CENTRE DES MALADIES DIGESTIVES LAUSANNE

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Faculté de biologie et de médecine

CHUV

Management of complications in IBD patients

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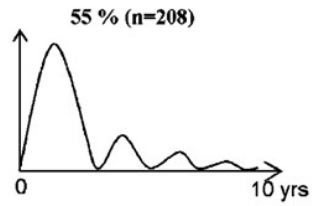
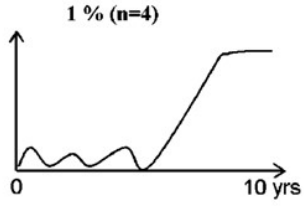
IBD disease behavior

- Hard to know in advance where your patient fits!
- Risk of complication differs depending on disease behavior

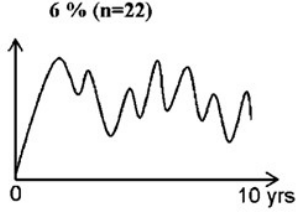
Ulcerative colitis



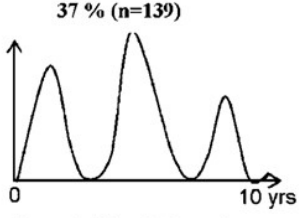
Curve1: Remission or mild severity of intestinal symptoms after initial high activity



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



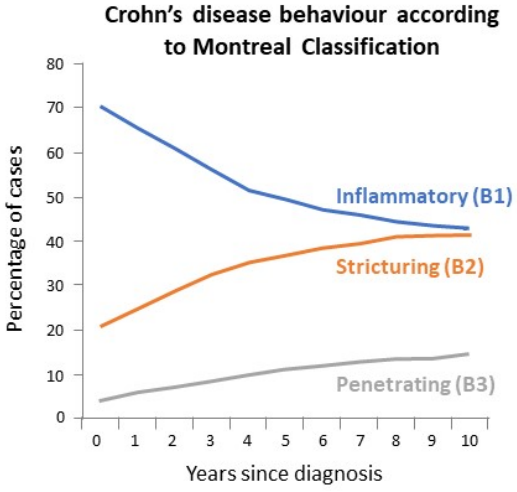
Curve 3: Chronic continuous symptoms

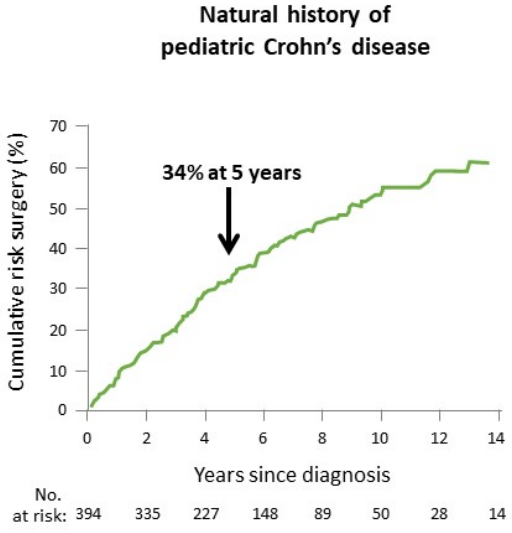


Curve 4: Chronic intermittent symptoms

Solberg IC, Lygren I, Jahnsen J, et al. Scand J Gastroenterol 2009;44:431e40.

