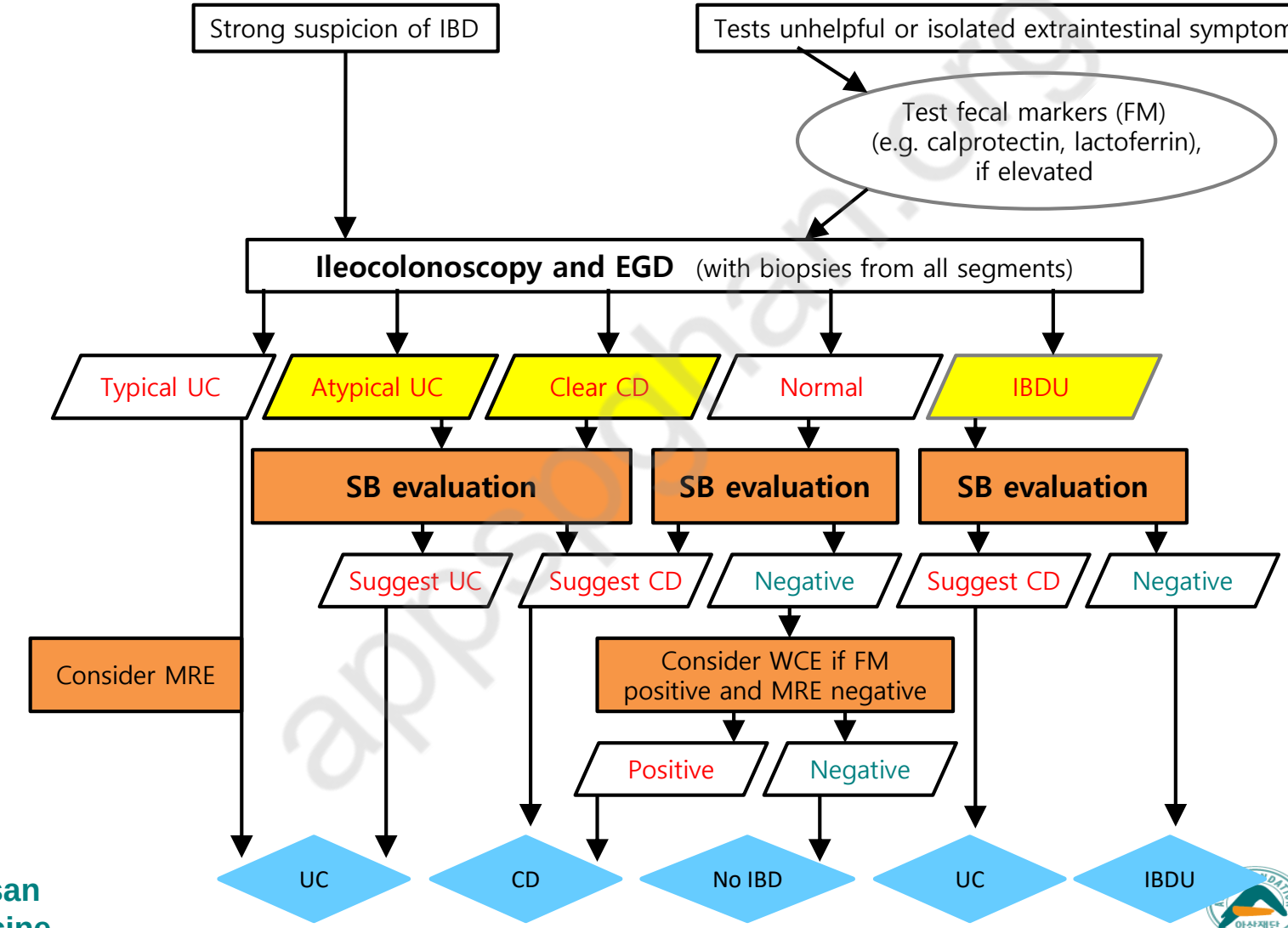
Endoscopic evaluation

- *Ileocolonoscopy and EGD are recommended as the initial work up for all children with suspected IBD*
  - possibly before the initiation of any medical treatment.

- *Multiple biopsies should be obtained from all sections of the GIT, even in the absence of macroscopic lesions.*
  - 2 or more per 5 sections of colon (cecum, A-T-D colon, rectum) and ileum
  - 2 or more from esophagus, stomach, duodenum

Levine A, J Pediatr Gastroenterol Nutr 2014
Annese V, J Crohns Colitis 2013

Application of ESPGHAN revised Porto criteria for diagnosis of PIBD at AMCCH



Levin A, JPGN 2014

Small bowel evaluation

- SB image is essential in children with CD, IBD-U or atypical UC.

- *MRE is currently the imaging modality of choice in PIBD at diagnosis.*
  - *detect small intestinal involvement*
  - *detect inflammatory changes in the intestinal wall*
  - *identify disease complications (fistula, abscess, stenosis)*
- *Wireless capsule endoscopy (WCE) is an useful alternative to identify SB mucosal lesions in children with suspected CD*
  - *when conventional endoscopy and image tools have been nondiagnostic*
  - *when MRE cannot be performed due to young age*
  - *in settings where MRI is not available or not feasible*

Typical CD

Typical macroscopic findings	Typical microscopic findings	Nonspecific microscopic findings
• Mucosal aphthous ulcers	• Noncaseating granuloma-must be remote from ruptured crypt	• Granuloma adjacent to ruptured crypt
• Linear or serpentine ulceration	• Focal chronic inflammation	• Mild nonspecific inflammatory infiltrate in lamina propria
• Cobble stoning	• Transmural inflammatory infiltrate	• Mucosal ulceration/erosions
• Stenosis/stricture of bowel with prestenotic dilatation	• Submucosal fibrosis	• Signs of chronicity (crypt architectural changes, colonic Paneth cell metaplasia, goblet cell depletion)
• Skip lesions		
• Jejunal or ileal ulcers		
• Image/surgical-bowel wall thickening with luminal narrowing		
• Perianal lesions: fistula, abscesses, anal stenosis, anal canal ulcers, large(>5mm) and inflamed skin tags		

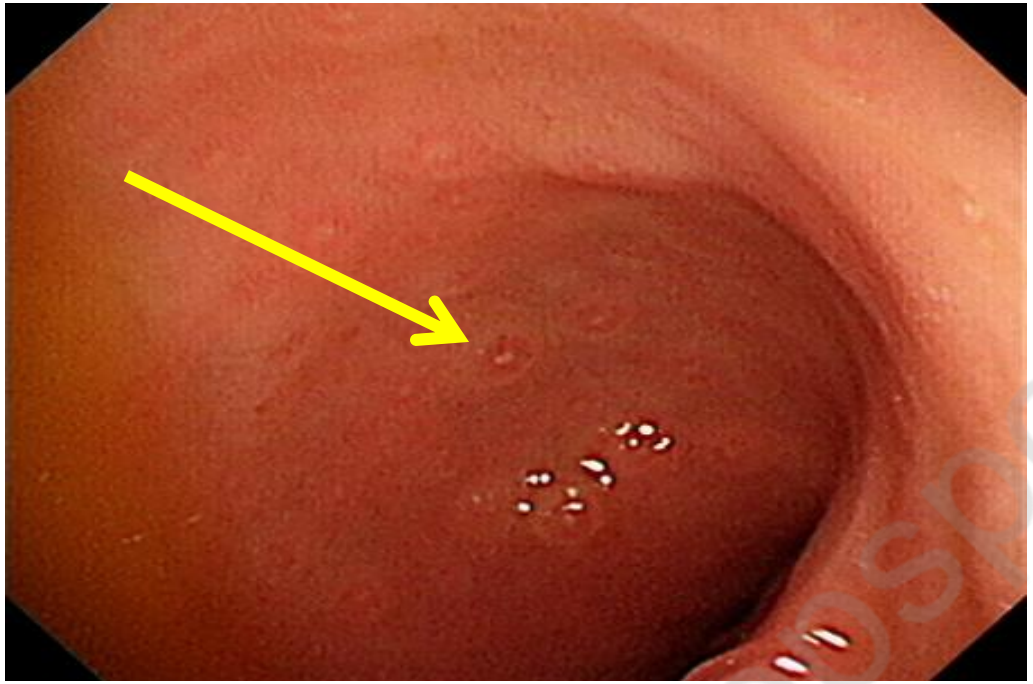
Levine A, J PCN 2014; Annese V, JCC 2013; Magro F, JCC 2013

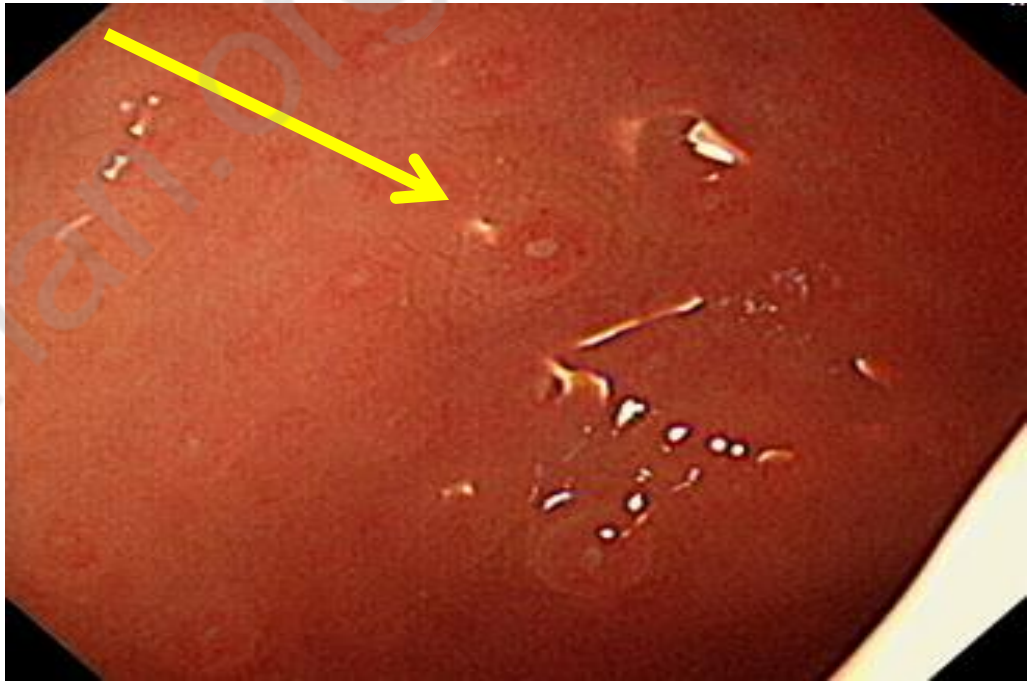
Endoscopic features of CD

- No endoscopic feature is specific for UC or CD
  (ECCO Statement 5A, *Annese V, J Crohns Colitis 2013)*.
- Patch (discontinuous & asymmetrical) distribution
  - Skip lesions
- Ulcers
  - Aphthous ulcer
  - Deep longitudinal ulcer
- Cobble stone appearance mucosa

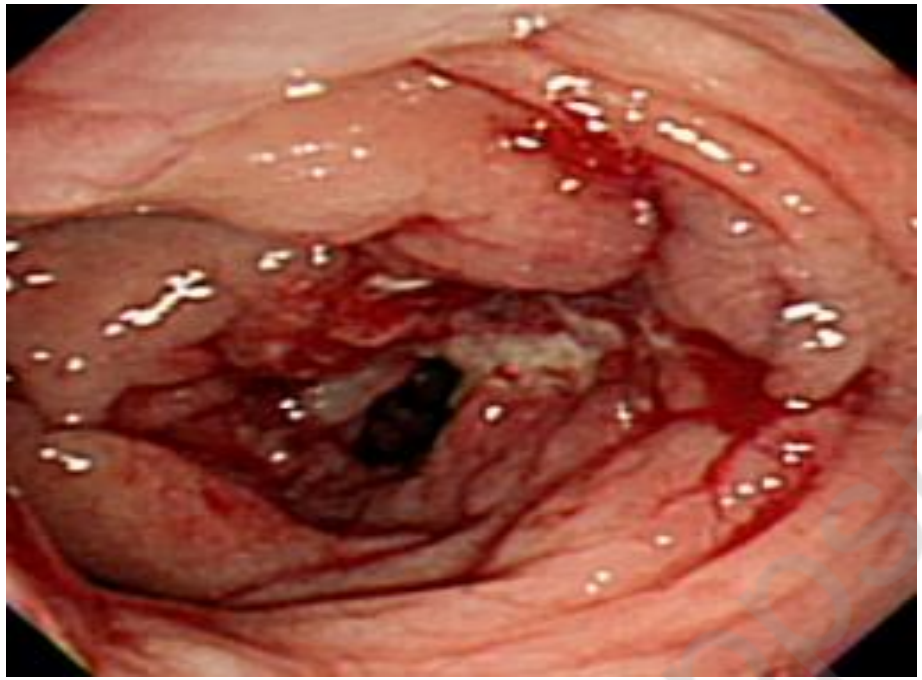
Discontinuity (skip lesions)

