IUS IN THE MANAGEMENT OF IBD: A PARADIGM, TRANSMURAL HEALING AS THE KEY TREATMENT TARGET

Dr. Kenneth Ernest-Suárez
Assistant Professor
Division of Gastroenterology
University of Alberta

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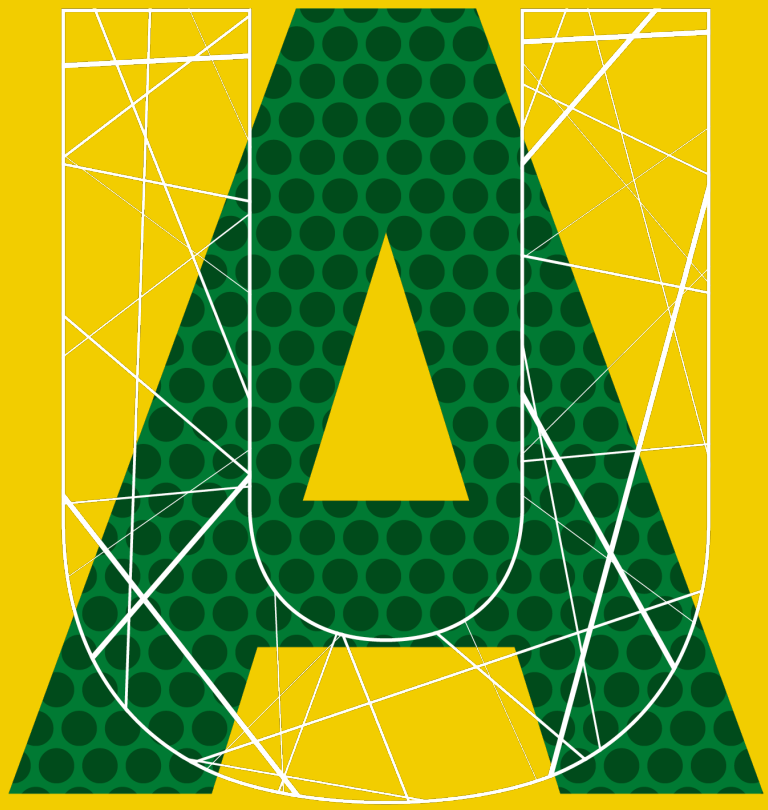

Conflicts of Interest

	Educational Support	Speaker fees	Advisor
Abbvie		✓	✓
AstraZeneca		✓	✓
Bayer		✓	
Clario			✓
Ferring		✓	✓
Johnson & Johnson	✓	✓	✓
Pfizer		✓	✓
Sandoz		✓	
SatisfAI			✓
Takeda			✓

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Objectives

- Trace the journey of mucosal healing as target in IBD
- Evaluate outcomes associated with TH in UC and CD
- Navigate the current consensus for TH
- Discuss reasons for not achieving TH and “middle ground” options

Is TH the key treatment target in IBD?

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YES

Some mucosal healing context...

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Mucosal Healing becoming a target in IBD management…

Mucosal healing in inflammatory bowel disease: impossible ideal or therapeutic target?

Paul Rutgeerts, Severine Vermeire, Gert Van Assche

Gut 2007;**56**:453–455. doi: 10.1136/gut.2005.088732

The main goal of treatment for Crohn's disease and ulcerative colitis has always been the induction and maintenance of symptomatic improvement or at best remission. It has been shown by many studies that the long-term outcome of these diseases is not influenced by standard treatments and that the need for surgery is not decreasing in this population over the years. There is recent evidence that with immunosuppression and treatment with infliximab long-term healing of the bowel can be achieved and that this affects the outcome of both Crohn's disease and ulcerative colitis. We propose that future studies should focus on healing and disease course as primary outcome measures.

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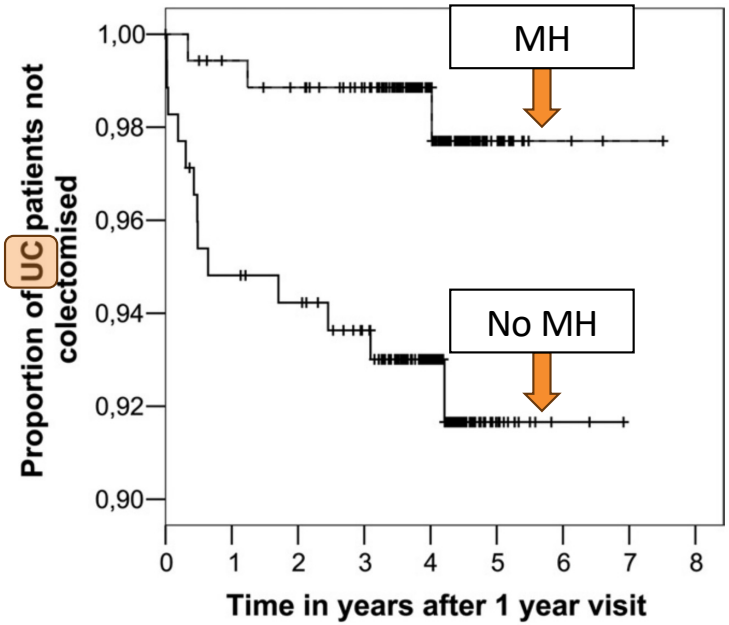
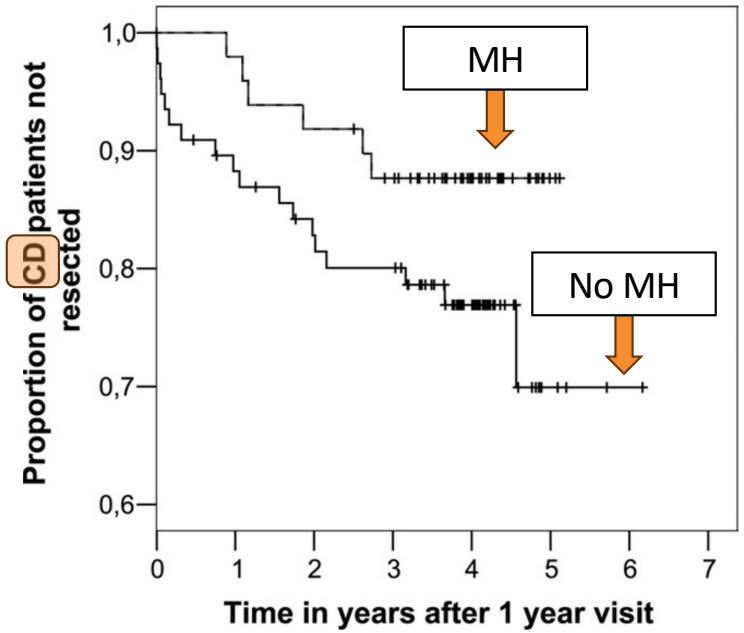
IBSEN (Norway): 740 IBD pts (1990-1994)





Endoscopic score of 0 –2

- 0, normal
- 1, light erythema or granularity
- 2, granularity, friability, and bleeding, with or without the addition of ulcerations

MH for UC and CD: 0-1

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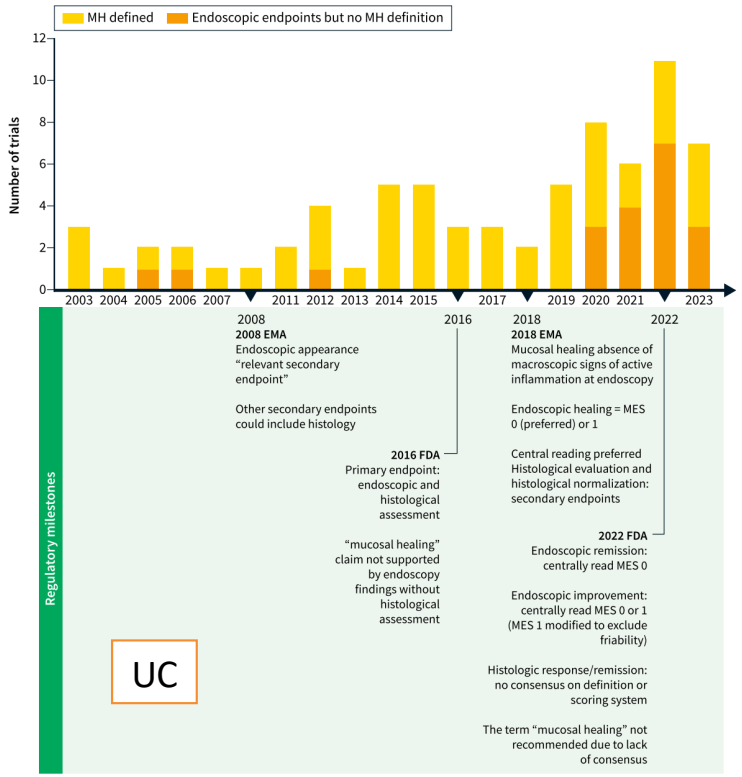
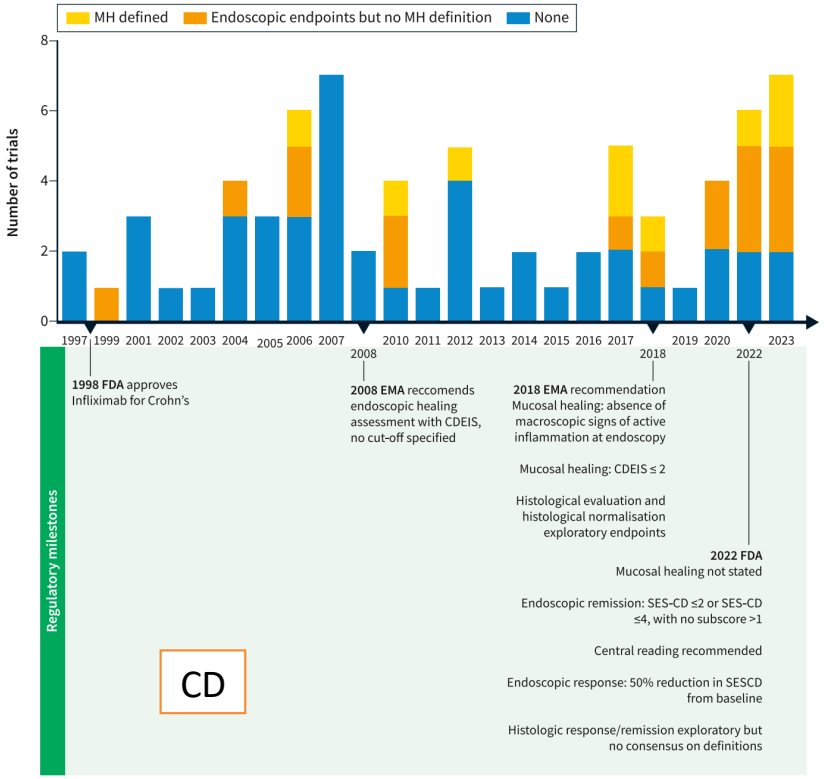
Frøslie, K et al. Gastroenterology 2007;133:412– 422