The Disease Course in Pediatric Crohn's Disease 1988–2002 (Conventional Therapy)

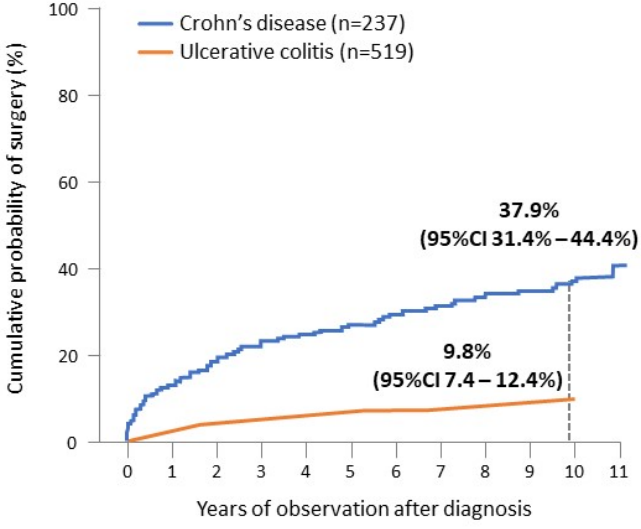




Vernier-Massouille G et al. *Gastroenterology* 2008;135:1106–1113.

Probability of Surgery in adult IBD over First 10 Years

Norwegian IBSEN cohort study (1990–1994)



Independent risk factors at CD diagnosis:[1]

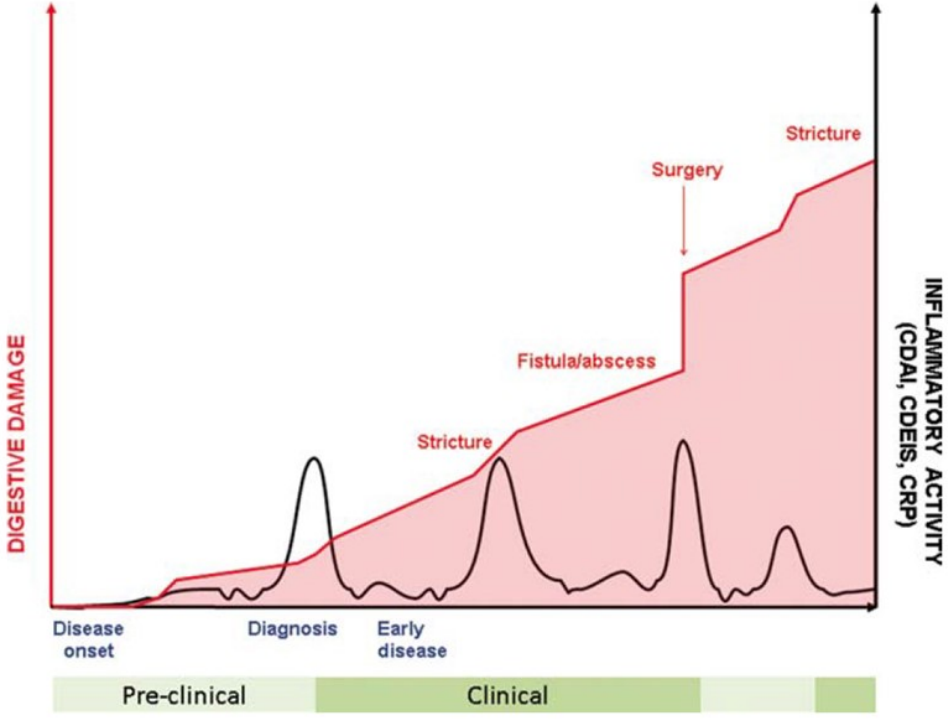
- Terminal ileal location
- Stricturing behaviour
- Penetrating behaviour
- Age younger than 40 years

Independent risk factors at UC diagnosis:[2]