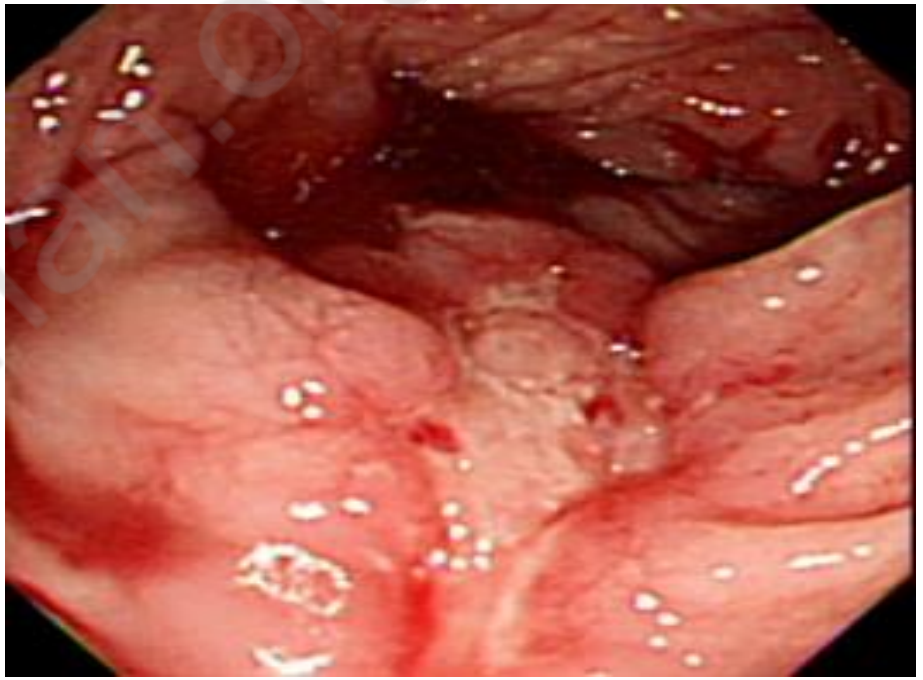
Aphthous Ulcer (or erosion)



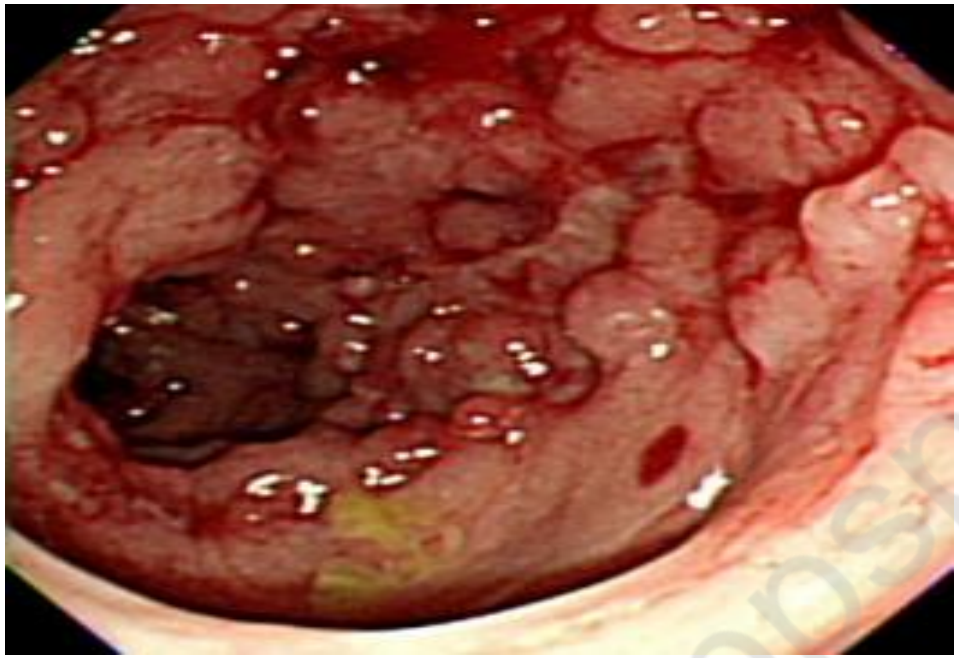


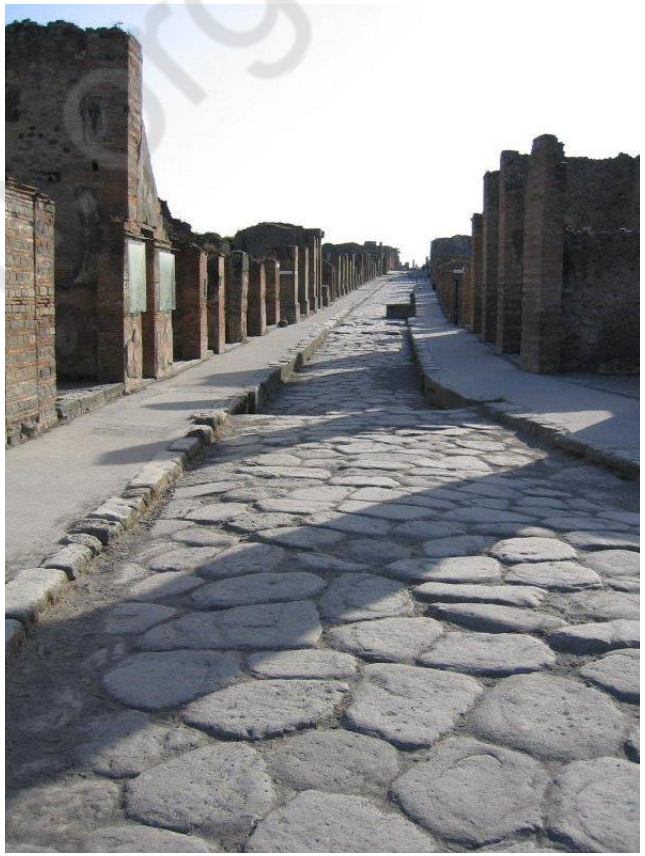
Ulcers (longitudinal)