Mucosal Healing Definitions





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Parigi TL, et al. United European Gastroenterol J. 2024 Nov;12(9):1266-1279

We all can agree that MH is an important target in IBD

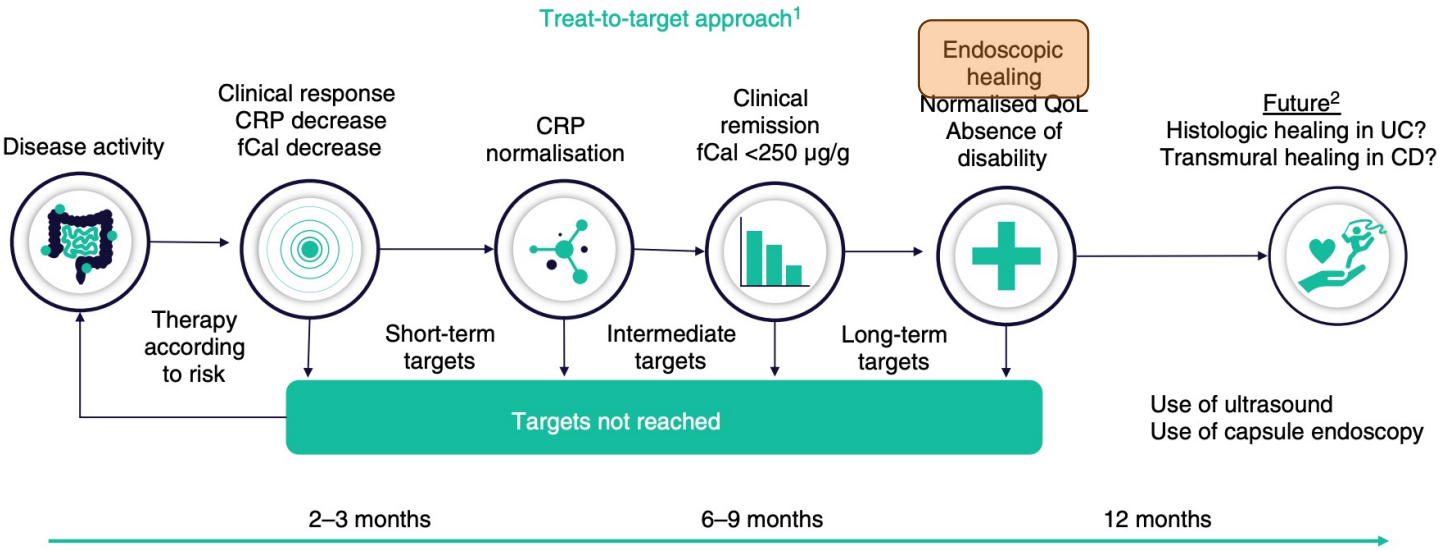

FIGURE 2 STRIDE-II evidence- and consensus-based recommendations for treat-to-target strategies in IBD. Treatment targets are time bound, with the ultimate long-term goal of achieving endoscopic healing and reduction in disability. Furthermore, targets should be adapted to individual patients to improve outcomes. Adapted from Turner et al., 2021.[6] CRP, C-reactive protein; fCal, faecal calprotectin; QoL, quality of life.

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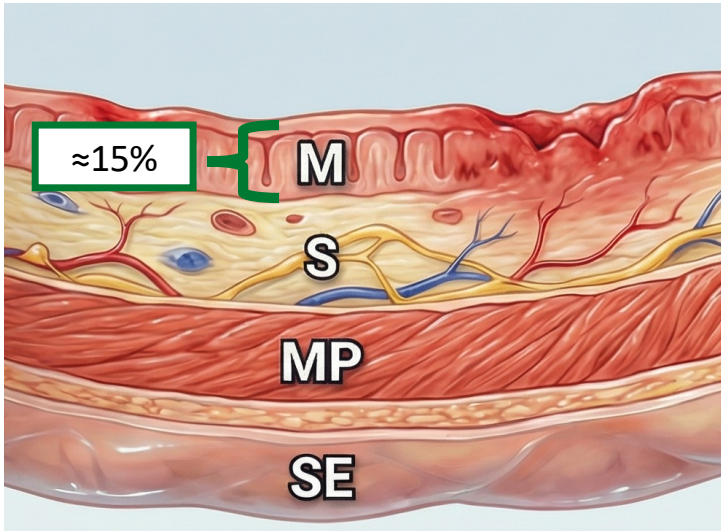
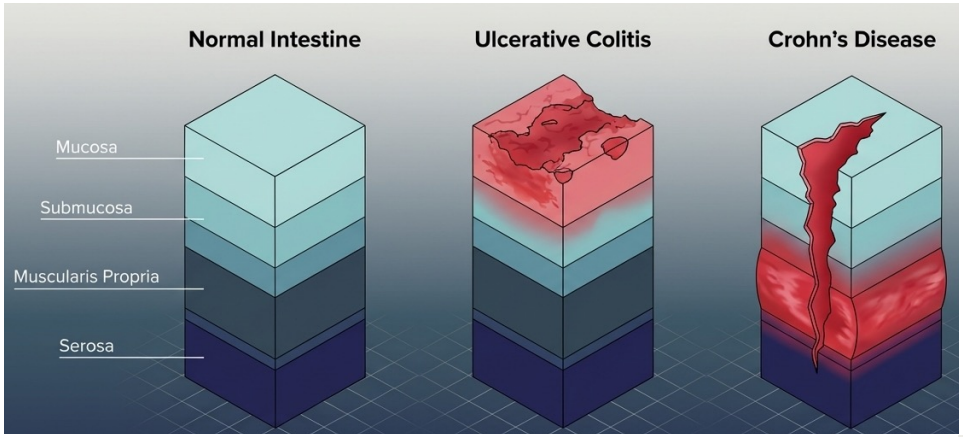
Dignass, A, et al. Aliment Pharmacol Ther. 2023 Sep;58(5):492-502.

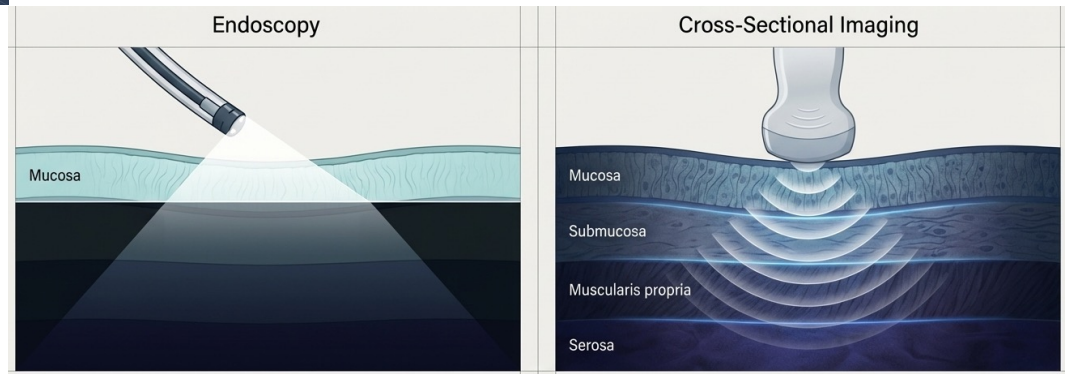
Is this proportion enough target?