- Extensive colitis
- ESR ≥30

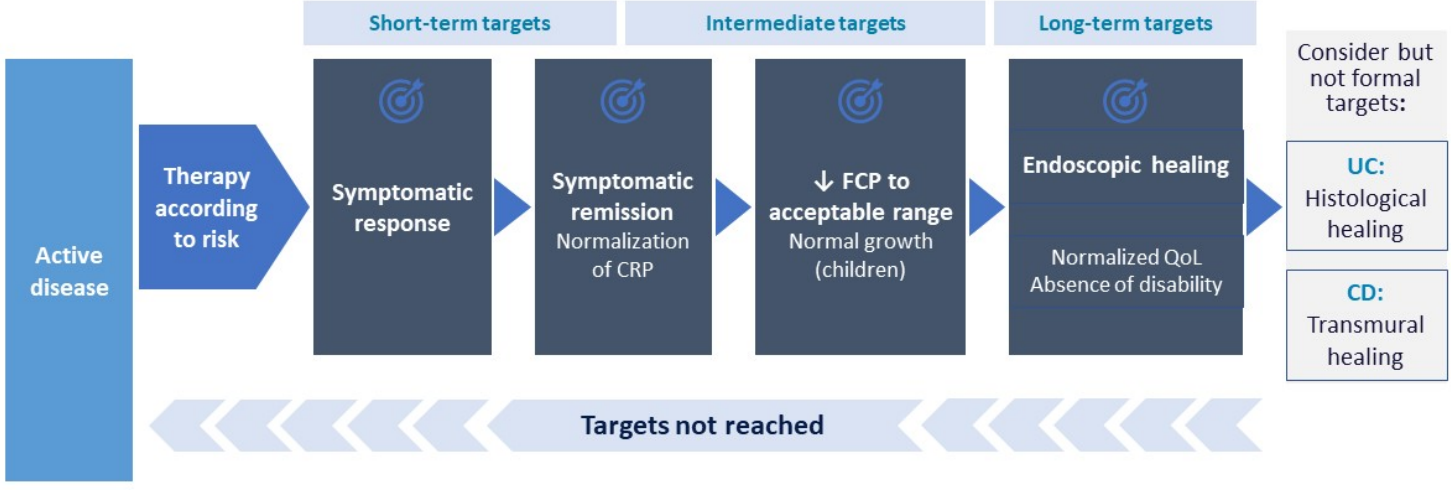
1. Solberg IC, et al. *Gastroenterol Hepatol* 2007;5:1430–1438. 2. Solberg IC, et al. Scan *J Gastroenterol* 2009;44:431–440.

Long term outcomes



Pariente B et al. Inflamm Bowel Dis 2011; 17: 1415-1422

How can we avoid complications? STRIDE II treat-to-target approach



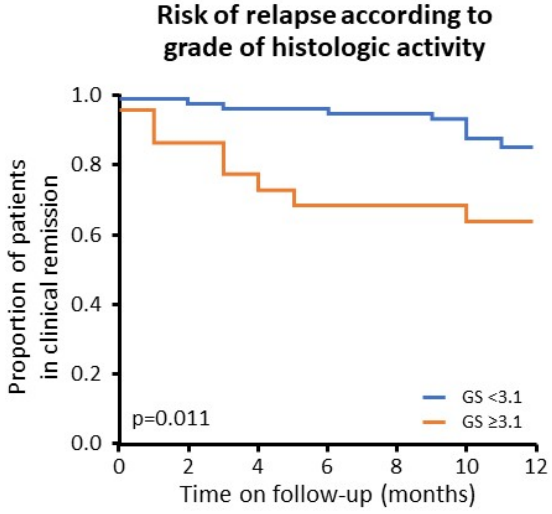
- STRIDE-II confirmed STRIDE-I long-term target of **endoscopic healing** and added absence of disability, restoration of QoL, and normal growth in children
- Symptomatic relief and normalization of serum and fecal markers have been determined as short-term targets

CRP, C-reactive protein; **FCP,** fecal calprotectin; **QoL,** quality of life; **STRIDE,** Selecting Therapeutic Targets in Inflammatory Bowel Disease; **UC,** ulcerative colitis.