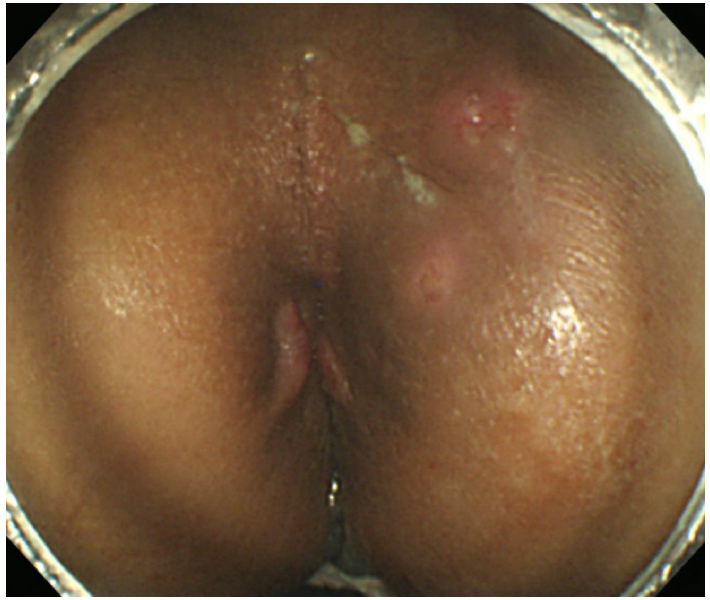
Cobble stones



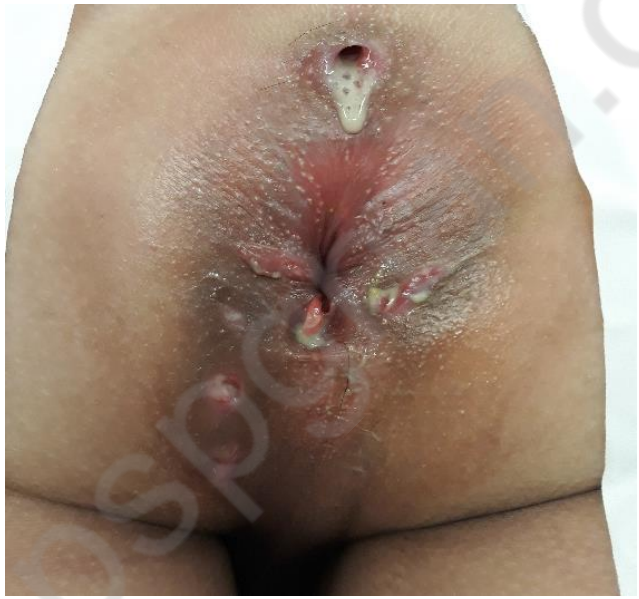


Paving of a "Roman" road

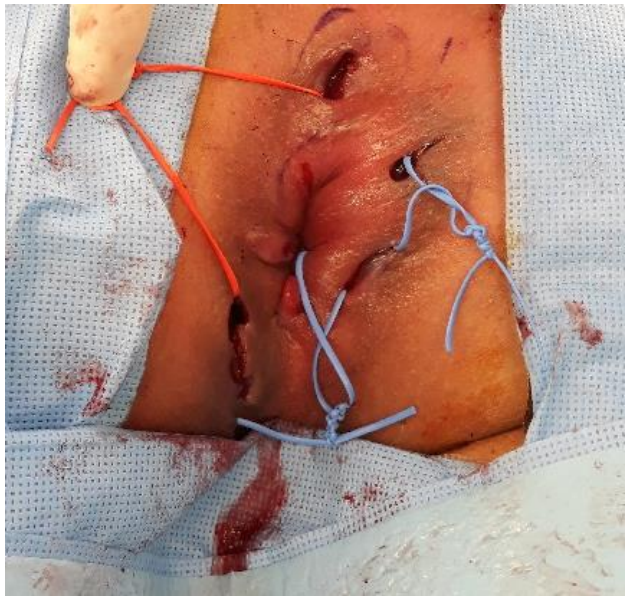
Perianal fistula



PE



EUA

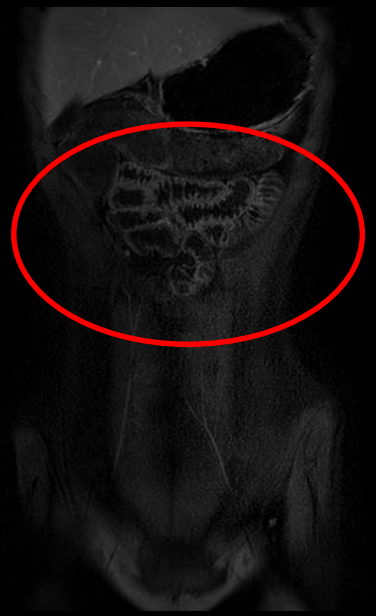


Seton

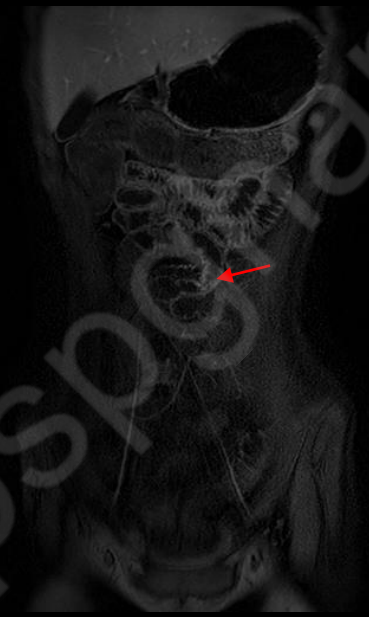
Crohn’s disease

MRE in CD patient

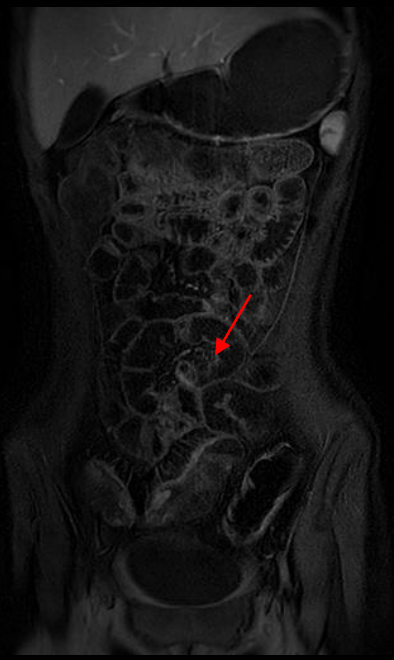
SB involvement: SB wall thickening



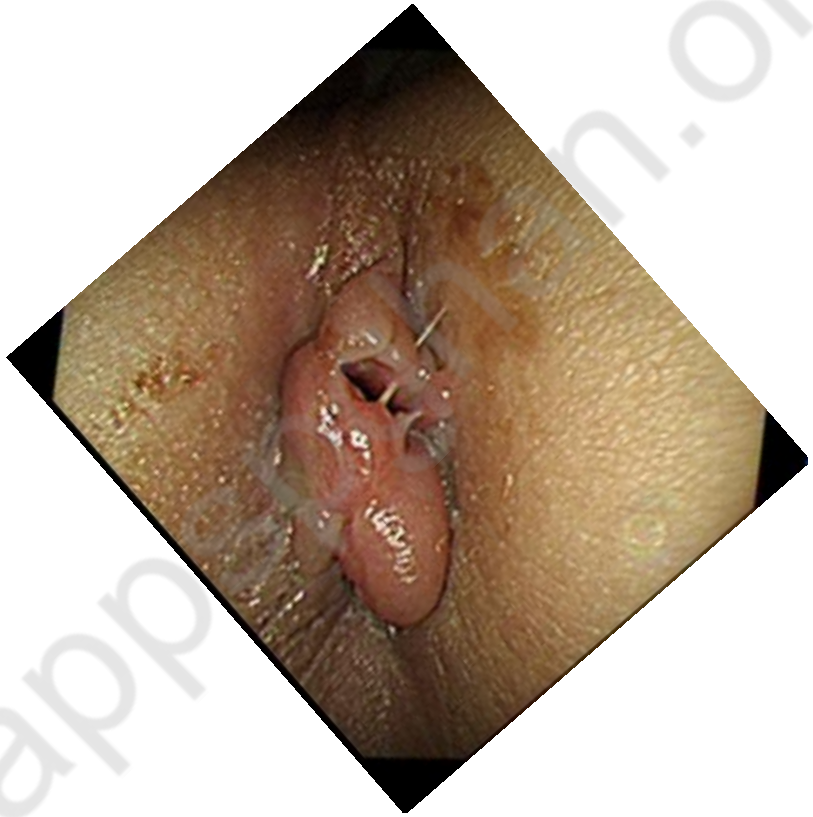
Enteric fistula



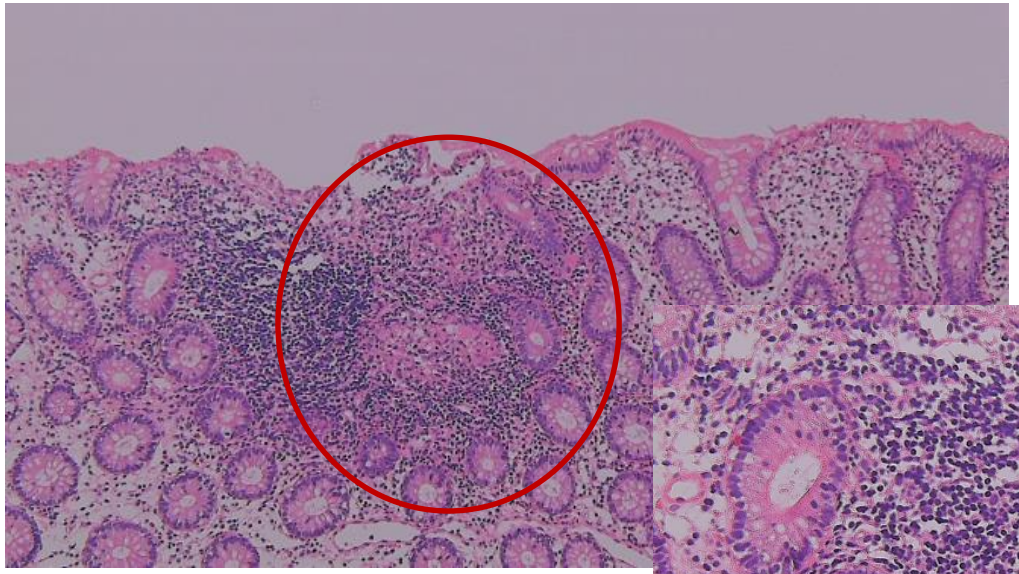
Enteric fistula

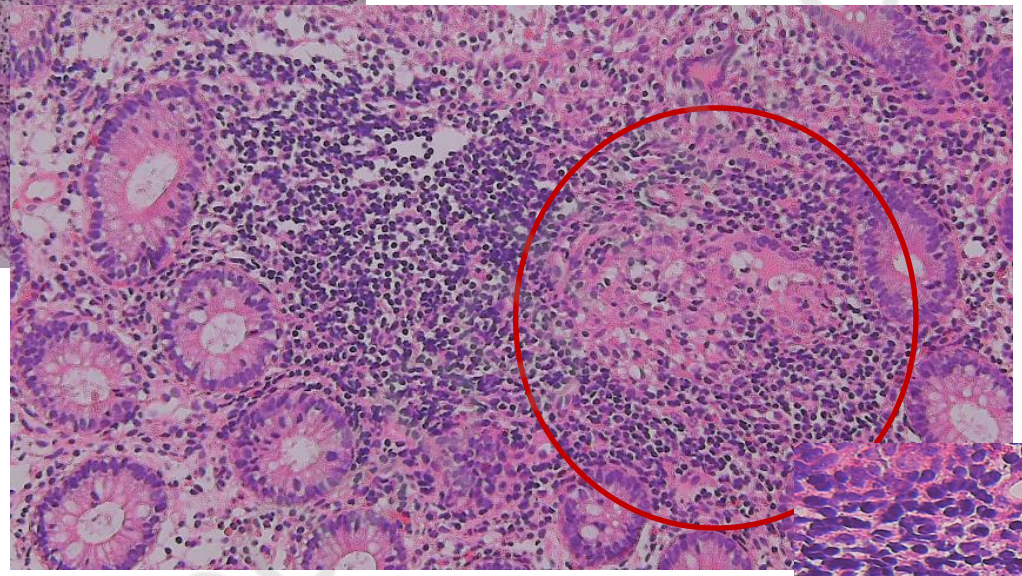


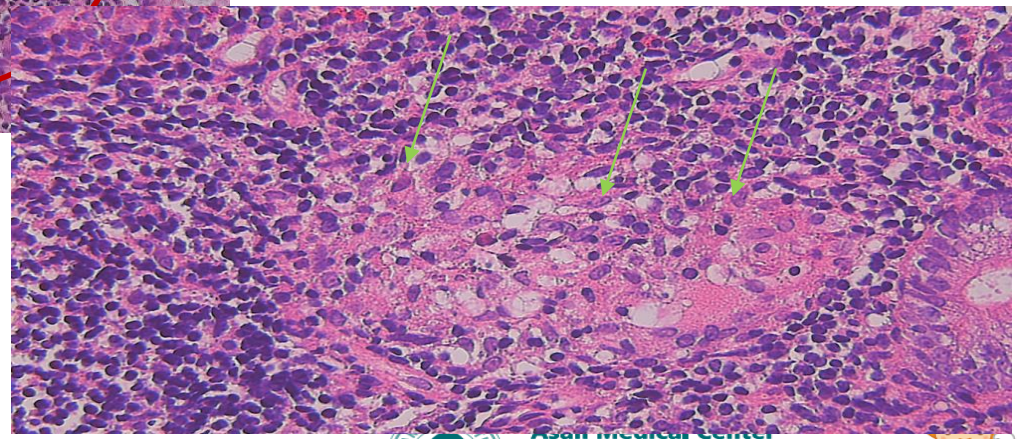
Large (>5mm) and inflamed skin tag



Colon granuloma







Endoscopic features of UC

- No endoscopic feature is specific for UC or CD
  (ECCO Statement 5A, *Annese V, J Crohns Colitis 2013)*.

- Continuous & symmetrical manner from rectum
- Erythema/hyperemia
- Loss of vascularity
- Granularity
- Friability
- Erosions & small superficial ulcers

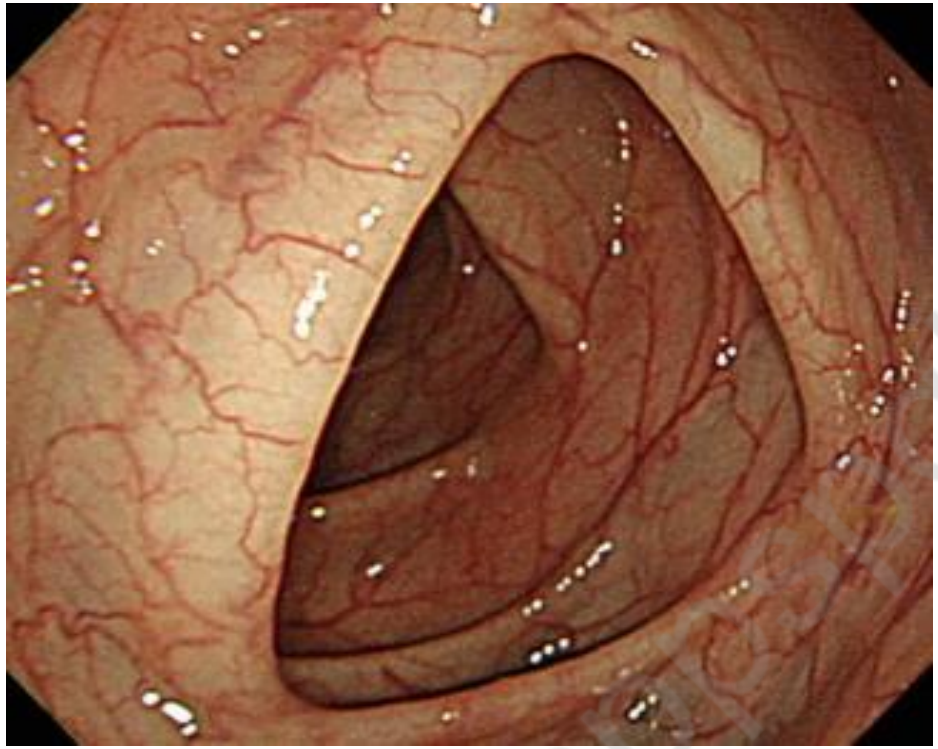
Typical UC

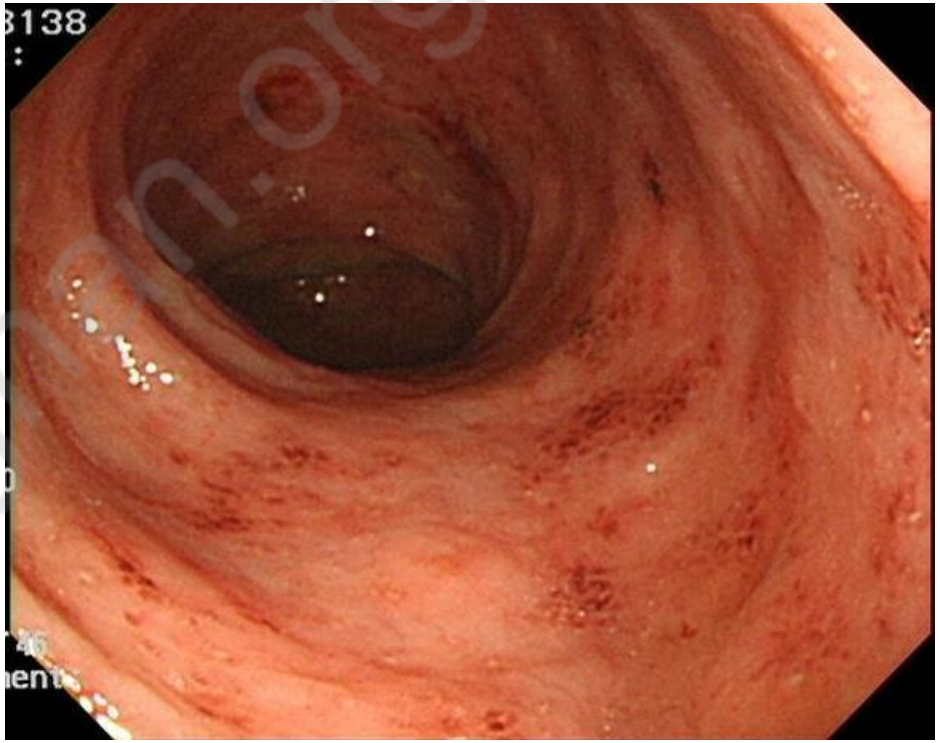
Macroscopic findings	Microscopic findings
• Contiguous mucosal inflammation of colon	• Architectural distortion, diffuse
• Starting distally from the rectum without SB involvement	• Basal lymphoplasmacytosis
• Erythema, granularity, friability, purulent exudates, superficial small ulcers	• No granuloma

Levine A, J Pediatr Gastroenterol Nutr 2014
Annese V, J Crohns Colitis 2013
Magro F, J Crohns Colitis 2013