Neurath, MF; Vieth, M. Gut. 2023 Nov;72(11):2164-2183.
NotebookLM

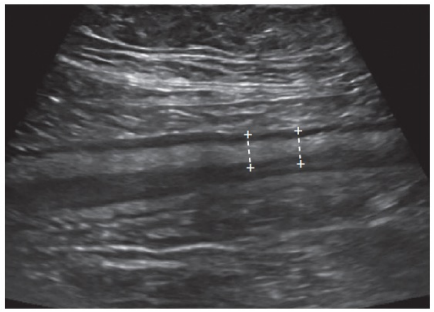
IBD is a full-thickness disease requiring a full-thickness target



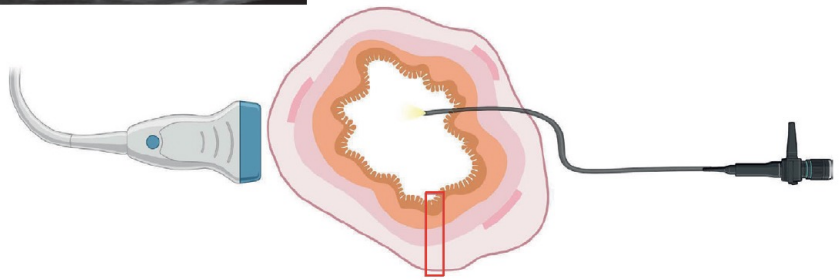


UC

Ultrasound image of the sigmoid of a patient with chronic, therapy-refractoy ulcerative colitis

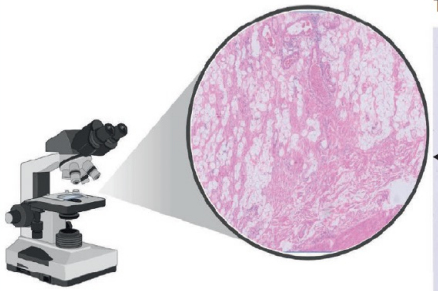


Ultrasound aspects beyond the mucosa:
- Thickened submucosa
- Loss of haustrations
- Mesenteric fibrofatty proliferation
- Loss of bowel wall stratification
- Increased bowel wall thickness

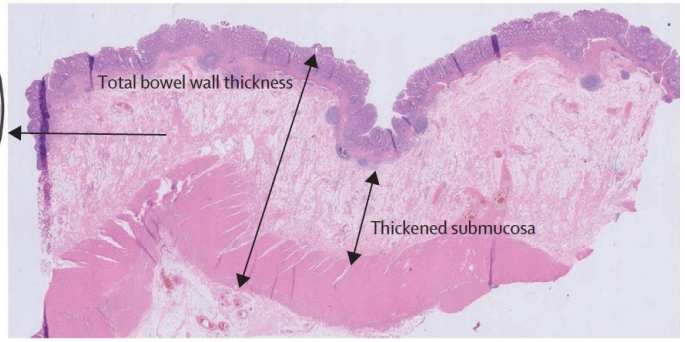


Endoscopy:
- Mayo endoscopic subscore 3

Transmural biopsy of a patient with chronic, therapy-refractoy ulcerative colitis



Submucosal fibrosis and increased fat cell deposition



Histopathology:
- Thickened muscularis mucosae
- Submucosal fibrosis
- Muscular remodelling and fibrotic shifts
- Increased fat cell deposition

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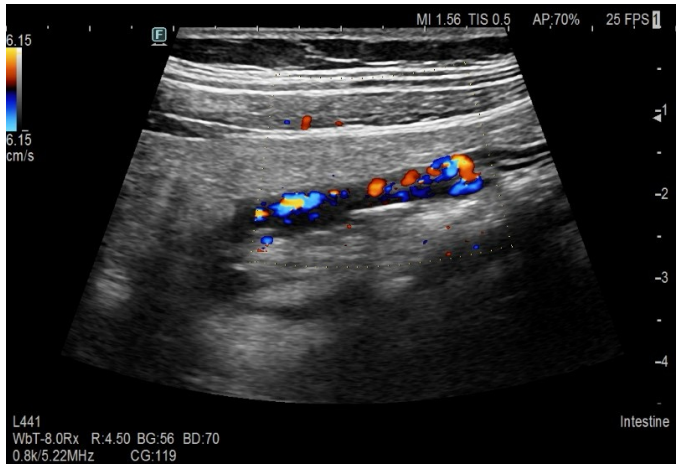
Eggermont, E et al. *Lancet Gastroenterol Hepatol* 2026; 11: 163–74

UC


MI 1.54 TIS 0.5 AP:100% 25 FPS
L441
WbT-8.0Rx R:5.00 BG:57 BD:70
Intestine


MI 1.56 TIS 0.5 AP:70% 25 FPS
6.15
6.15
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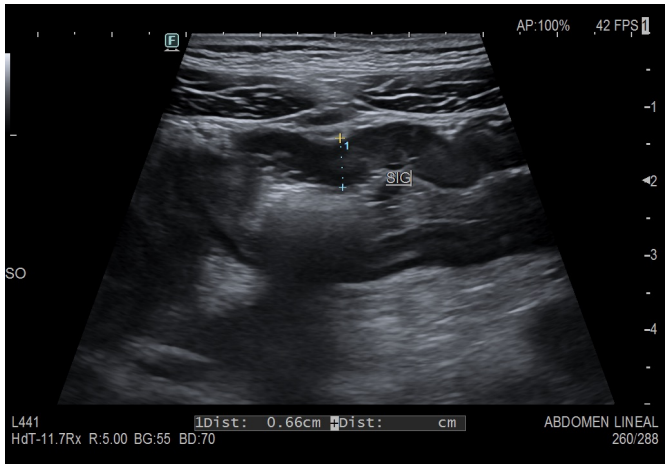
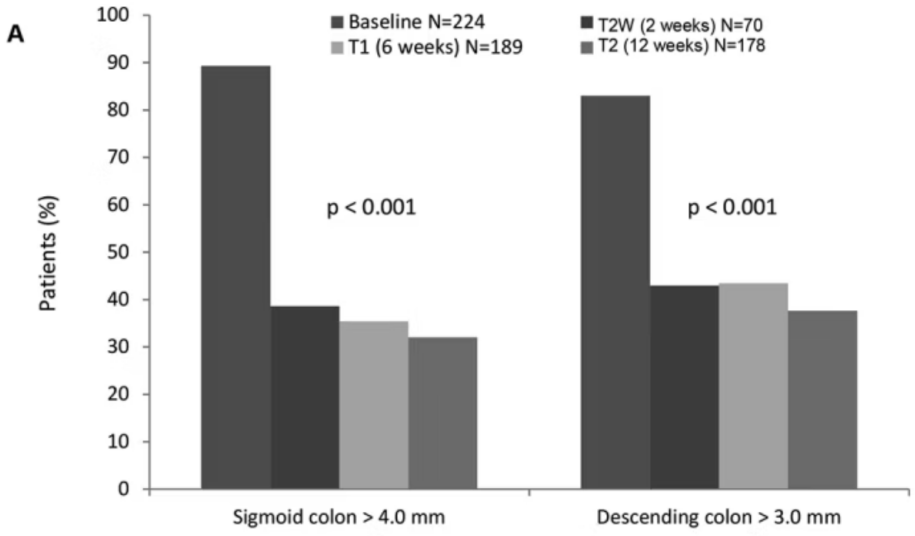
WbT-8.0Rx R:4.50 BG:56 BD:70
0.8k/5.22MHz CG:119
Intestine


AP:100% 42 FPS
SIC
SO
L441
HdT-11.7Rx R:5.00 BG:55 BD:70
1Dist: 0.66cm +Dist: cm
ABDOMEN LINEAL
260/288

TRUST&UC

- 224 UC pts
- Management as per
- physician's criteria
- IUS at 12 weeks



Normalization of BWT and clinical response after 12 weeks of treatment showed a high correlation (P < .001)

Reduction of BWT correlates with reduction of fecal calprotectin

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Maaser C, et al. Gut 2020;69:1629–1636

TRUST&UC *post-hoc*

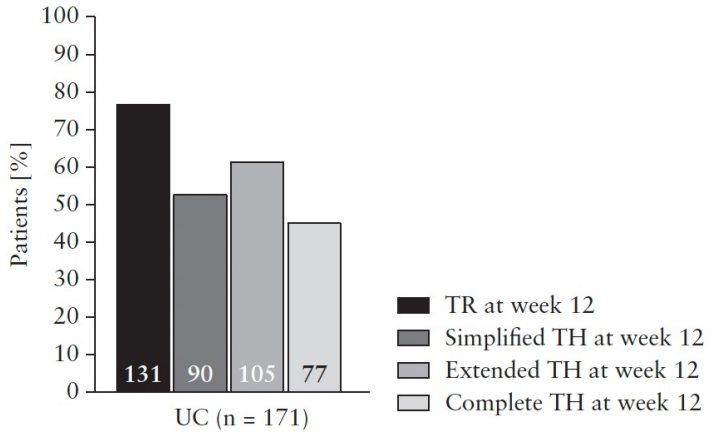
Table 1. Definitions of transmural response and healing and corresponding parameters* at baseline

Transmural response	BWT normalization†	Colour Doppler normalization	No loss of stratification	No fibro-fatty proliferation
Simplified transmural healing	X	X		
Extended transmural healing	X	X	X	X
		2 of 3 parameters were assessed, 1 could be not documented/not assessed		
Complete transmural healing	X	X	X	X
		All 3 parameters were assessed		

BWT, bowel wall thickness.
*All assessed for the most affected segment [segment with the most pronounced increase in BWT].