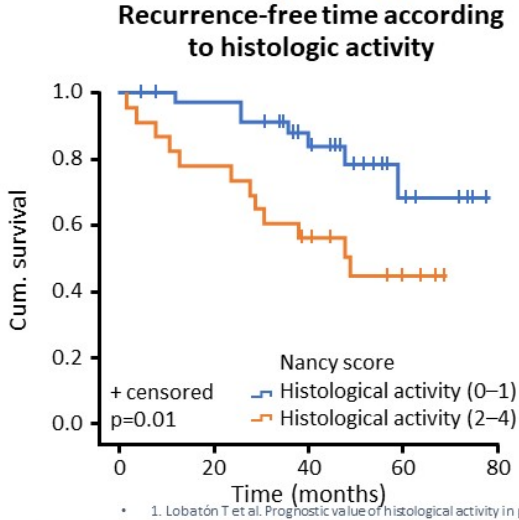
Adapted from Turner D et al. STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. *Gastroenterology* vol. 160,5 (2021): 1570-1583.

Histologic remission is associated with reduced risk of relapse in UC

Prospective study of asymptomatic patients with ESS ≤1 (n=96)[1]



Prospective study of patients with UC in clinical remission and endoscopic remission (ESS ≤1) (n=60)[2]

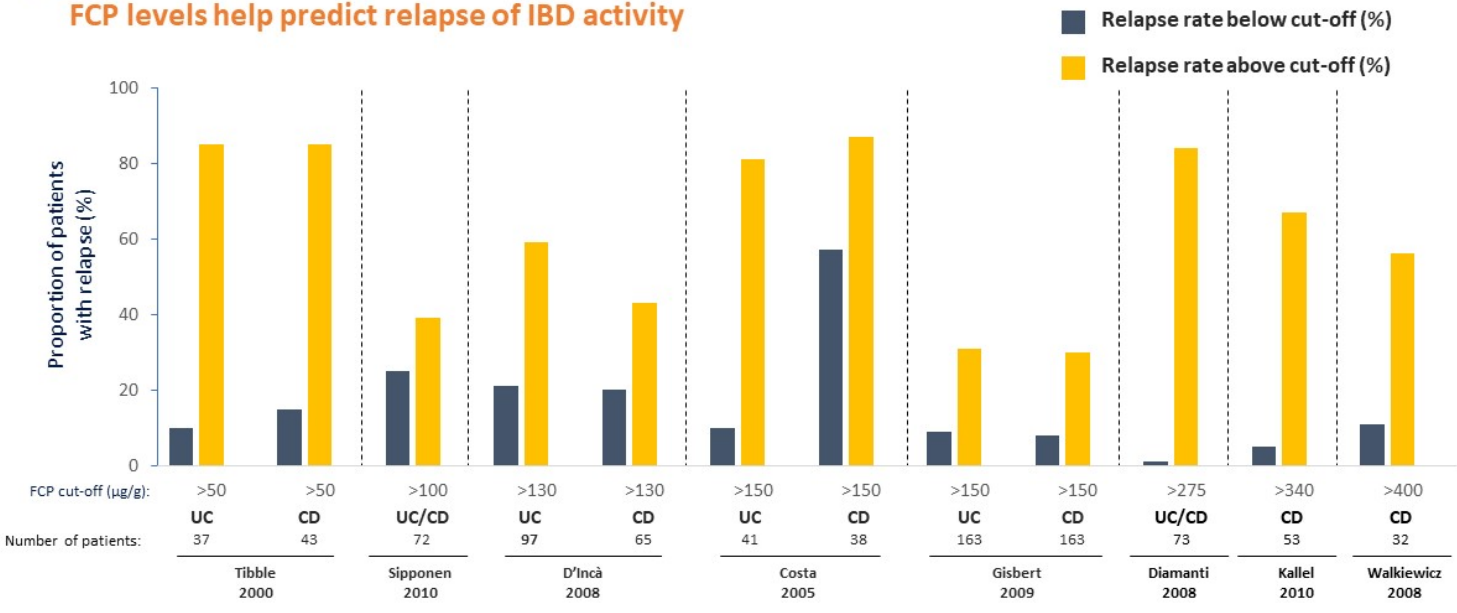


- Histologic activity was evaluated by the validated Nancy score: scores of 0–1 are considered inactivity and scores of 2–4 are considered activity
Recurrence was defined as partial Mayo score ≥2, therapy to induce remission, hospitalization, or colectomy
88.3% of patients received aminosalicylates as maintenance therapy, and 11.7% received immunosuppression
ESS, endoscopic subscore; **GS**, Geboes score; **UC**, ulcerative colitis