Erythema/hyperemia

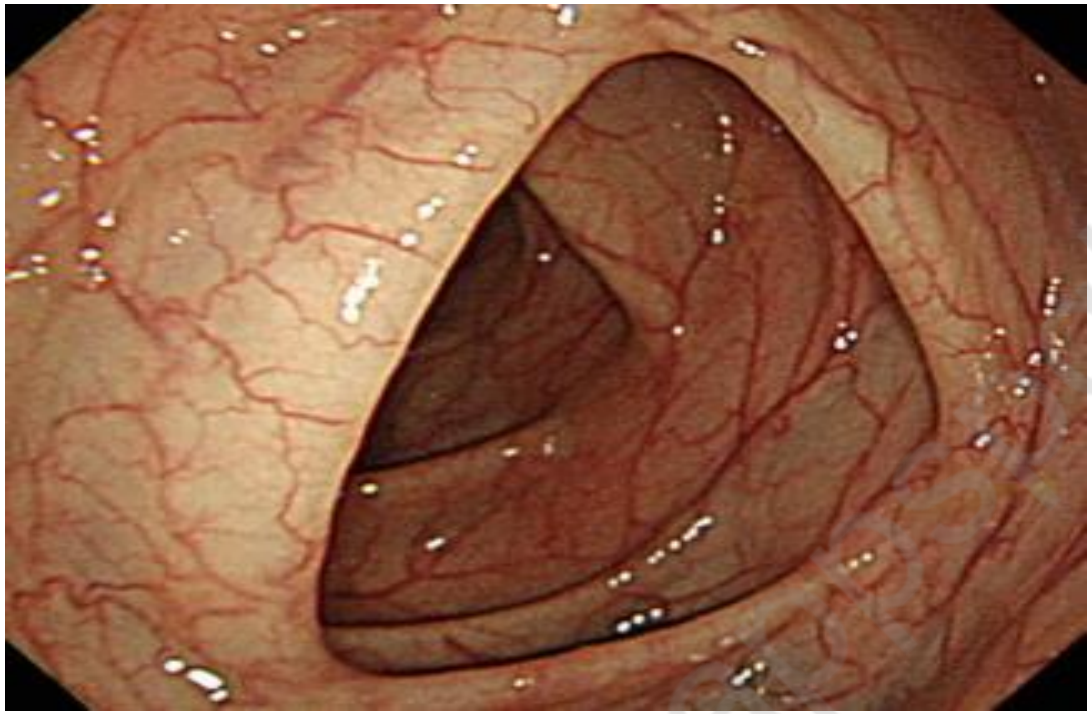
Normal mucosa



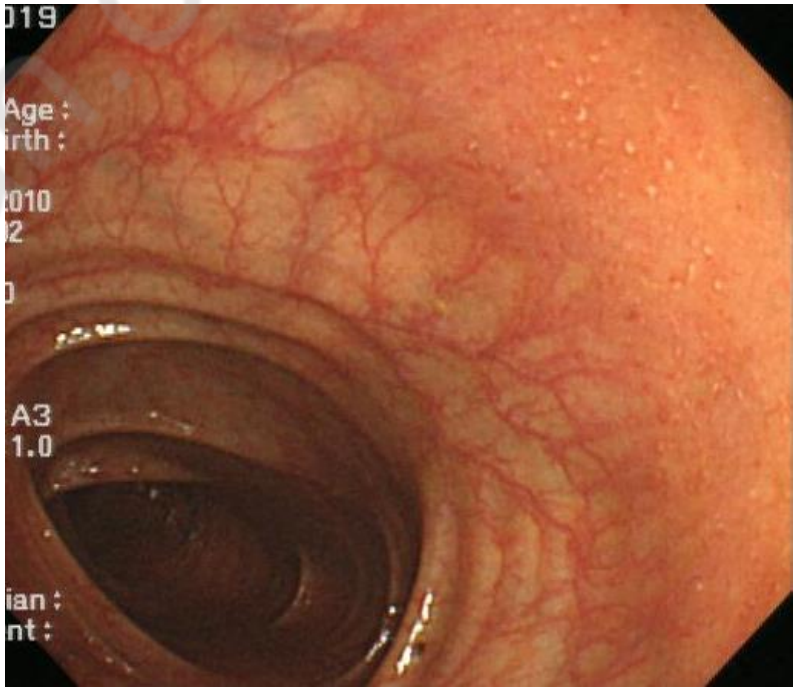


Loss of vascularity

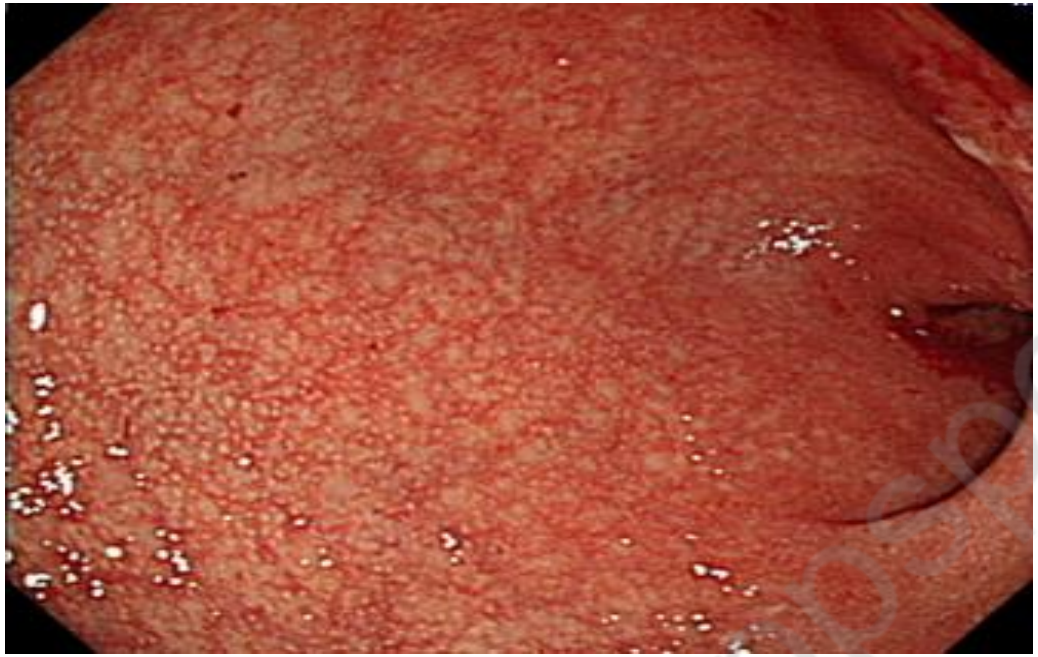
Normal mucosa vascularity



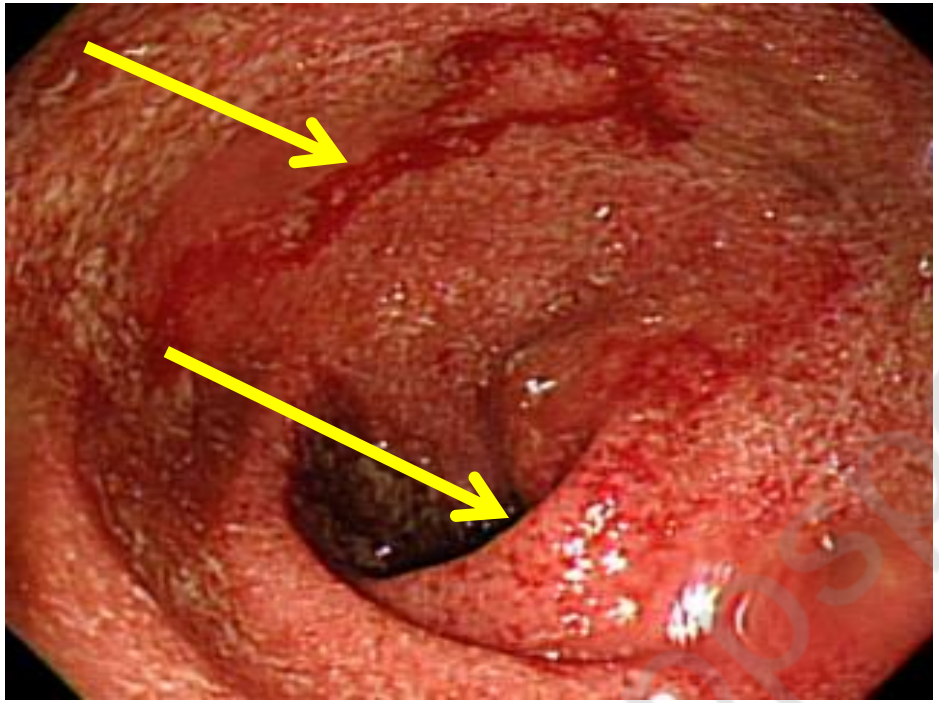
Loss of mucosa vascularity

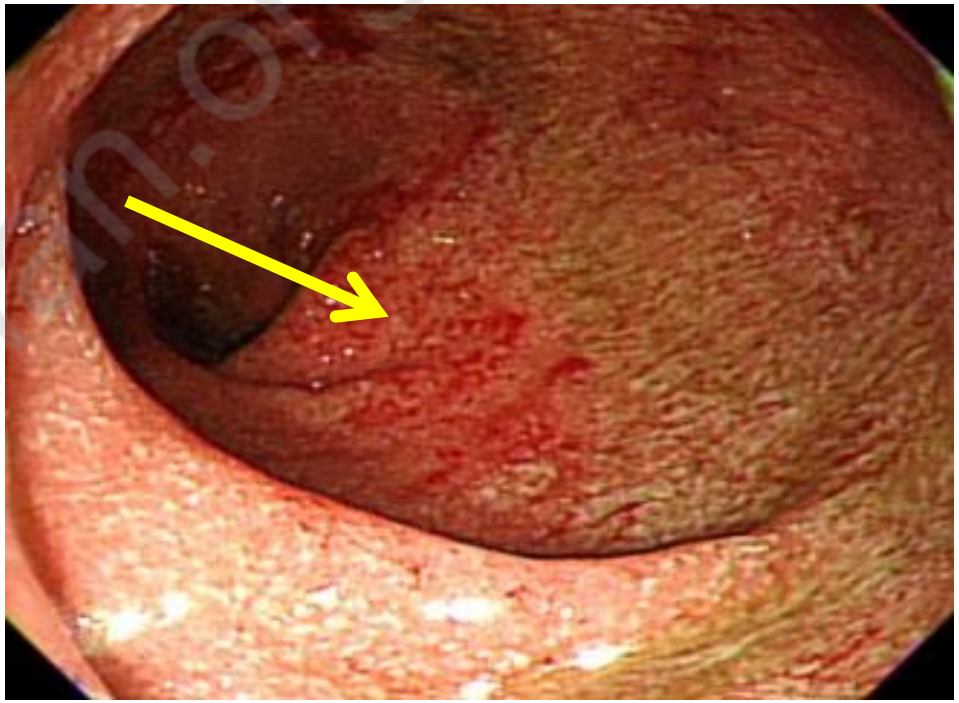


Granularity

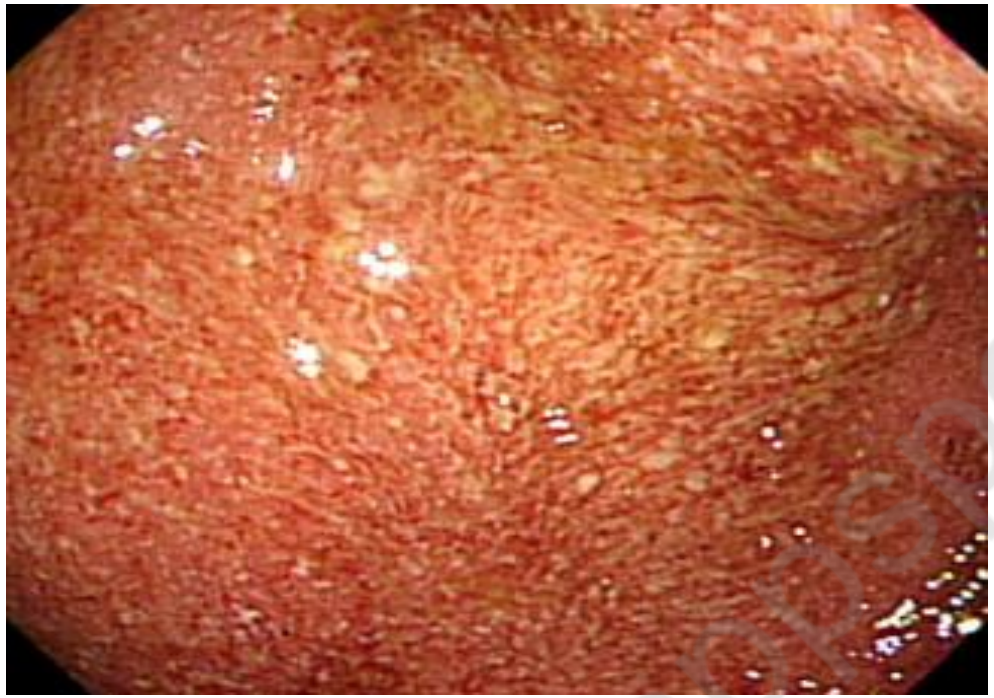


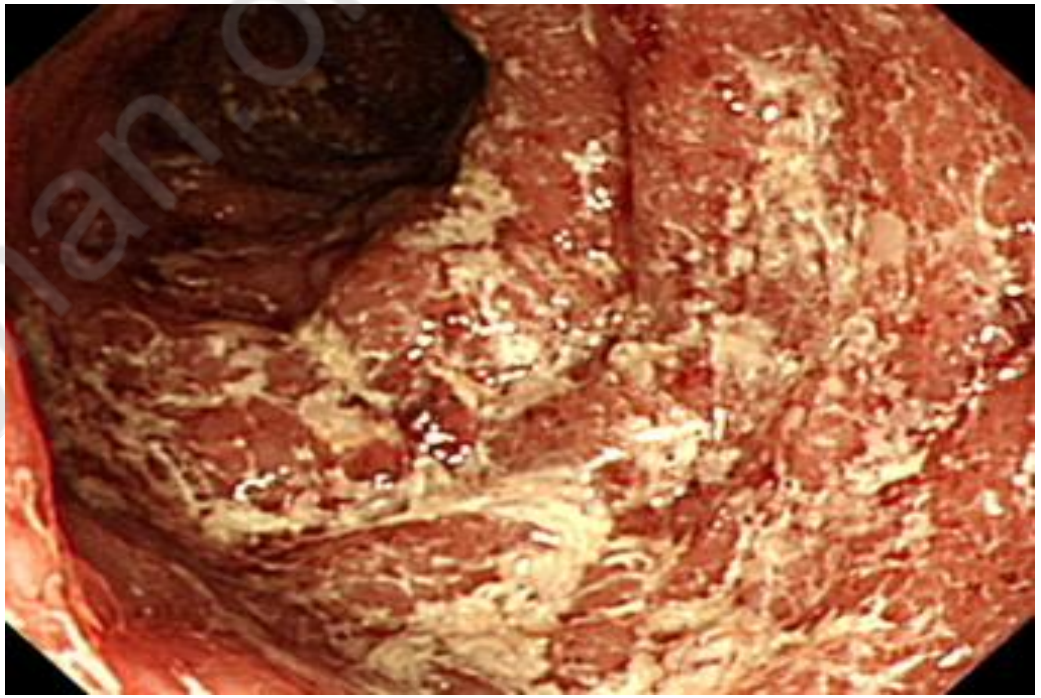
Friability



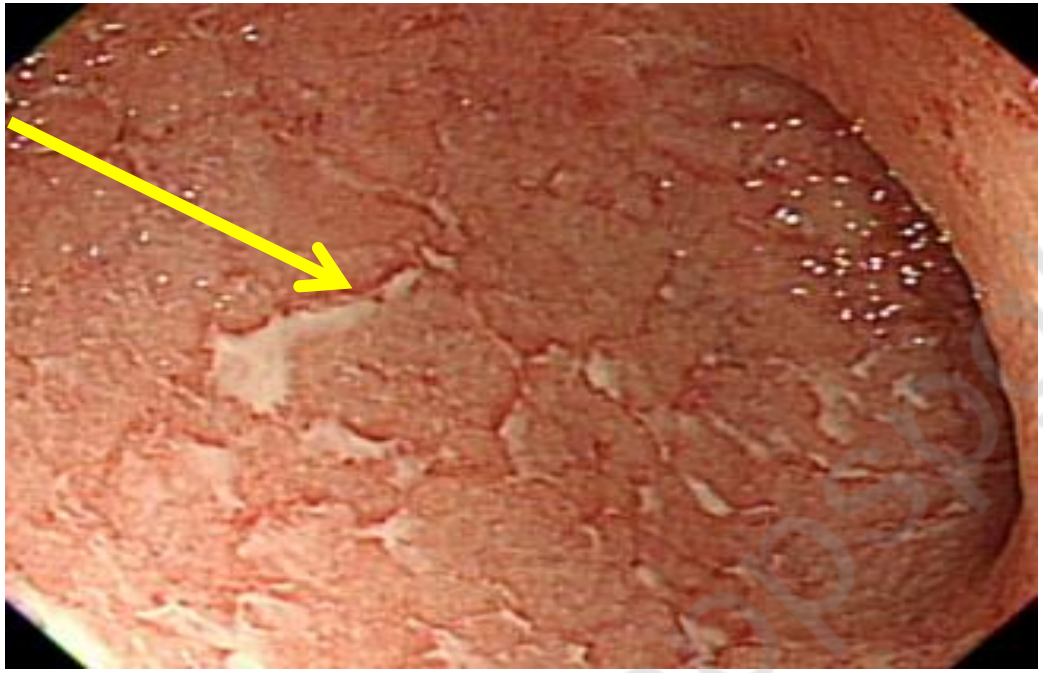


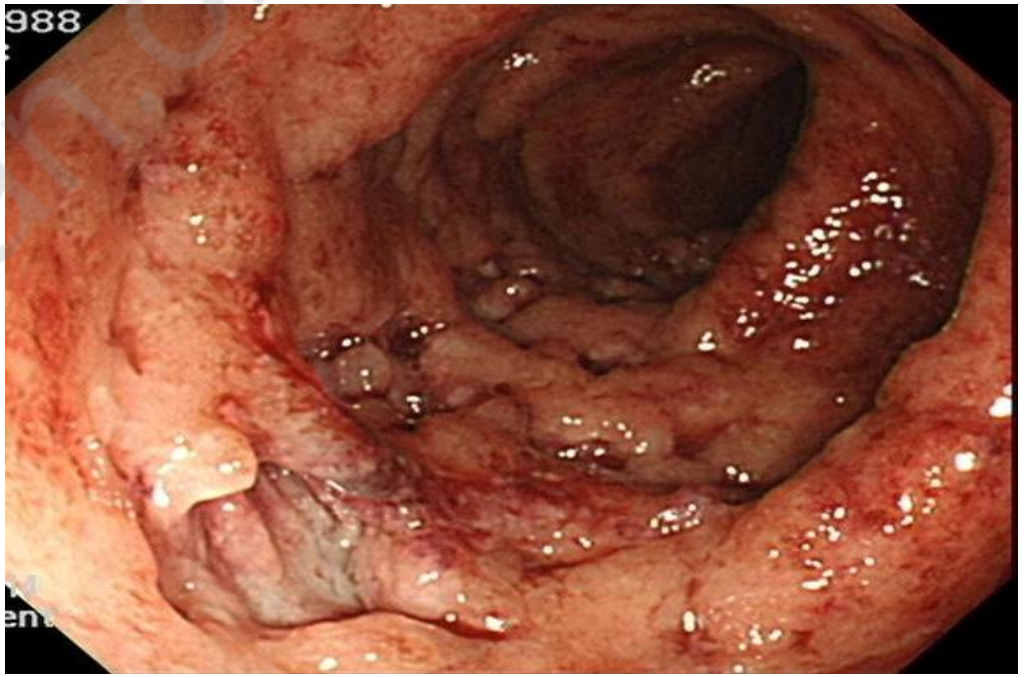
Exudates





Erosions & ulcers





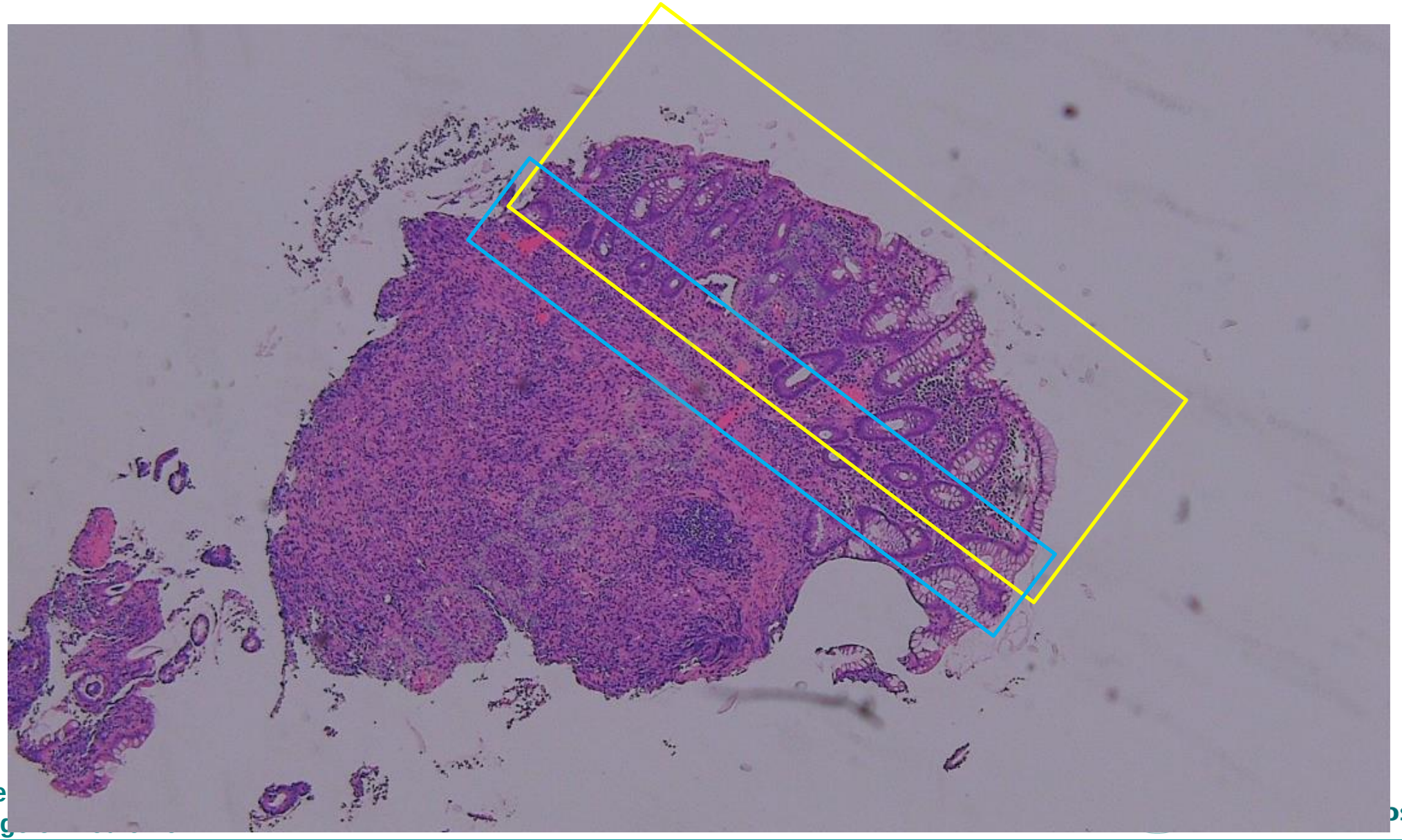
Terminal ileal involvement in UC

- Continuous extension of macroscopic or histological inflammation from the caecum into the most distal ileum in 6~20% of UC with pancolitis (termed "backwash ileitis")