TR: Reduction ≥25% BWT

TH/TR can be documented…and pretty fast…



IUS response or remission increase OR of achieving clinical response at 12 weeks

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Helwig, U et al. Journal of Crohn's and Colitis, 2022, 57–67

Short-term prediction

Intestinal ultrasound is accurate to determine endoscopic response and remission in patients with moderate to severe ulcerative colitis

Cohort and design

n=30 starting tofacitinib

endoscopic Mayo score (EMS) ≥ 2

Baseline *Week 8*

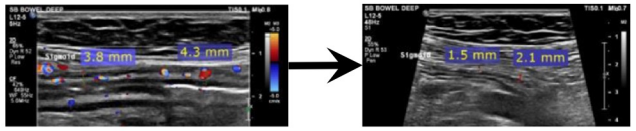
Bowel wall thickness BWT

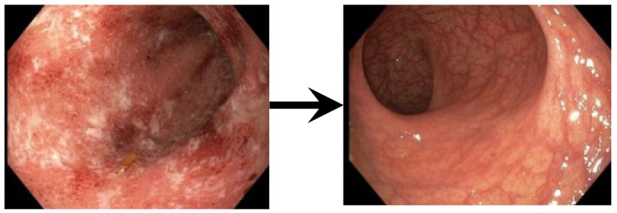
EMS

Robarts Histopathology Index (RHI)

Results

Baseline *Week 8*





score = 26 score = 1

Remission EMS=0 } **BWT** 2.8 mm

Improvement EMS≤1 } 3.9 mm

Response EMS≥1 decrease } 32% decrease

ρ=0.49: RHI vs BWT

Gastroenterology

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Floris de Voogd Gastroenterology 2022;163:1569–1581

Longer-term use (Europe – IBD-DACH)

111 UC treated with Upadacitinib with IUS data at baseline, Week 8, and Week 52

Sigmoid Bowel Wall Thickness (BWT):

- Baseline: 5.0 mm (3.9-6 mm)
- Week 8: 3.0 mm (2-4 mm)
- Week 52: 2.85 mm (2-3.6 mm)

Early Response Predicts Long-Term Outcomes:

- BWT ≤ 3 mm at Week 8 → 62% in symptomatic remission at Week 52
- BWT > 3 mm at Week 8 → 38% in remission at Week 52

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S Zeissig, et al. *Journal of Crohn's and Colitis*, Volume 19, Issue Supplement_1, January 2025, Pages i1647–i1648

Transmural remission (TR) as target in early UC

- Copenhagen prospective cohort (n=193 **recent** UC diagnosis)
- **TR: BWT≤3mm + no CDS**
- 82/140 (59%) TR at 3 months
- 95/126 (75%) TR at 12 months

- TR at 3 months => higher rates of CS-free remission at 6, 9, 12 months
- TR at 3 months => lower risk of CS use (6% vs 19%, p=0.036)

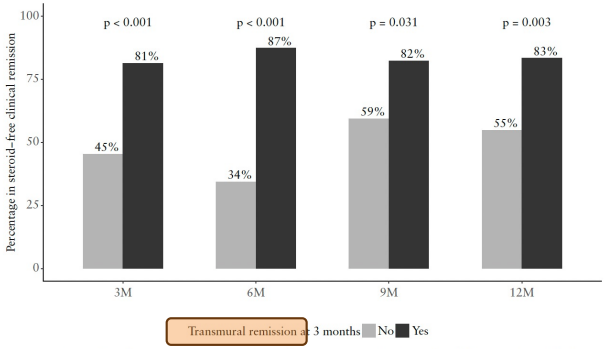

Figure 2. Development of steroid-free clinical remission rates during the first year after an ulcerative colitis (UC) diagnosis, stratified by transmural remission 3 months after diagnosis.

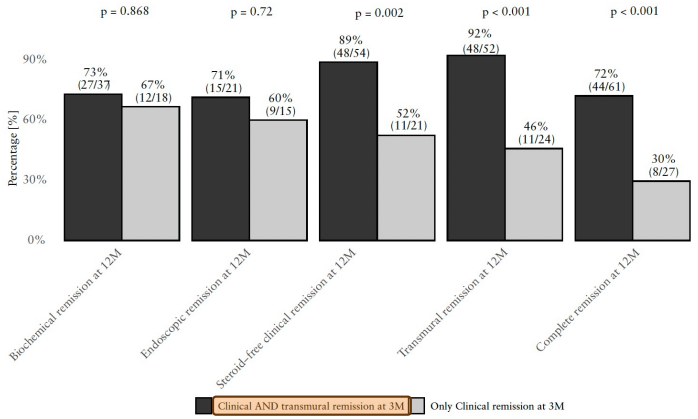

Figure 3. Remission rates 1 year after ulcerative colitis (UC) diagnosis among patients who were in clinical remission after 3 months, stratified by whether they also had transmural remission after 3 months.

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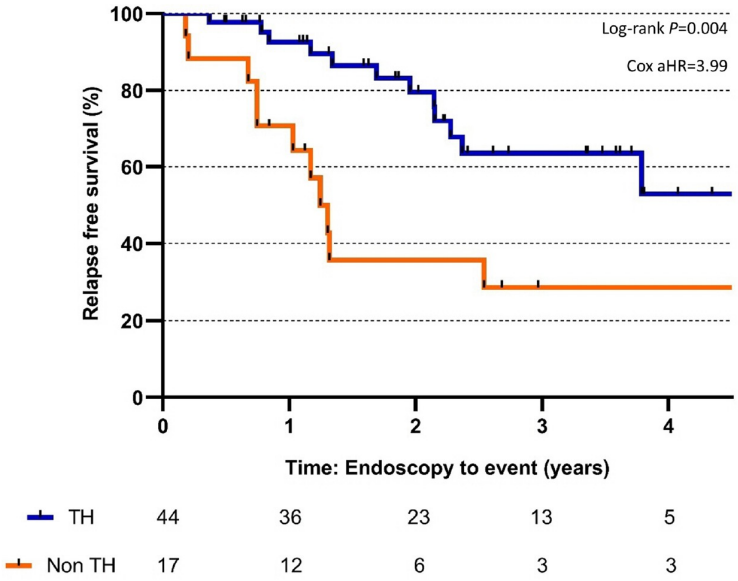
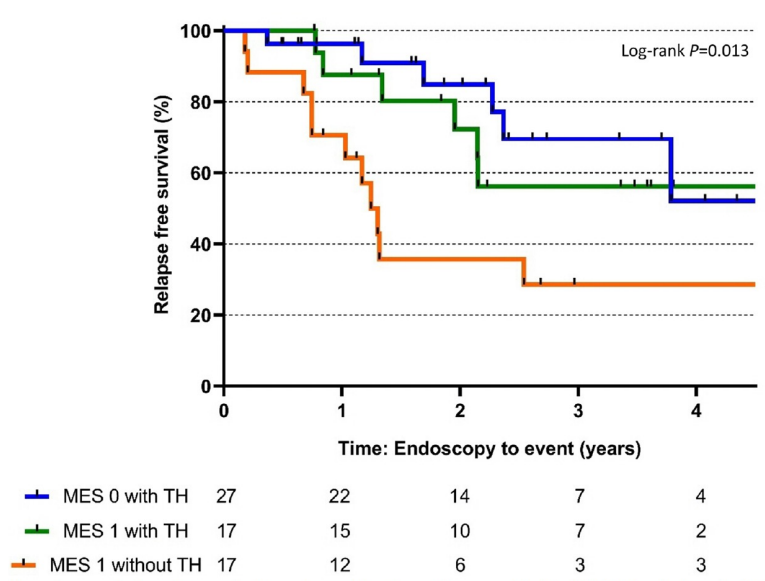
Madsen, GR et al. J Crohns Colitis. 2025 Apr 4;19(4):jiaf033

MH + TH > MH in CU

- Amsterdam, retrospective, n= 61
- Stable UC MES ≤1
- TH: BWT≤3 mm, documented in 72.1%

- **1-Year Relapse Risk:** 7.5% TH vs. 29.4% no TH
- **2-Year Relapse Risk:** 20.5% TH vs. 64.3% no TH
- **Time to Flare:** TH mean 20.9 vs. 12.2 months, P=0.042





BWT>3 mm predicts clinical relapse (HR: 3.99, P=0.015)

MES 0 vs. MES 1 not associated with relapse (HR 1.06, P=0.924)

TH = longer medication change-free survival (P=0.001), avoiding steroids

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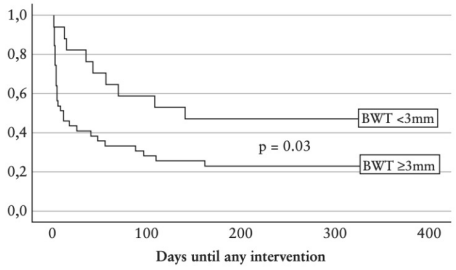
Lim, CT et al. J Crohns Colitis. 2025 Sep 28;19(9):jjaf149

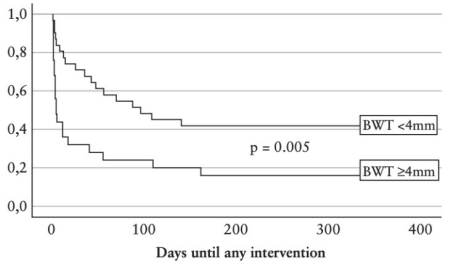
Response prediction ASUC – IV Steroids – LT Outcomes