- 1. Lobatón T et al. Prognostic value of histological activity in patients with ulcerative colitis in deep remission: A prospective multicenter study. United European gastroenterology journal vol. 6,5 (2018): 765-772. 2. Ponte A et al. Impact of Histological and Endoscopic Remissions on Clinical Recurrence and Recurrence-free Time in Ulcerative Colitis. Inflammatory bowel diseases vol. 23,12 (2017): 2238-2244.

Elevated FCP levels in patients in clinical remission are associated with increased risk of disease relapse within 1 year

FCP levels help predict relapse of IBD activity



Calprotectin <150 indicates IBD remission with low risk of relapse.
CD, Crohn's disease; **FCP**, faecal calprotectin; **IBD**, inflammatory bowel disease; **UC**, ulcerative colitis.

Burri E and Beglinger C. Faecal calprotectin -- a useful tool in the management of inflammatory bowel disease. Swiss medical weekly vol. 142 w13557. 5 Apr. 2012,.

Despite this seemingly clear path…

There are so many ways to fail!

1. **Complications of the disease**
   - Strictures
   - Fistula
   - Hospitalizations
   - Infections
   - Cancer
   - …
2. **Complications of the extra-in… …anifestations**
3. **Complications of the… …erapies**
   - Infectious
   - Cancer
   - Toxic…
4. **Complications of the surgical therapies**

Focus on infections and strictures

Intestinal infections in IBD: A real problem!

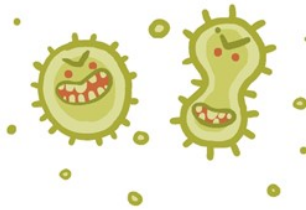


Table 2. Specific pathogens associated flare of prevalent IBD.

	CD	UC
Bacteria	+ *Campylobacter* species	+ *Campylobacter* species
	+ *Clostridioides difficile*	+ *Plesiomonas shigelloides*
		+ Enteroaggregative *Escherichia coli*
		+ Enteropathogenic *Escherichia coli*
		+ *Clostridioides difficile*
Viruses	+ Norovirus	– Norovirus
		+ Cytomegalovirus
Parasites	– *Giardia lambia*	– *Giardia lambia*
	– *Cryptosporidium*	– *Cryptosporidium*
	– *Cyclospora cayetanensis*	– *Cyclospora cayetanensis*
	– *Entamoeba histolytica*	– *Entamoeba histolytica*

+, Increased cross-sectional prevalence during flare compared to symptomatic patients without IBD.
–, Decreased cross-sectional prevalence during flare compared to symptomatic patients without IBD.
CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

- Around 17% IBD flares are related to a GI infection
- **Endoscopically very similar to an IBD exacerbation**
- High risk of C.Difficile
- Parasitic infections are rare
- **Frailty seems a key parameter in vedolizumab tt patients (aHR, 1.69; 95% CI, 1.03-2.79)**

Axelrad, J. E. *et al. American J gastroenterol 2018;* **113:** 1530–1539.
Axelrad JE *et al.* Ther Adv Gastroenterol 2021; 14: 1-17
Singh S, et al. Inflamm Bowel Dis. 2021;27(10):1626-1633.

Which treatment is more at risk?