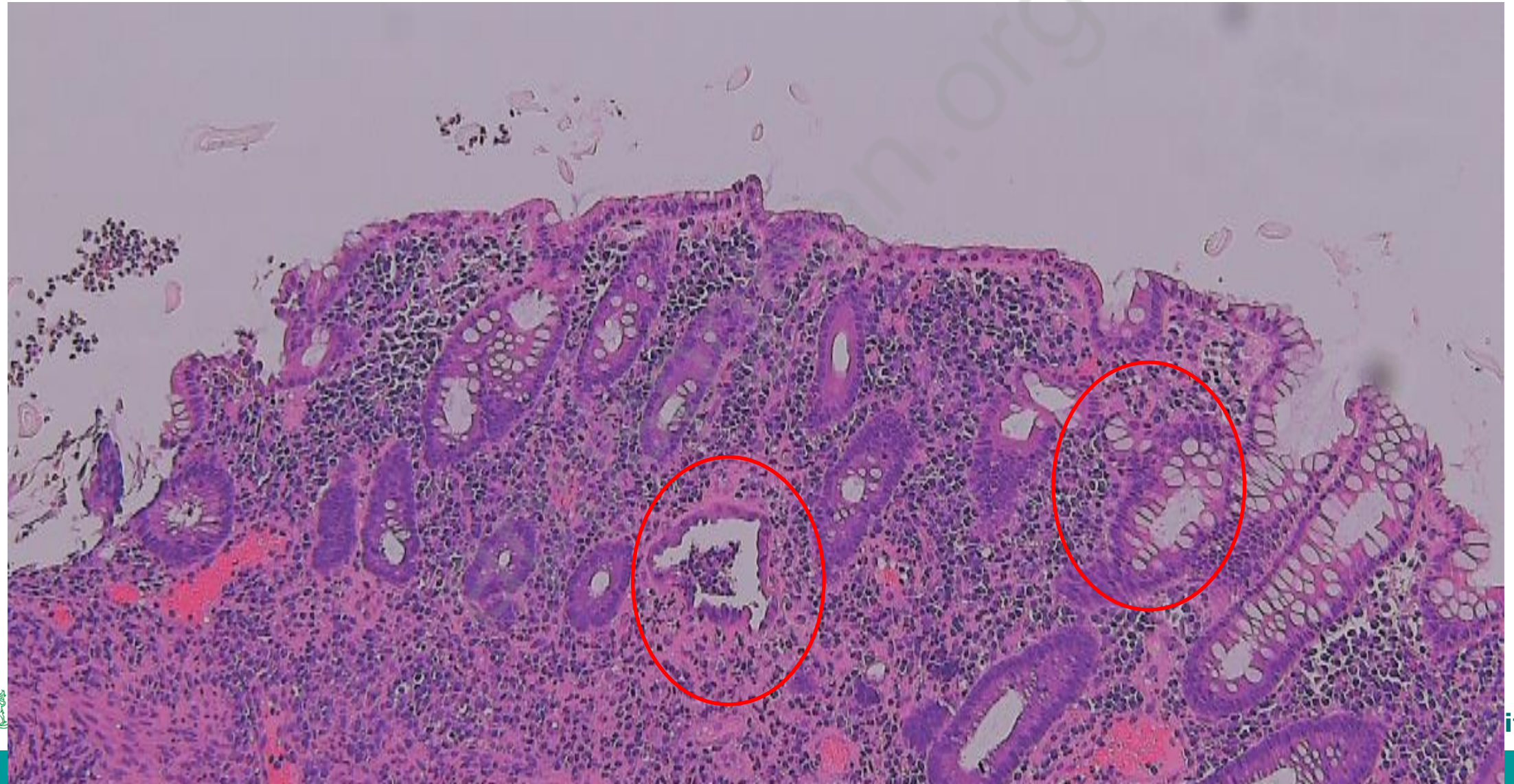
- Pathologic findings: neutrophilic cryptitis without surface ulcerations, superficial small ulcers, mild degree of villous atrophy, and lymphocytic infiltration in lamina propria

Levine A. et al. JPGN
2014;58:795

Crypt atrophy and basal lymphoplasmacytosis



Crypt abscess, crypt distortion, crypt branching

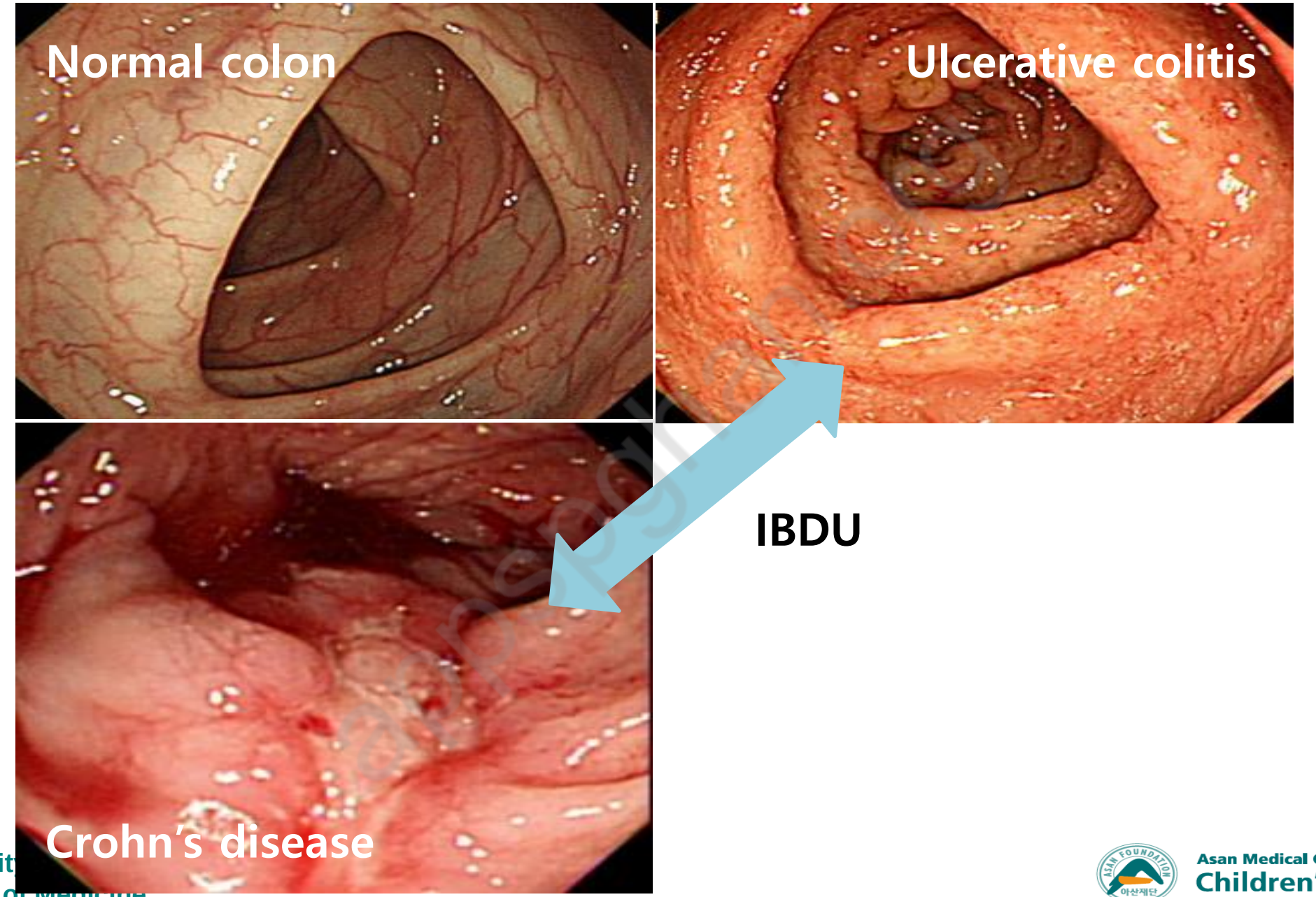


IBDU

Classical definition of IBD

- CD
- UC
- IBDU – mucosal inflammation, limited to colon, inconclusive

Silverberg MS, Can J Gastroenterol 2005


Normal colon
Ulcerative colitis
IBDU
Crohn's disease

IBDU

- IBDU is a real IBD subtype
- A validated classification scheme can accurately classify IBDU from CD/UC
- Around 5-25% of all PIBD
- Treatment along lines of UC