A



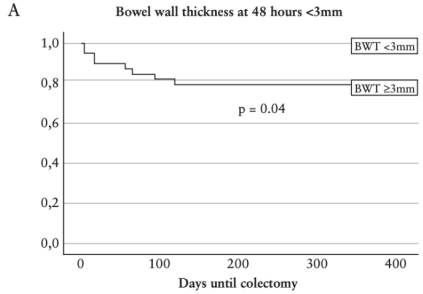
	Total (n)	Any intervention (n)	Mean (days)	95%CI	Median (days)	95%CI	p
BWT ≥3mm	39	30	102	56 - 148	11	0 - 27	
BWT <3mm	17	9	199	124 - 274	140	-	0.03

B



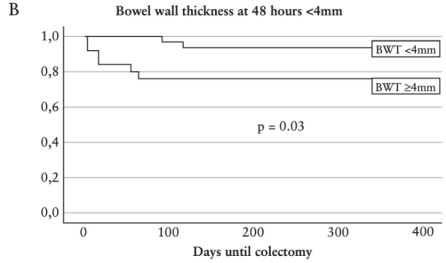
	Total (n)	Any intervention (n)	Mean (days)	95%CI	Median (days)	95%CI	p
BWT ≥4mm	25	21	75	24 - 127	4	1 - 7	
BWT <4mm	31	18	176	119 - 233	96	4 - 188	0.005

A



	Total (n)	Colectomy(n)	Mean (days)	95%CI	Median (days)	95%CI	p
BWT ≥3mm	39	9	-	-	-	-	
BWT <3mm	17	0	-	-	-	-	0.04

B



	Total (n)	Colectomy (n)	Mean (days)	95%CI	Median (days)	95%CI	p
BWT ≥4mm	25	7	-	-	-	-	
BWT <4mm	31	2	-	-	-	-	0.03

MULTIVARIATE ANALYSIS – NEED OF ANY INTERVENTION AT 3 MONTHS:

BWT>3 MM + CDS>0 (AT 48 H): OR13.2 (95CI 2.4-112.5), P=0.007

MULTIVARIATE ANALYSIS – NEED FOR COLECTOMY:

BWT>4 MM (AT 48 H)

3 MONTHS: OR13.5 (95CI 1.8-289), P=0.003

12 MONTHS: OR12.4 (95CI 1.6-281), P=0.004

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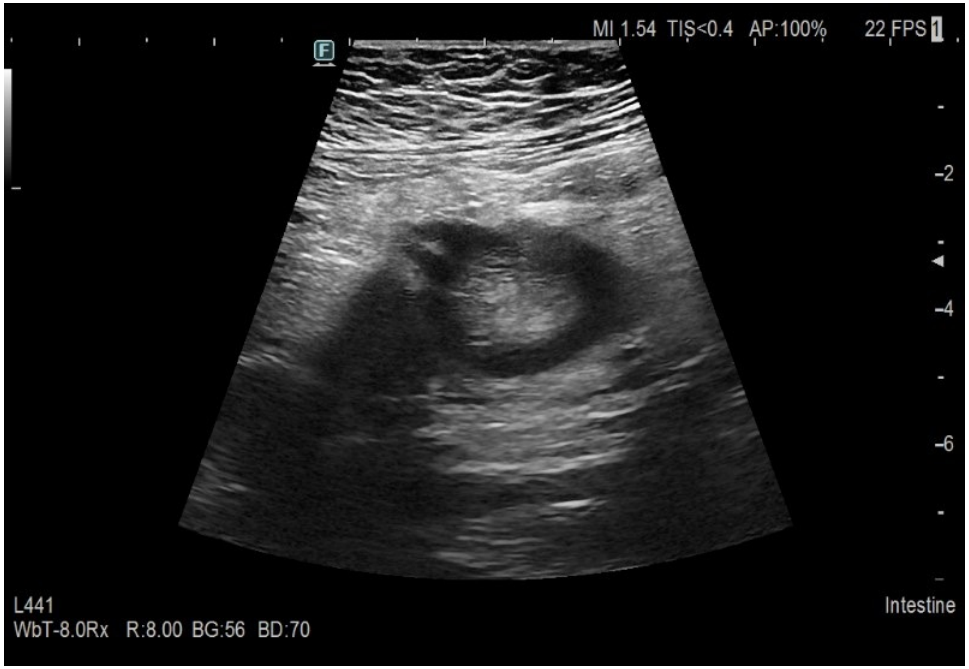
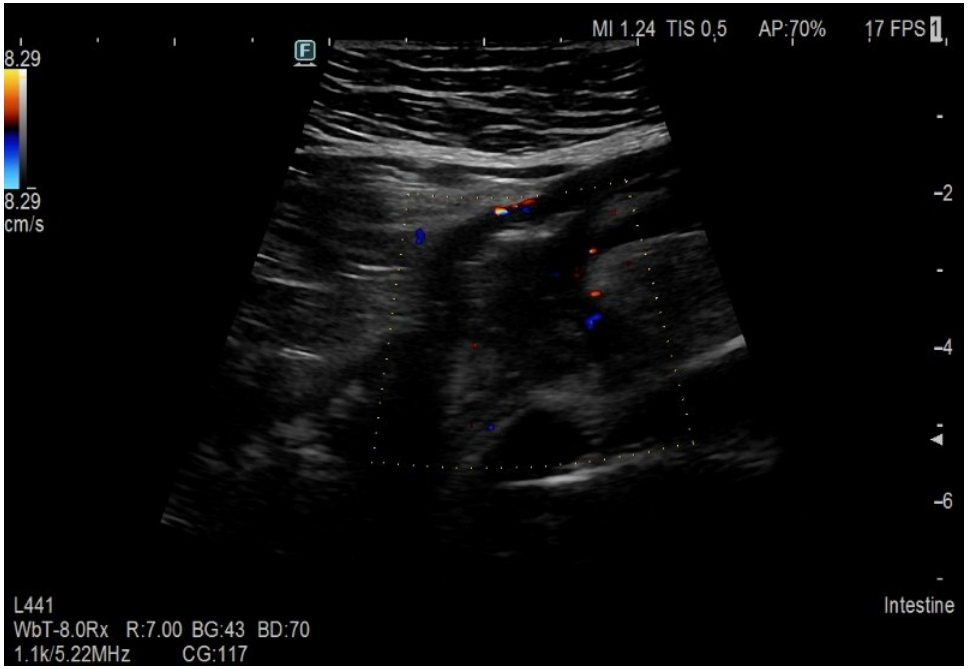
Ilvemark J, et al. Journal of Crohn's and Colitis, 2024, 18, 1976–1986

CD





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Different TH definitions in the literature

	Design of the study	Cross-sectional imaging method	Definition of transmural healing
Castiglione et al, 2013 (n=133)[23]	Prospective, single centre	Bowel sonography	BWT ≤3 mm
Ripollés et al, 2016 (n=51)[34]	Prospective, multicentric	Bowel sonography	BWT ≤3 mm
Deepak et al, 2016 (n=150)[32]	Retrospective, single centre	CTE and MRE	BWT ≤3 mm plus segmental mural hyperenhancement
Eder et al, 2016 (n=26)[27]	Retrospective, single centre	MRE	≥50% decrease in SEAS-CD score
Sauer et al, 2016 (n=101)[28]	Retrospective, single centre study	MRE	Normal BWT without contrast enhancement
Civitelli et al, 2016 (n=32)[26]	Prospective, single centre	Bowel sonography	BWT ≤3 mm plus doppler plus bowel sonography parameters (resolution of colour signals in the bowel wall, loss of the normal five-layer appearance of the bowel wall, stenosis, node enlargement, and mesenteric fat hypertrophy)
Fernandes et al, 2017 (n=214)[31]	Retrospective, multicentric	MRE	BWT ≤3 mm plus other MRE parameters (increased contrast enhancement and complications) plus normal endoscopy
Castiglione et al, 2017 (n=40)[18]	Prospective, single centre	Bowel sonography and MRE	BWT ≤3 mm without hypervascularisation signs
Laterza et al, 2018 (n=53)[30]	Prospective, single centre	CTE	Normal findings (BWT ≤3 mm plus other parameters [complications, target sign, comb sign, lymphadenopathy >1 cm, sinus tracts, fibrofatty proliferation, perienteric stranding, and free fluid in the abdomen]) plus mucosal healing
Orlando et al, 2018 (n=30)[25]	Prospective, single centre	Bowel sonography	BWT ≤3 mm
Weinstein-Nakar et al, 2018 (n=151)[29]	Prospective, multicentric	MRE	Less than 19·5 mm on a 0–100 visual analogue scale (equivalent to a MaRIA score of <7)
Paredes et al, 2019 (n=36)[24]	Prospective, single centre	Bowel sonography	BWT ≤3 mm plus colour doppler grade 0 or 1
Buisson et al, 2019 (n=63)[36]	Retrospective, single centre	MRE	No segmental MaRIA score higher than 7, or no segmental Clermont score higher than 8·4
Castiglione et al, 2019 (n=218)[22]	Prospective, single centre	Bowel sonography	BWT ≤3 mm
Noh et al, 2020 (n=268)[35]	Retrospective, single centre	CTE and MRE	BWT <3 mm plus no mural hyperenhancement, normal mural signal, and no perienteric infiltration or complications
Hallé et al, 2020 (n=115)[33]	Retrospective, single centre	MRE	BWT <7 mm plus absence of segmental mural hypersignal, no comb sign or lymphadenopathies, and no complications
Lafeuille et al, 2021 (n=154)[37]	Retrospective, single centre	MRE	No active inflammation, no extraenteric sign, no complications

BWT=bowel wall thickness. CTE=CT enterography. MaRIA=Magnetic Resonance Index of Activity. MRE=magnetic resonance enterography. SEAS-CD=Simple Enterographic Activity Score for Crohn's disease.