Risk of serious infections with advanced therapies for IBD

Meta-analysis of 20 head-to-head studies

Ustekinumab vs. TNFα antagonists
(5 cohorts; 23,232 patients)

- **CD**: **51% lower risk** of serious infections with ustekinumab
- **UC**: Knowledge gap

Vedolizumab vs. TNFα antagonists
(17 cohorts; 51,596 patients)

- **CD**: **No difference** in risk of serious infections (OR, 1.03)
- **UC**: **32% lower risk** of serious infections with vedolizumab

Ustekinumab vs. vedolizumab
(5 cohorts; 1,420 patients)

- **CD**: **60% lower risk** of serious infections with ustekinumab
- **UC**: Knowledge gap

Safety profile of advanced therapies for IBD varies, and is influenced by treatment effectiveness and intrinsic immune suppression Clinical Gastroenterology and Hepatology

Solitano V et al. Clin Gastro Hepatol 2022, in press

Peri-operative risk of infections

- Biologic therapies do not modify the risk of iperi-operative nfections in most studies (Anti-TNF, vedolizumab, ustekinumab)
- Few data on tofacitinib but increased risk of thrombo-embolic events
- Immunomodulators have no impact however
- Clear increase (1,7x) in infectious risk under steroids (>20mg Prednisone per day over > 6 weeks).

- Conclusion: Most treatments can safely be continued during surgery but steroids should be weaned off

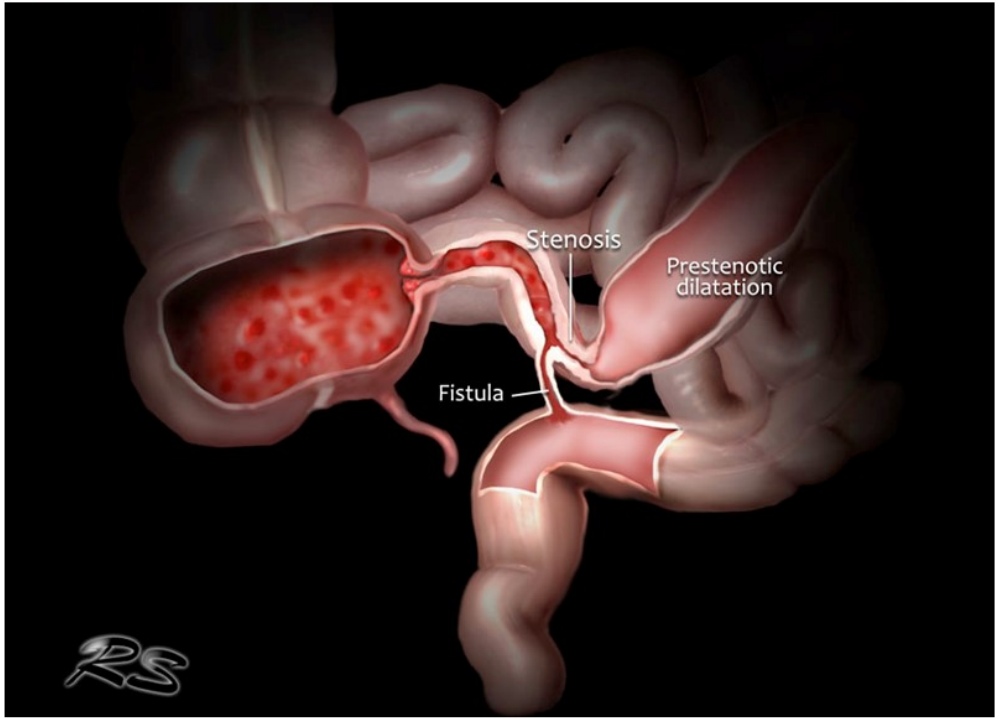
Shaji S et al. ECCO topical review: Roadmap to optimal peri-operative care in IBD. JCC 2022; in press

How can we prevent post-operative complications?