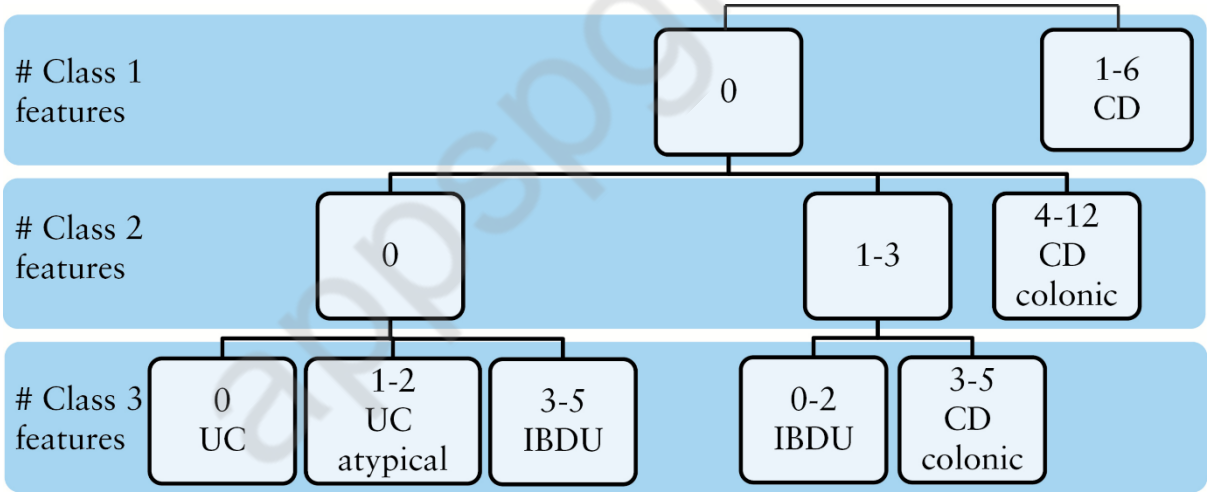
Sawczenko A, Arch Dis Child 2003;
Birimberg-Schwartz L, J Crohns Colitis 2017
Silverberg MS, Can J Gastroenterol 2005

Journal of Crohn's and Colitis, 2017, 1078–1084
doi:10.1093/ecco-jcc/jjx053
Advance Access publication April 18, 2017
Original Article

Original Article

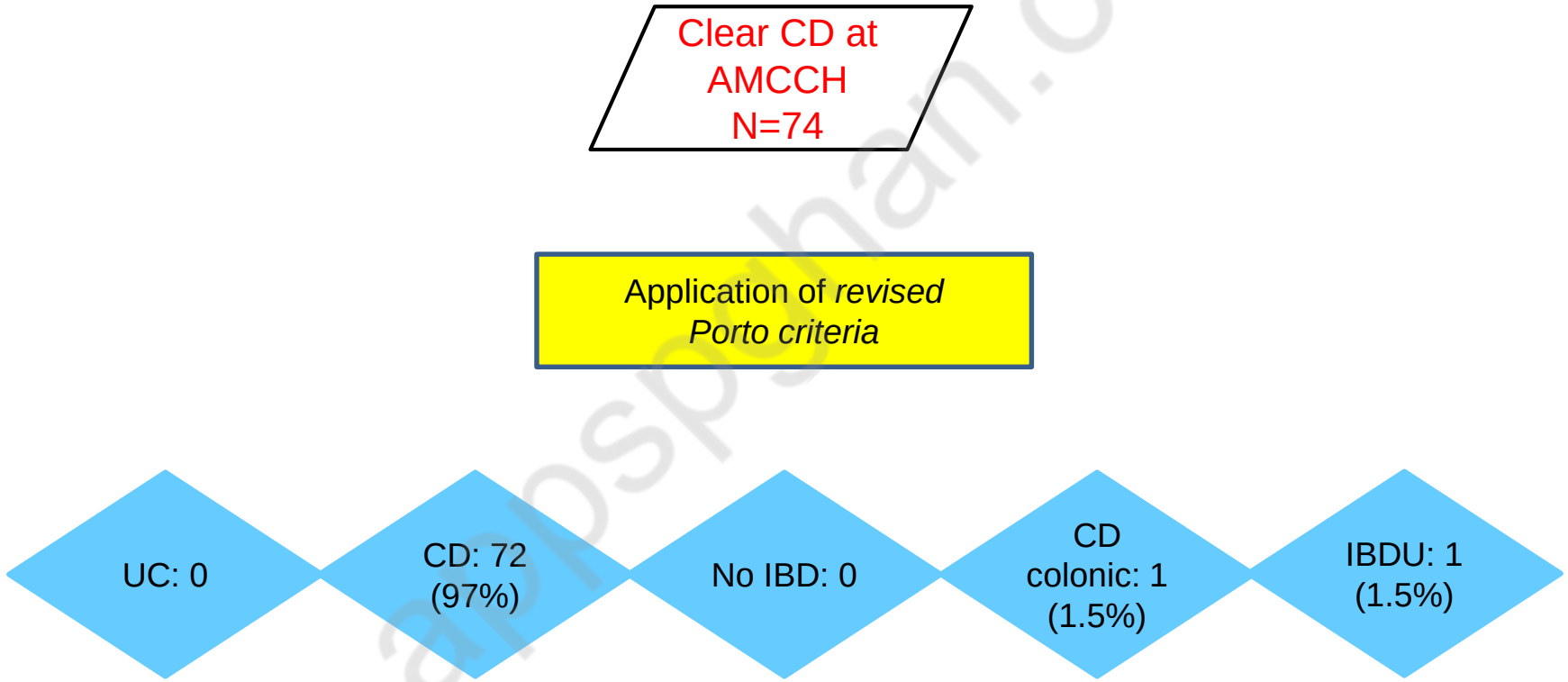
Development and Validation of Diagnostic Criteria for IBD Subtypes Including IBD-unclassified in Children: a Multicentre Study From the Pediatric IBD Porto Group of ESPGHAN

Liron Birimberg-Schwartz,[a] David M. Zucker,[b] Amichay Akriv,[b] Salvatore Cucchiara,[c] Fiona L. Cameron,[d] David C. Wilson,[d] Iza Łazowska,[e] Lambri Yianni,[f] Siba Prosad Paul,[g] Claudio Romano,[h] Sanja Kolaček,[i] Stephan Buderus,[j] Anders Pærregaard,[k] Richard K. Russell,[l] Johanna C. Escher,[m] Dan Turner[a,b]; on behalf of the Pediatric IBD Porto group of ESPGHAN

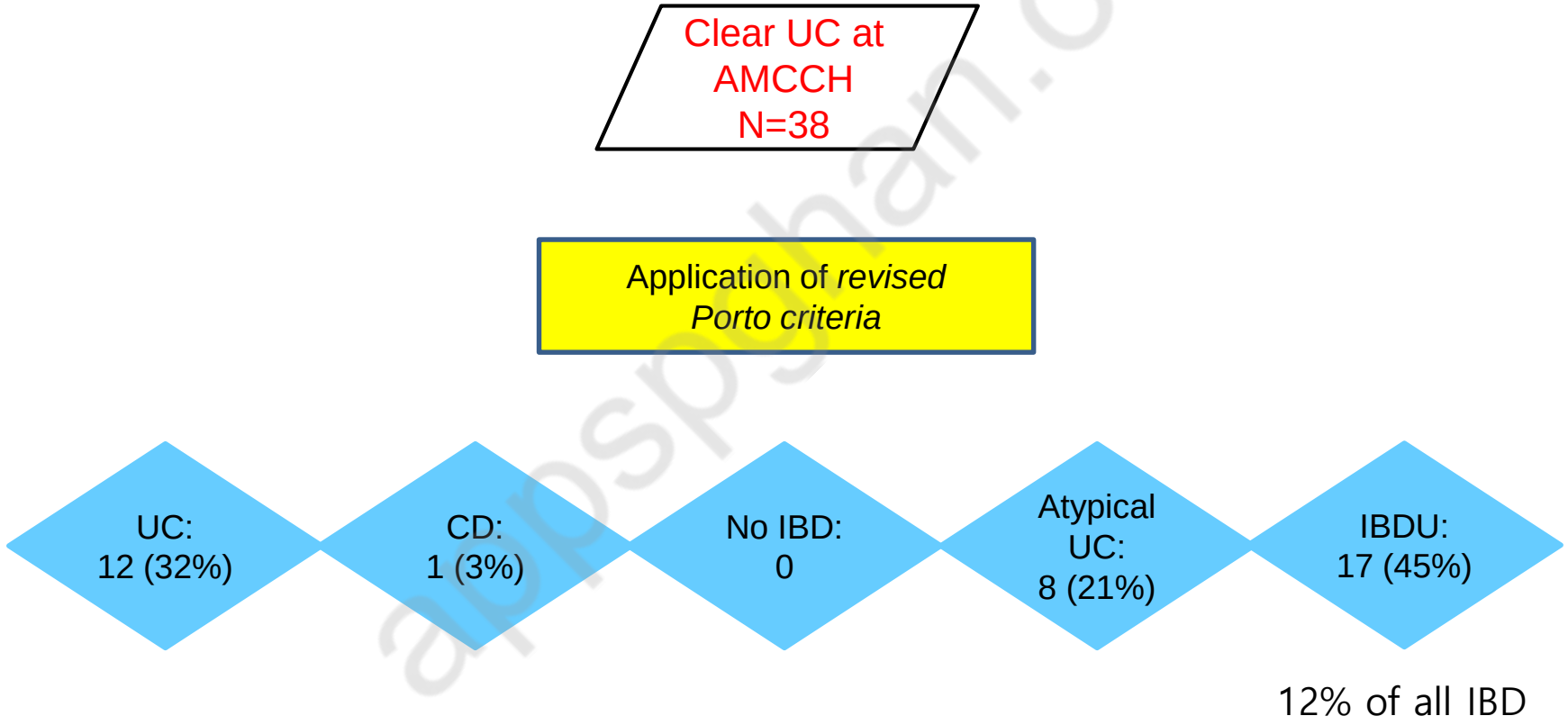


Levine A, JPGN 2014
Birimberg-Schwartz L, JCC 2017

Reclassification analysis of PCD at AMCCH by revised Porto criteria



Reclassification analysis of PUC at AMCCH by revised Porto criteria



12% of all IBD

Lee SH et al, submitted to ECCO 2019

At time of diagnosis of IBD

- Assess classification
  - the location, behavior, severity and complications
- Assess growth and nutritional status

Classification of CD

Levine A, IBD 2011

	Montreal (2005)	Paris (2011)
Age at diagnosis	A1: <17yr	A1a: 0 - <10yr
		A1b: 10- <17yr
	A2: 17-40yr	A2: 17-40yr
	A3: >40yr	A3: >40yr
Disease location	L1: terminal ileum ± limited cecal disease	L1: distal 1/3 ileum ± limited cecal disease
	L2: Colonic	L2: Colonic
	L3: Ileocolonic	L3: Ileocolonic
	L4: isolated upper disease	L4a: upper disease proximal to ligaments of Treitz
		L4b: upper disease distal to ligaments of Treitz and proximal to distal 1/3 ileum
Disease behavior	B1: nonstricturing, nonpenetrating	B1: nonstricturing, nonpenetrating
	B2: stricturing	B2: stricturing
	B3: penetrating	B3: penetrating
		B2B3: both structuring and penetrating
	P: perianal disease modifier	P: perianal disease modifier
Growth		G0: no evidence of growth delay
		G1: growth delay