Table 1: **Characteristics of studies on transmural healing**

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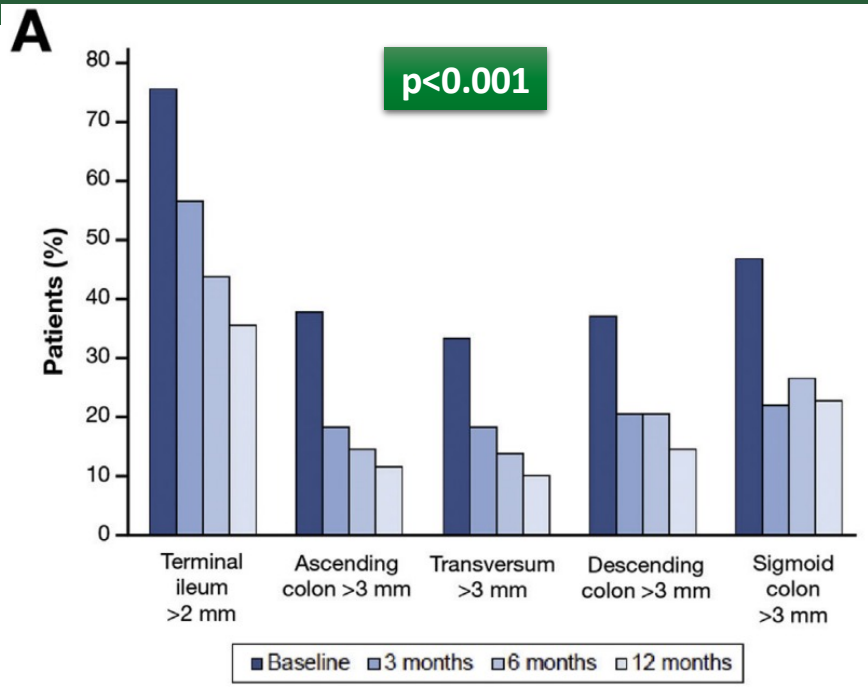
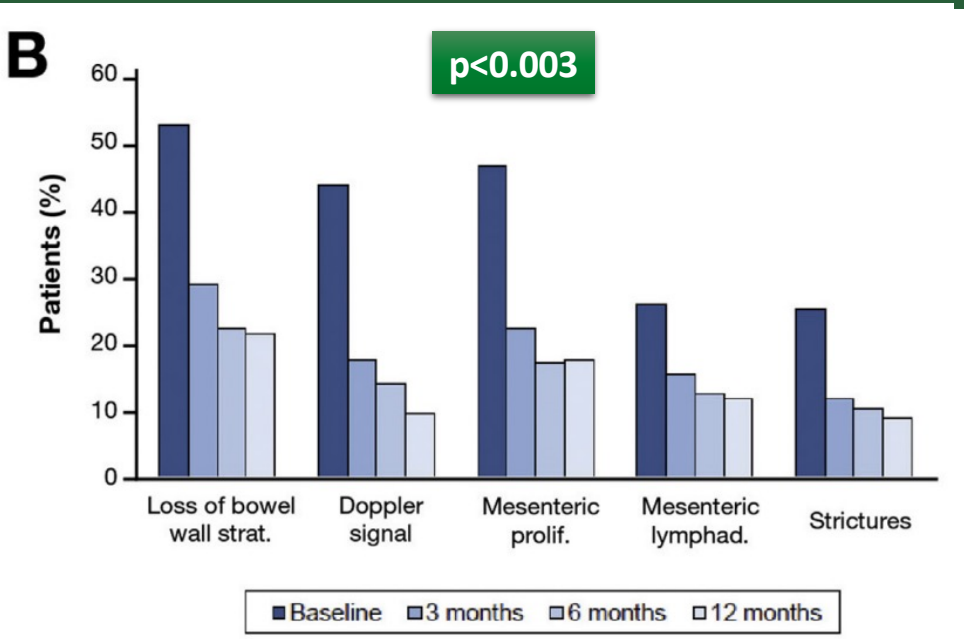
Geyl S, et al. Lancet Gastroenterol Hepatol 2021; 6: 659–67

TRUST



234 CD patients
Management according to each physician



Improvement => significant correlation with CRP

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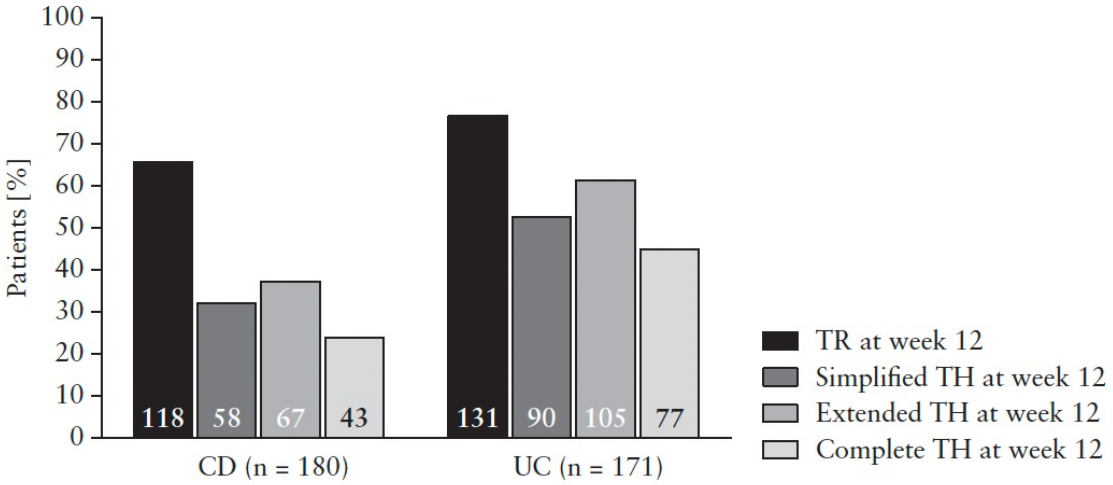
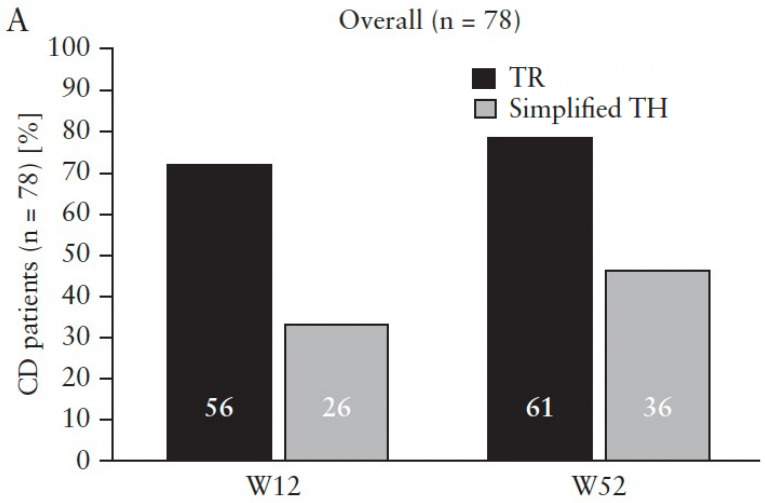
Kucharzic T et al. Clinical Gastroenterology and Hepatology 2017;15:535–542