- Pré-op antibiotics and bowel prep before colonic surgery
- Nutritionnal status optimisation in the pre-op phase (ca 70% CD patients are malnourished)
- Exclusive enteral nutrition in patients with strictures or fistula.
- Other: Psychological support, iron substitution if needed, thrombo-embolic prophylaxis …
- Post-operative: treatment can be started 2-3 weeks after surgery

Shaji S et al. ECCO topical review: Roadmap to optimal peri-operative care in IBD. JCC 2022; in press
Unger LW et al. Wien Klin Wochenschr 2019;131(5):113–9

Stricturing CD: A feared long-term complication



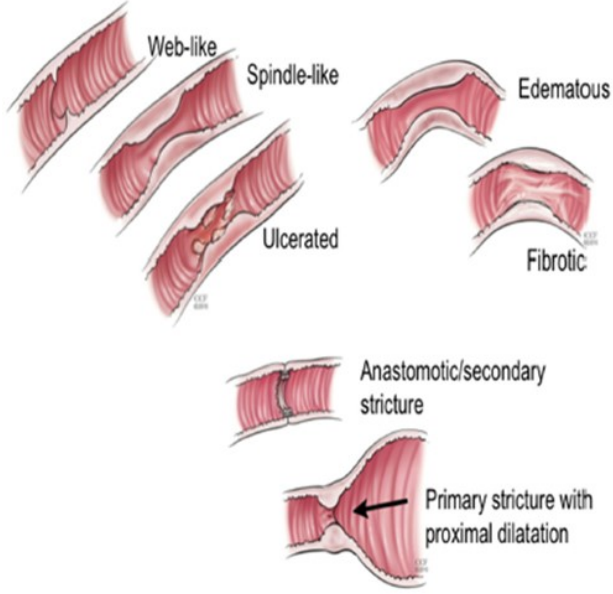
Stenotic complications of Crohn's Disease (CD)

- CD: transmural inflammatory disorder
- Long-standing and uncontrolled inflammation: increased risk of stenosis
- About **1/3 of patients** will develop a stenotic complication over 10 years follow-up
- **Main location**s: Smalll intestine (ileum), ileo-caecal valve, colon
- Colonic strictures are associated with a **high risk of colorectal cancer** (7.5% at 10 years)

Lovasz, B. D. *et al*. *J Gastrointestin Liver Dis* **22,** 265–268 (2013).

Phenotypic subtypes of stenosis

- Several types of strictures
- Description should include: location, length, intubation, etiology, inflammatory content, number
- Symptoms vary based on those parameters



Paine E, Shen B. *Gastrointestinal endoscopy* **78,** 819–835 (2013).

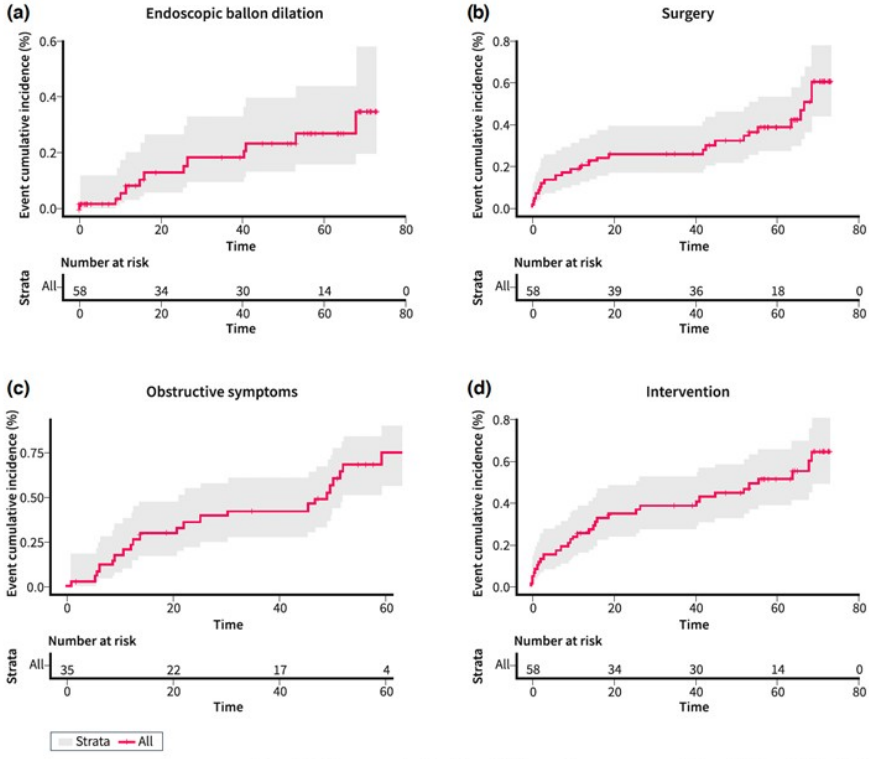
Natural history of ileal strictures in CD