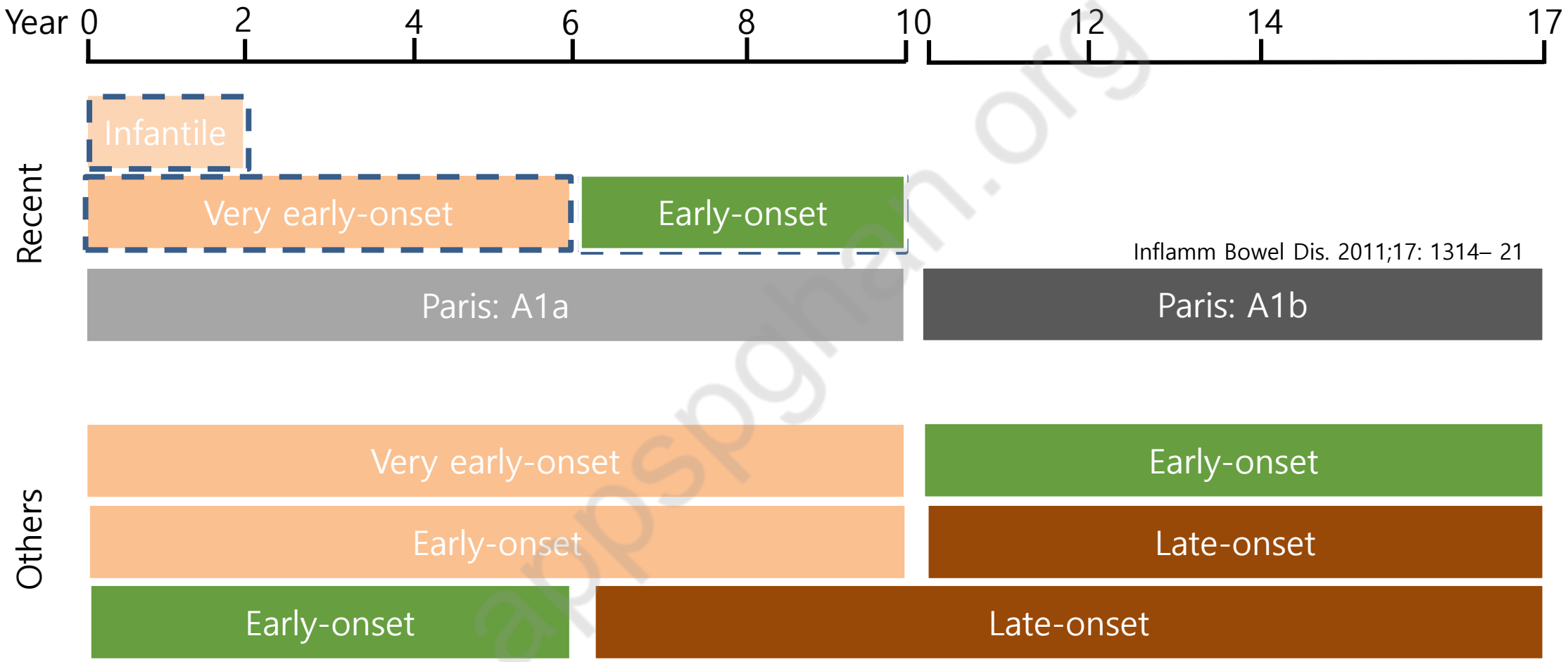
Classification of UC

Levine A, IBD 2011

	Montreal (2005)	Paris (2011)
Age at diagnosis	A1: <17yr	A1a: 0 - <10yr
		A1b: 10- <17yr
	A2: 17-40yr	A2: 17-40yr
	A3: >40yr	A3: >40yr
Extent	E1: ulcerative proctitis	E1: ulcerative proctitis
	E2: Lt-sided UC (distal to splenic flexure)	E2: Lt-sided UC (distal to splenic flexure)
	E3 : extensive (proximal to splenic flexure)	E3 : extensive (hepatic flexure distally)
		E4 : pancolitis (proximal to hepatic flexure)
Severity	S0: clinical remission	S0 : never severe*
	S1: mild UC	S1 : ever severe
	S2: moderate UC	
	S4: severe UC	

*Severe : PUCAI >65

Definition of PIBD according to age



Assessment of disease activity

Clinical disease activity:

Pediatric CD activity index (PCDAI)

remission <10
mild 10-30
moderate
severe

Hyams JPGN 1997

Clinical disease activity:

Pediatric UC activity index (PUCAI)

remission<10
mild 10-30
moderate 35-60
severe 60-85

Turner D, IBD 2009

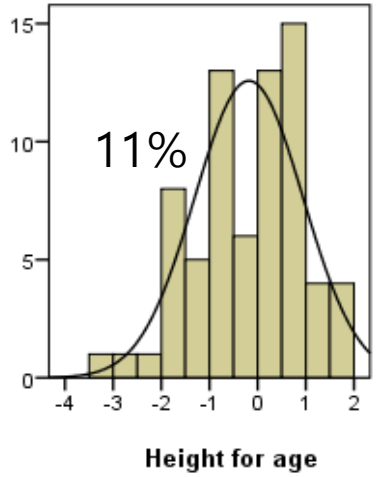
Assessment of Endoscopic Severity

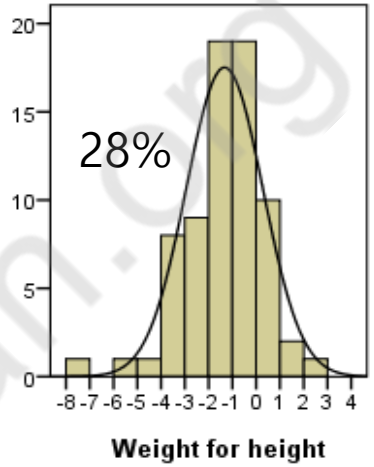
- CD
  - CDEIS *(Mary JY, Gut 1989)*
  - SES-CD *(Daperno M, Gastrointest Endosc 2004)*
- Postoperative CD
  - Rutgeerts score *(Rutgeerts P, Gastroenterology 1990)*
- UC
  - UCEIS *(Travis SP, Gut 2012)*

Assessment of nutrition and growth/puberty

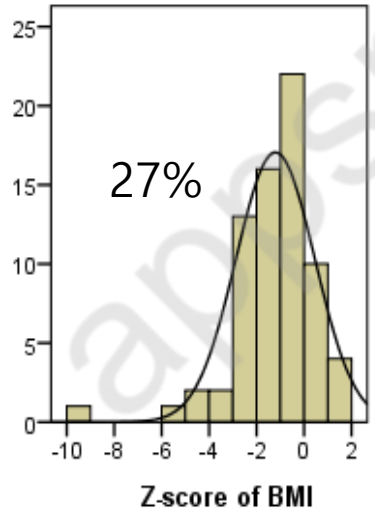
Prevalence of growth and nutritional failure (Z score<-2)

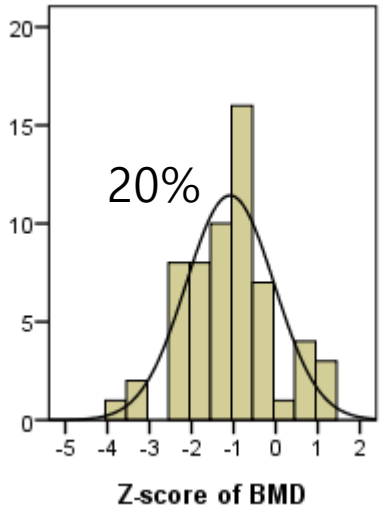
Western 9-24%





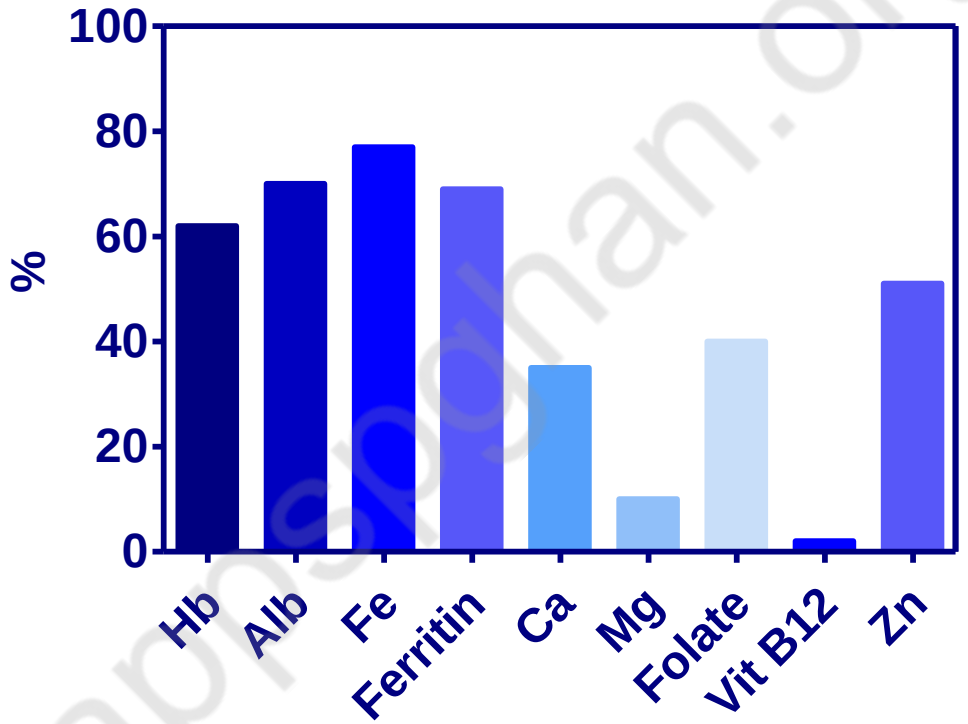
Western 10-57%





Song SM, Gut Liver 2014
Kim HJ, J Crohns Colitis 2017

Prevalence of subnormal serum level of biochemical markers



*hemoglobin levels used to define anemia: children 6 months to 5 years: 11.0 g/dl, children 5-11 years: 11.5 g/dl, children 12-13 years: 12.0 g/dl, men 13.0 g/dl, non-pregnant woman 12.0 g/dl

Pubertal rating according to Tanner stages

Carel JC, NEJM 2008

Two monogenic VEO-IBD: IL10RA & XIAP in AMC

Gut Liver. 2015 Nov 23;9(6):767-75. doi: 10.5009/gnl15176.

Is Whole Exome Sequencing Clinically Practical in the Management of Pediatric Crohn's Disease?

Oh SH[1], Baek J[2], Kim KM[1], Lee EJ[2], Jung Y[2], Lee YJ[1], Jin HS[3], Ye BD[4], Yang SK[4], Lee JK[5], Seo EJ[6], Lim HT[7], Lee I[8], Song K[2].

Author information

Abstract

BACKGROUND/AIMS: The aim of this study was to identify the profile of rare variants associated with Crohn's disease (CD) using whole exome sequencing (WES) analysis of Korean children with CD and to evaluate whether genetic profiles could provide information during medical decision making.

METHODS: DNA samples from 18 control individuals and 22 patients with infantile, very-early and early onset CD of severe phenotype were used for WES. Genes were filtered using panels of inflammatory bowel disease (IBD)-associated genes and genes of primary immunodeficiency (PID) and monogenic IBD.

RESULTS: Eighty-one IBD-associated variants and 35 variants in PID genes were revealed by WES. The most frequently occurring variants were carried by nine (41%) and four (18.2%) CD probands and were ATG16L2 (rs11235604) and IL17REL (rs142430606), respectively. Twenty-four IBD-associated variants and 10 PID variants were predicted to be deleterious and were identified in the heterozygous state. However, their functions were unknown with the exception of a novel p.Q111X variant in XIAP (X chromosome) of a male proband.

CONCLUSIONS: The presence of many rare variants of unknown significance limits the clinical applicability of WES for individual CD patients. However, WES in children may be beneficial for distinguishing CD secondary to PID.

J Crohns Colitis. 2016 Nov;10(11):1366-1371. Epub 2016 May 13.

A Synonymous Variant in IL10RA Affects RNA Splicing in Paediatric Patients with Refractory Inflammatory Bowel Disease.

Oh SH[1], Baek J[2], Liany H[3], Foo JN[3], Kim KM[1], Yang SC[2], Liu J[3], Song K[4].

Author information

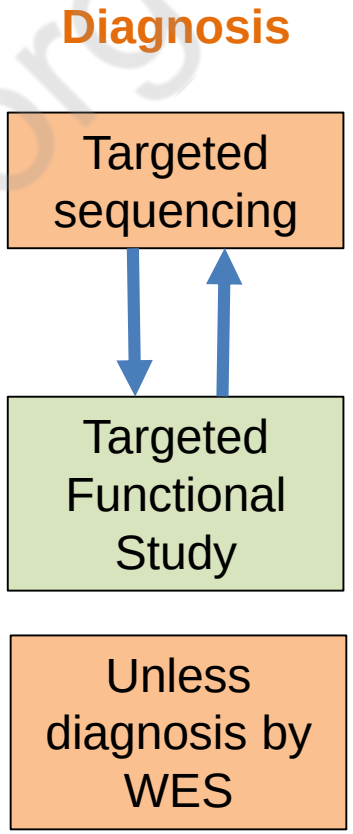
Abstract

Interleukin-10 receptor [IL10R] mutations are associated with severe childhood inflammatory bowel disease [IBD]. Two unrelated patients who died of very early-onset severe IBD and sepsis were identified as harbouring the same compound heterozygous mutations in IL10RA [p.R101W; p.T179T]. A third patient was found to be homozygous for p.T179T. The missense change of p.R101W has been reported. The synonymous change of p.T179T, with a minor allele frequency of 0.035% in the population, was novel. The p.T179T mutation was located before the 5' splice donor site, leading to exon skipping and out-of-frame fusion of exons 3 and 5, causing altered STAT3 phosphorylation in IL10-induced peripheral blood mononuclear cells. The patient developed colitis at 6 years of age, the oldest reported age of onset among patients with IL10RA mutations, and did not suffer from perianal disease. We report three paediatric patients with a rare, synonymous p.T179T variant causing a splicing error in IL10RA.