TRUST *post-hoc*



TH increased OR of achieving clinical remission at 12 weeks



Favourable sonographic outcome (OR 5.59 [1.97–15.8]; p = 0.001) at week 52

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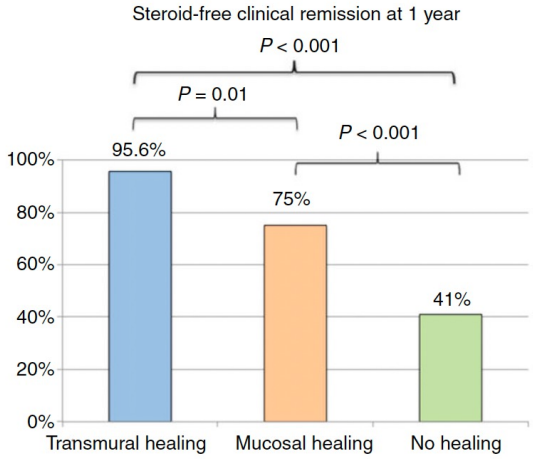
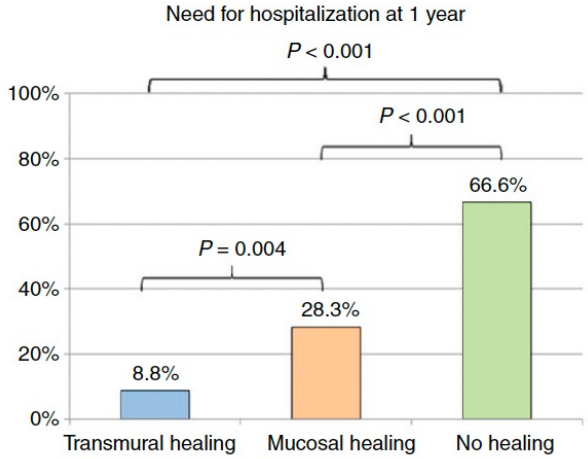
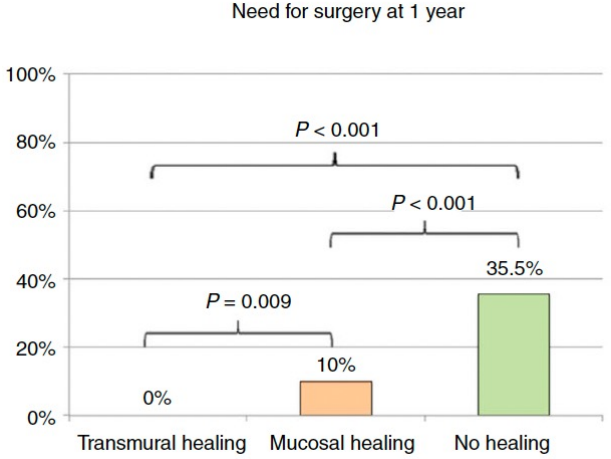
Helwig, U et al. Journal of Crohn's and Colitis, 2022, 57–67

Long-Term Outcomes in CD (Italy)

218 CD patients who completed 2 years on anti-TNF
TH: BWT<3mm // MH: SES-CD<3
After 2 years of therapy, 31.2% achieved TH, 27.5% MH and 41.3% no healing.







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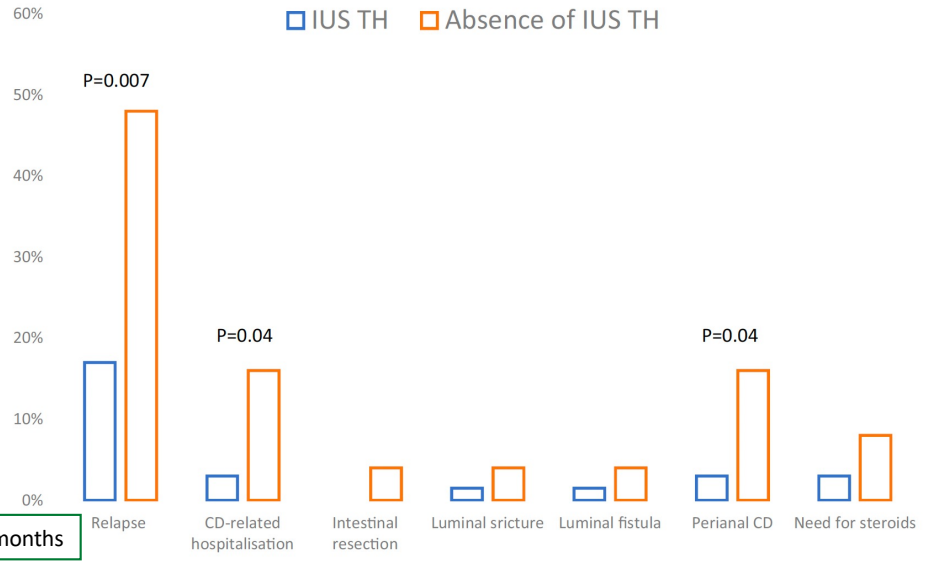
Castiglione, F et al. Aliment Pharmacol Ther. 2019 Apr;49(8):1026-1039

MH + TH > MH

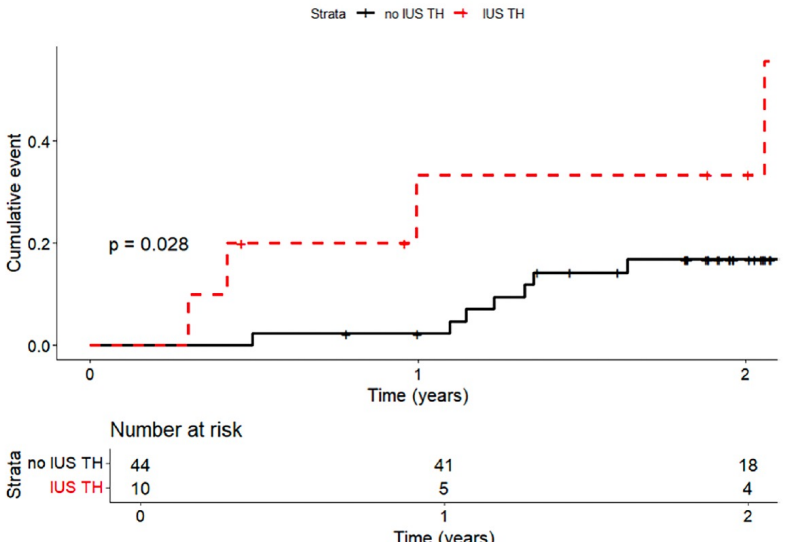
93 CD patients with mucosal healing (CDEIS<4)
TH: BWT<3mm + no CDS
27% of patients with MH had transmural activity



Mean 22.4 months

FIGURE 1 | Risk of disease relapse among patients with endoscopic healing according to transmural healing status. CD, Crohn's disease.

CD-related hospitalisation (3% vs. 16%, p = 0.04)
Perianal CD (3% vs. 16%, p = 0.04)



CDEIS=0, risk of relapse

Yzet C, et al. Aliment Pharmacol Ther. 2026 Apr;63(7):992-999

MH vs TH, 12-month outcomes

Table 2. Multivariate analysis for long-term outcomes.

Variables	Steriod-free CR			Drug escalation			Hospitalization			Surgery		
	OR	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Smoking habits	0.1	0.1–0.8	**0.04**							6.6	1.3–34.1	**0.02**
Thalidomide alone				0.1	0.01–1.1	**0.06**						
TH	52.6	9.7–167.2	<**0.001**	0.1	0.03–0.4	**0.002**	0.05	0.07–0.4	**0.005**			
MH				0.3	0.1–1.0	**0.05**						

CI, confidence interval; CR, clinical remission; MH, mucosal healing; OR, odds ratio; TH, transmural healing. Variables with a p value < 0.1 in the multivariante analysis were listed in bold.

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n=77
32% TH // 40% MH => at 6 months
TH: IUS BWT ≤3mm + all other parameters normal

Ma L et al. Ther Adv Gastroenterol 2021, Vol. 14: 1–11

Is TH the key treatment target in IBD? YES

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Is TH possible in all IBD patients?

Probably not

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Disease Characteristics

- **Duration**
  - Castiglione et al. => DD reduces chances of achieving TH (*OR 3.03; 95% CI, 1.15–7.94; p = 0.02)*
  - *Maconi et al. => inverse association between disease duration and TH achievement (−0.94 [−1.75 to −0.13], p = 0.02)*

- ***Phenotype***
  - *Ripollés et al. => 42% without complications achieved TH, vs. 5% with fistulizing or stricturing disease*
  - *Maconi et al => inflammatory phenotype TH 59% vs. 15% in non-inflammatory; p = 0.002)*

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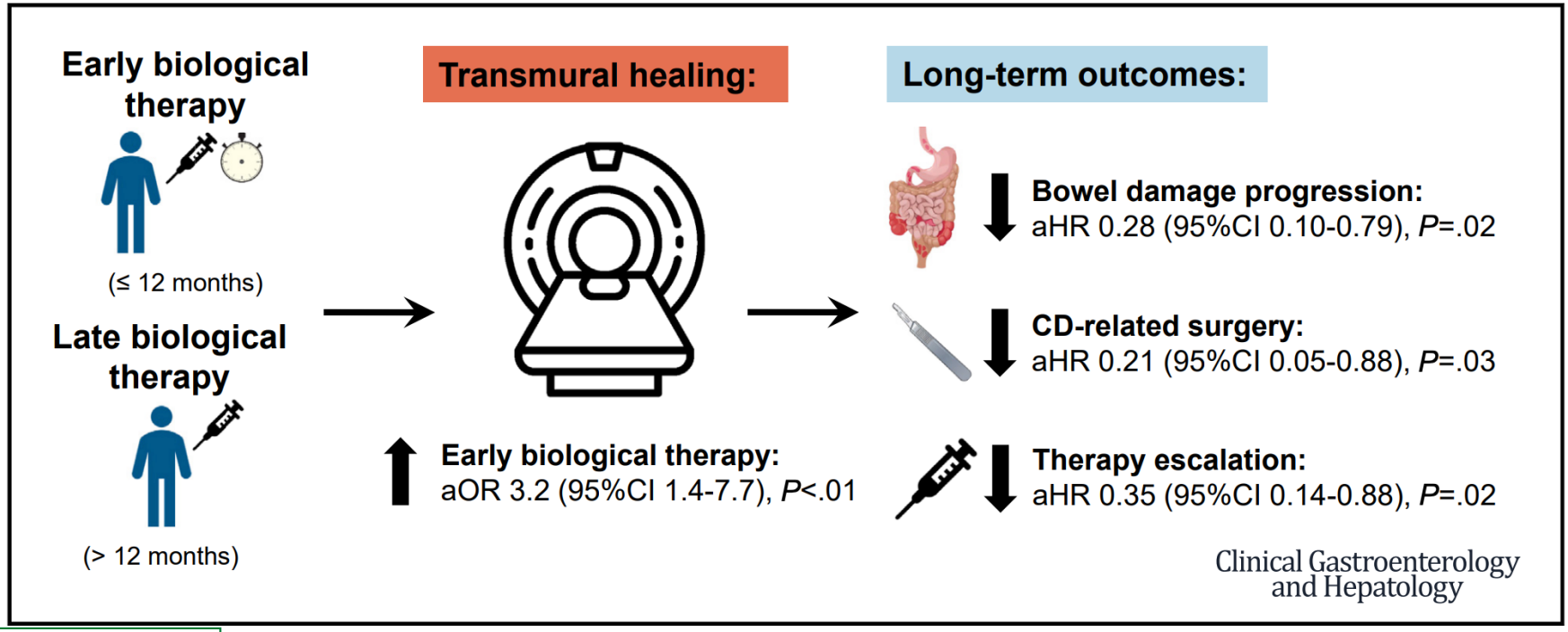
Castriglione F, et al, Dig. Liver Dis. 2017, 49, 484–489. Maconi, G. et al. Dig. Liver Dis. 2024, 56, 2052–2059. Ripollés, T et al. Inflamm. Bowel Dis. 2016, 22, 2465–2473