➔ N=22 with PIBD
IL10RA n=3, XIAP n=1

Diagnosis of Monogenic IBDs in real practice

- Defective IL10 signaling
  - App. 10% among VEO-IBD
  - **5 pediatric CD in AMCCH**
  - Symptom onset: 4 < 15mo, 1 = 6y
  - Two successful HSCT
- XIAP deficiency
  - 4% of male pediatric CD
  - **6 male pediatric CD in AMCCH**
  - **Symptom onset: 5~12y**
  - One successful HSCT
- Chronic granulomatous disease
  - 4% among VEO-IBD
  - **Manage by immunologist in AMCCH**



Gut 2015;64:66-76
Am J Gastroenterol 2011;106:1544
JPGN 2015;60:332-8
JCC 2016;10:1366

Consider monogenic IBD: YOUNG AGE MATTERS MOST

Young age onset (2y)

Multiple family members and consanguinity

Autoimmunity

Thriving failure

Treatment with conventional medication fails

Endocrine concerns

Recurrent infections

Severe perianal disease

Macrophage activation syndrome/HLH

Obstruction and atresia of intestine

Skin infections, dental caries and hair abnormalities

Tumors

Uhlig HH, Gastroenterology 2014

Monitoring methods

to reach the Treatment Goal

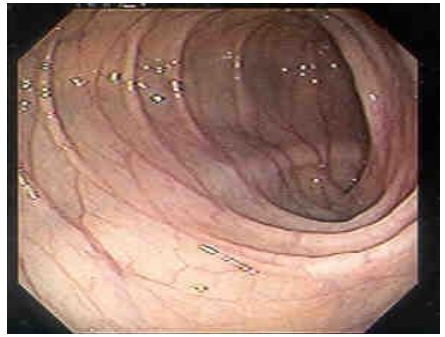
Targets to treat in PIBD

TRADITIONAL TREATMENT GOALS

- Induce and maintain clinical remission (symptom control)
- Facilitate growth (a marker of success of therapy)
- Insufficient for preventing long-term bowel damage

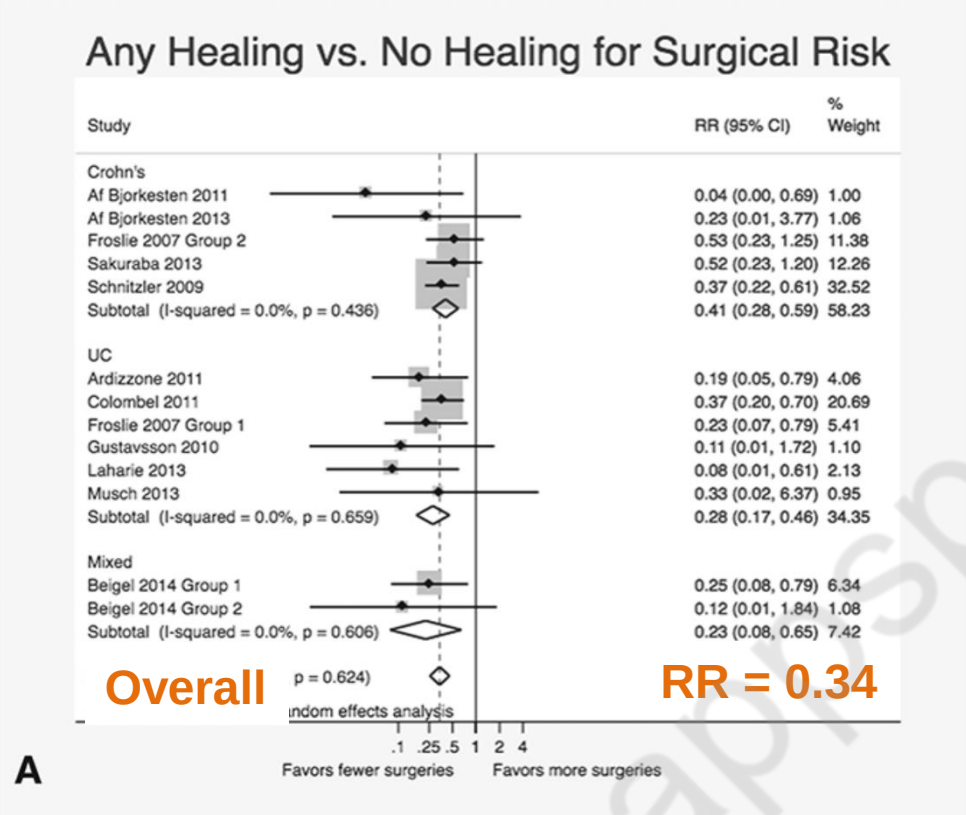
CURRENT TREATMENT GOALS

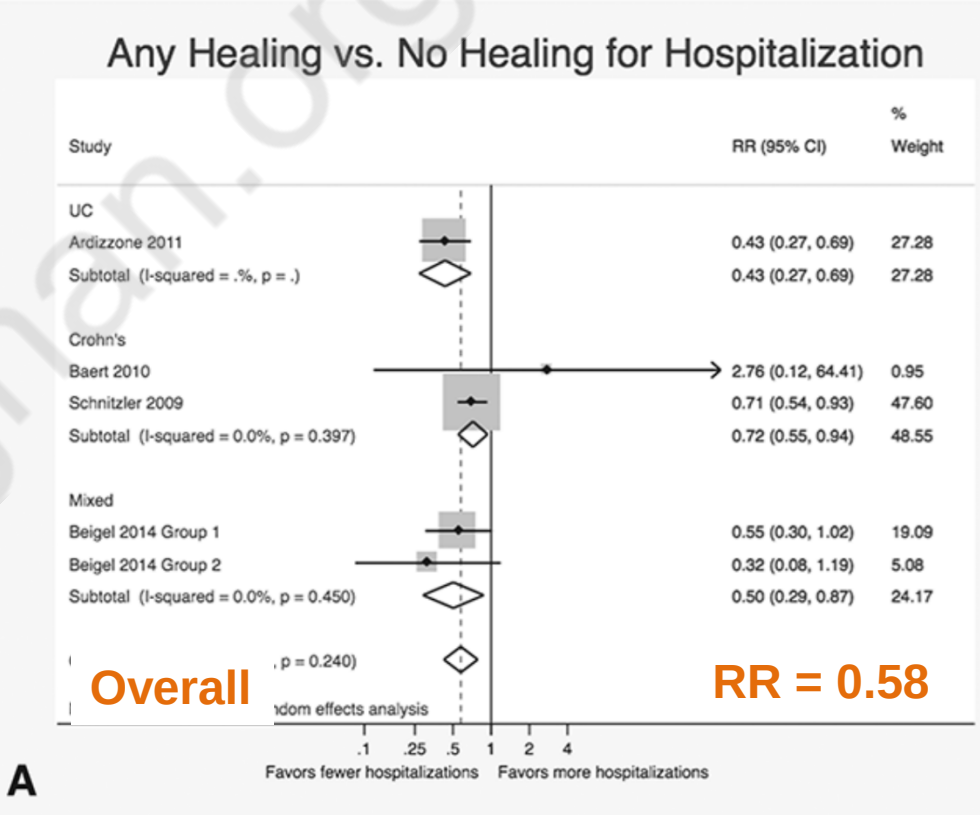
- Achieve and maintain mucosal healing



- To achieve preventing long-term bowel damage

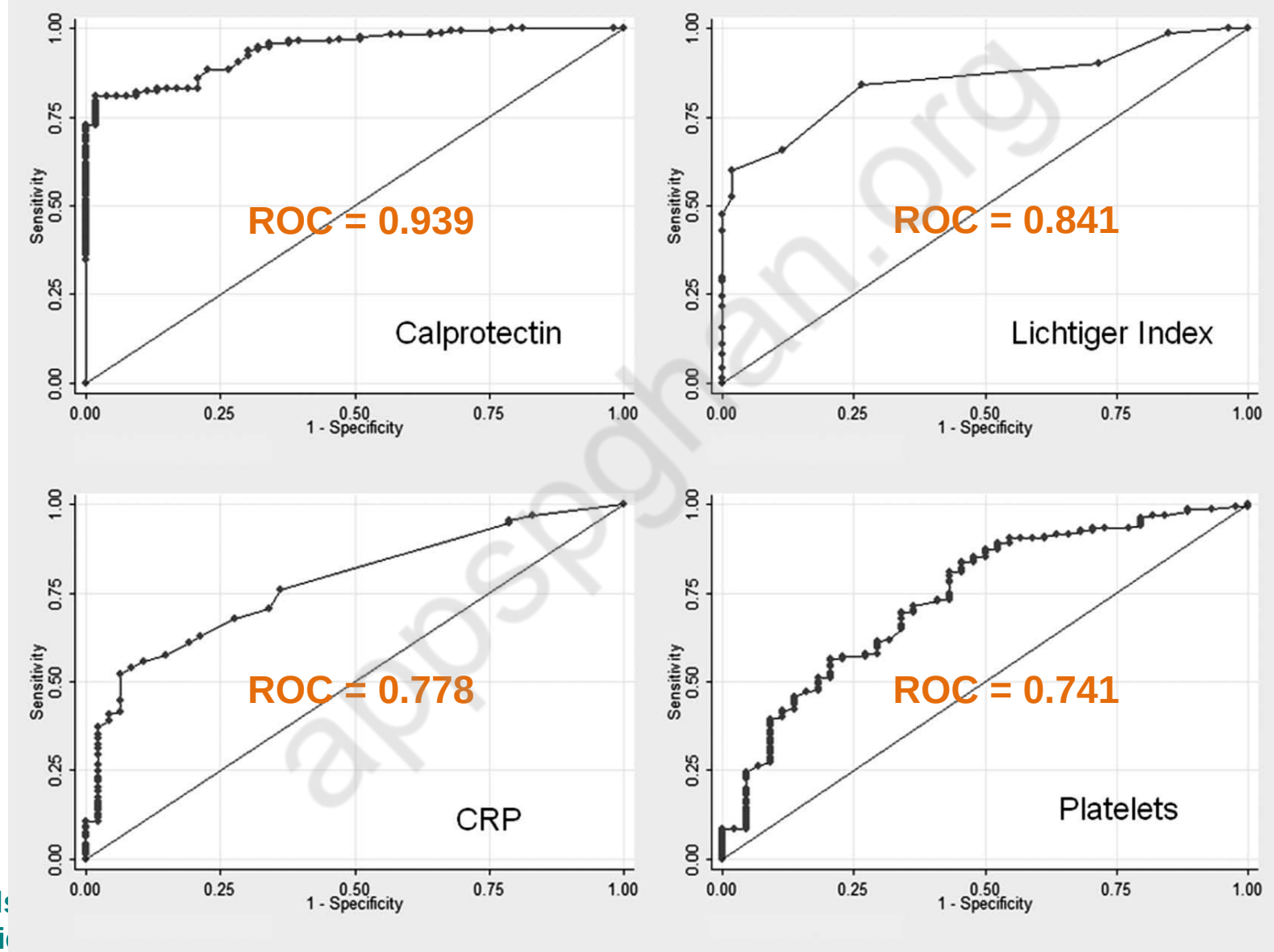
Endoscopic Mucosal Healing Predicts Favorable Clinical Outcomes in IBD: A Meta-analysis





Reinink AR, Inflamm Bowel Dis 2016

Fecal Calprotectin Correlates Best with Endoscopic Activity in UC



Schoepfer AM,
Inflamm Bowel Dis 2013

Targets for disease monitoring in PIBD

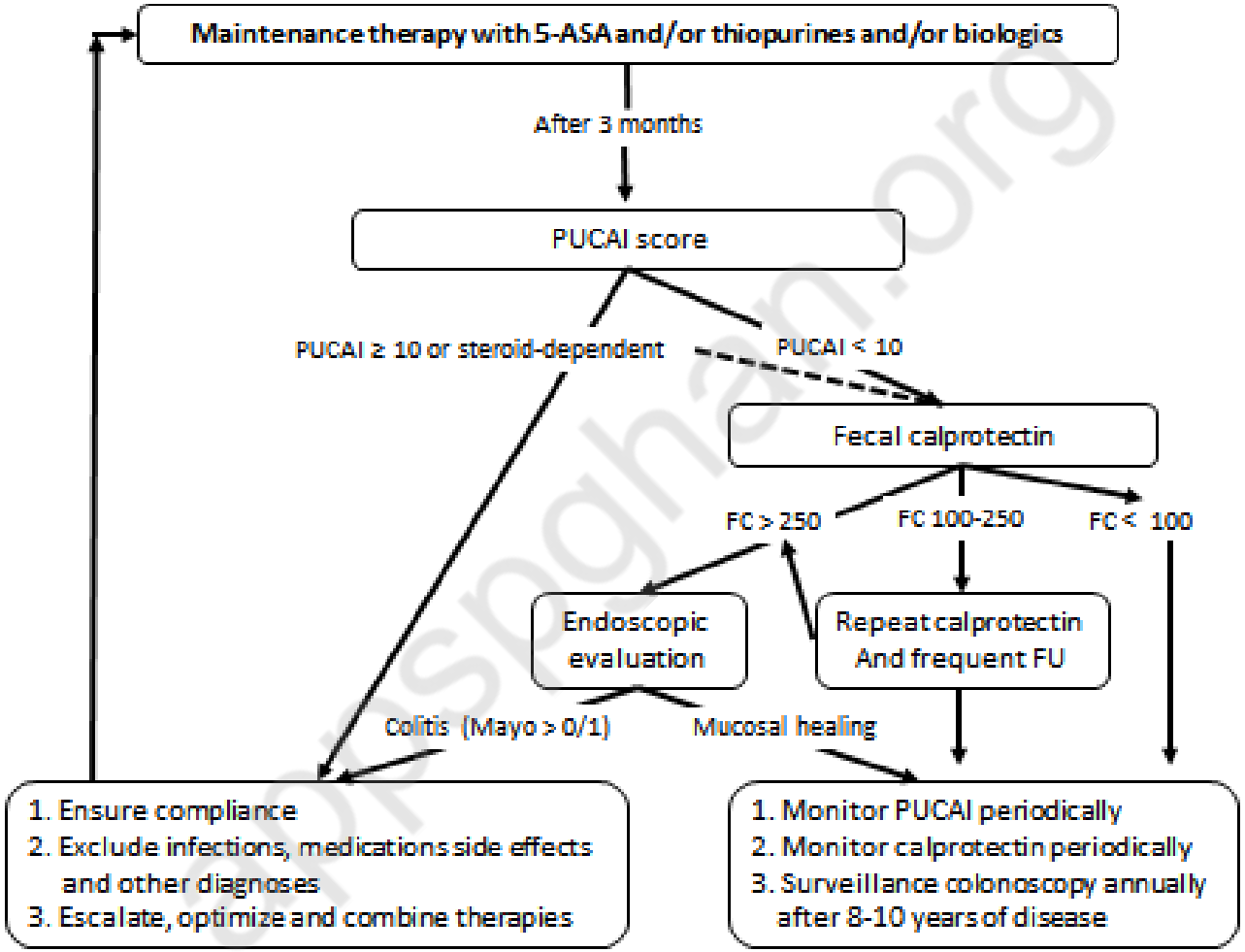
Method	Validity	Responsiveness to changes in condition	Practicality
Endoscopy	Gold standard	Gold standard	Low
Symptoms	Poor-Moderate	Moderate	High
CRP	Moderate	Moderate	High
Calprotectin	Good	Good	High

Heida A, IBD 2017

Monitoring

- Activity index periodically: every visit
- Anthropometry periodically: every visit
- Monitor CRP and calprotectin: periodically
- Endoscopy ?

Management of Pediatric UC (ESPGHAN Guideline)



Turner D, JPGN 2018

Summary

- Suspect diagnosis according to typical or atypical symptoms.
- Laboratory or fecal marker test before Endoscopy.
- Full understanding of endoscopy and histology is essential for diagnosis.
- Use guideline for standardization.
- Complete work up is necessary at initial diagnosis.