Time to Advanced Therapy



n= 154 CD patients

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Revés, J et al. Clin Gastroenterol Hepatol. 2025 Jun;23(7):1194-1203.

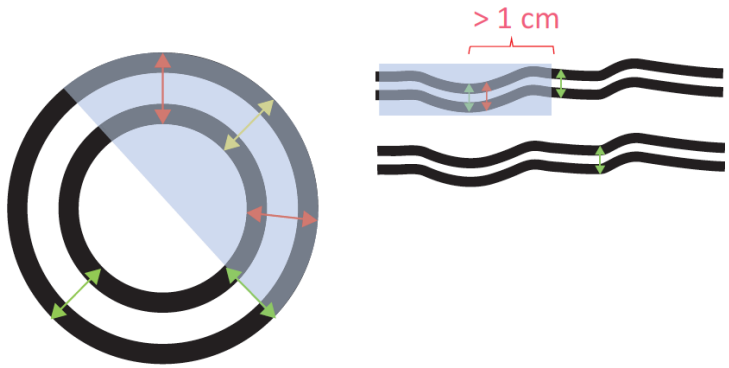
More data is needed…but it's growing

Trial Name	Status	Study Design & Population	TH Focus
VECTORS	Ongoing	RCT (CD, Vedolizumab)	Standard care vs. treat-to-target strategy aiming for corticosteroid-free TH on IUS by week 38.
REASON	Ongoing	Phase 3b RCT (CD, Guselkumab)	High vs. low dose guselkumab in achieving TH using the MRI MaRIA score at week 48 (IUS assessment included)
TRENCH 1	Ongoing	Multicenter Prospective (CD)	Depth and grading of TH based on specific radiologic features to standardize MRE interpretation.
STRIDENT	Completed	RCT (Stenosing CD, Adalimumab)	Stricture resolution and TH using both IUS and MRI, (~29% of strictures resolved)
DIVERGENCE 1	Completed	Phase 2 RCT (Small Bowel CD, Filgotinib)	Small molecules incorporating TH as an endpoint, evaluating radiological healing (MaRIA < 7) in the small bowel.
VERSIFY & STARDUST	Completed	Phase 3 Sub-studies (CD)	Progressive TH achievement with vedolizumab (MRE) and ustekinumab (IUS), proving deep healing increases with longer treatment duration.

Lovett, GC, et al. Inflamm. Bowel Dis 2025, izaf073 / VECTORS (NCT06257706)/ REASON (NCT06408935)/TRENCH1 (NCT05903066) / D'Haens G et al. Gastroenterology 2023, 165, 289–292.e3/ Rimola J et al. Clin. Exp. Gastroenterol. 2024, 17, 9–23

Expert Consensus

- Response depends on disease duration
- Response depends on the type of therapy
- Response differs in the presence of complications



Yellow arrow represents first measurement. Green arrows are allowed second measurement, red arrows are false second measurements

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Ilvemark F, et al. Journal of Crohn's and Colitis, 2022, 554–580
Noval KL et al. Journal of Crohn's and Colitis, 2021, 609–616

Current IBUS Consensus

	CROHN'S DISEASE	ULCERATIVE COLITIS
RESPONSE	25% BWT Reduction or > 2 mm or > 1 mm + 1 point reduction in mLimberg	
ASSESSMENT	14 +/- 2 WEEKS 26 Y 52 WEEKS	
REMISSION	BWT ≤3 mm + 0 Limberg Score (Sigmoid 4 mm)	
ASSESSMENT	26 Y 52 WEEKS (EARLY AS WEEK 12)	WEEK 14 +/-2 (EARLY AS WEEK 4)

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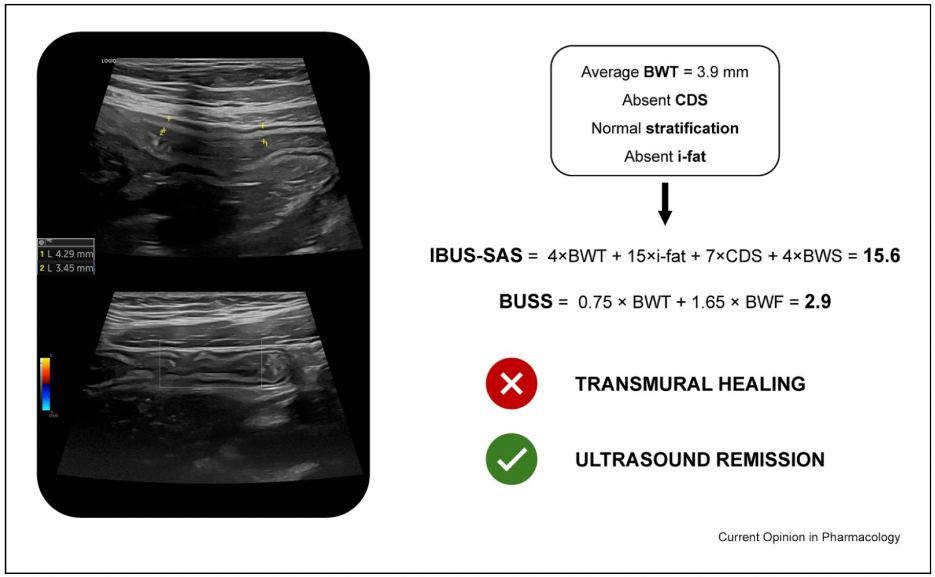
Ilvemark F, et al. Journal of Crohn's and Colitis, 2022, 554–580

Table 4. Summary of intestinal ultrasound response and remission definitions

Intestinal ultrasound response definitions	Intestinal ultrasound remission definitions
Decrease in bowel wall thickness ranging from 0.5 to 2.5 mm from baseline[8,18,24,28,30,32,38,46,59]	Bowel wall thickness ≤ 3 mm[10,18,20,21,24–26,28,29,33,35,36,38,40,59,61]
Decrease in bowel wall thickness of 25% from baseline[9,16,60]	Color Doppler signal = 0–1[18,21,24,28,38,59]
Decrease in color Doppler signals of 1 grade from baseline[8,16,18,24,28,37,38,59]	Simplified: normalization of bowel wall thickness and color Doppler signal[60]
Ultrasonographic activity scores for CD: • IBUS-SAS, International Bowel Ultrasound Segmental Activity Score < 25[39] • BUSS, Bowel Ultrasound Score ≤ 1.2 points from baseline[41]	Extended: normalization of bowel wall thickness and at least two additional parameters among color Doppler signal, bowel wall stratification, and absence of inflammatory fat[60]
Ultrasonographic activity scores for UC: • MUC, Milan Ultrasound Criteria ≤ 2 points from baseline[51]	Complete: normalization of all four parameters[60]
CEUS, contrast-enhanced ultrasound: reduction in mural enhancement ≥ 20% from baseline[24]	Ultrasonographic activity scores for CD: • IBUS-SAS, International Bowel Ultrasound Segmental Activity Score ≤ 32.5[39] • BUSS, Bowel Ultrasound Score ≤ 3.52[41] Ultrasonographic activity scores for UC: • MUC, Milan Ultrasound Criteria ≤ 6.2 (for MES = 0–1)[51] • MUC, Milan Ultrasound Criteria ≤ 4.3 (for MES = 0)[51] CEUS, contrast-enhanced ultrasound: percentage of increase of enhancement < 46%[21]

A good potential middle ground

- IUS Scores => US Remission ≠ TH
- Frequency of monitoring
- Findings stability over time



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Innocenti, T et al. Current Opinion in Pharmacology 2026, 86:102584

Conclusions

- IBD is a transmural disease => TH should be a therapeutic target
- Achieving TH predicts meaningful outcomes in CD and UC
- IUS is the viable, patient centric modality for TH monitoring
- Are we ready for IUS in STRIDE-III? I think we're getting there

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Thank you!

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