Intervention rates at 12, 24 and 48 months: 26%, 35% and 45%, respectively

TABLE 4 Multivariable model predicting intervention with split sample validation

Risk factor	HR	95% CI	*p*-value
Obstructive index	1.44	1.13–1.85	**0.004**
Length of stricture	1.04	1.01–1.07	**0.007**
Duration of stricture	0.97	0.95–0.995	**0.016**
Biologics before baseline	2.12	0.88–5.08	0.09
Maximal wall thickness of stricture	1.12	0.98–1.28	0.09

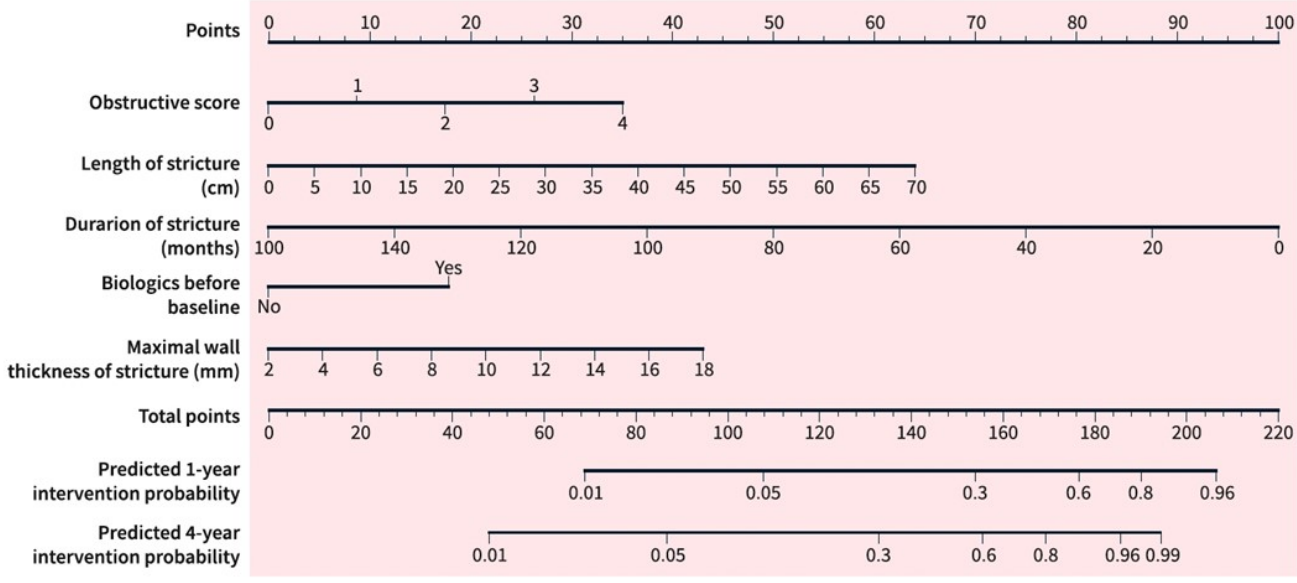
Note: Bold values denote statistical significance at the $p < 0.05$ level.



Ouali, S. *et al. United Eur Gastroent* **10**, 958–972 (2022).

Nomogram to predict outcome of stricturing CD

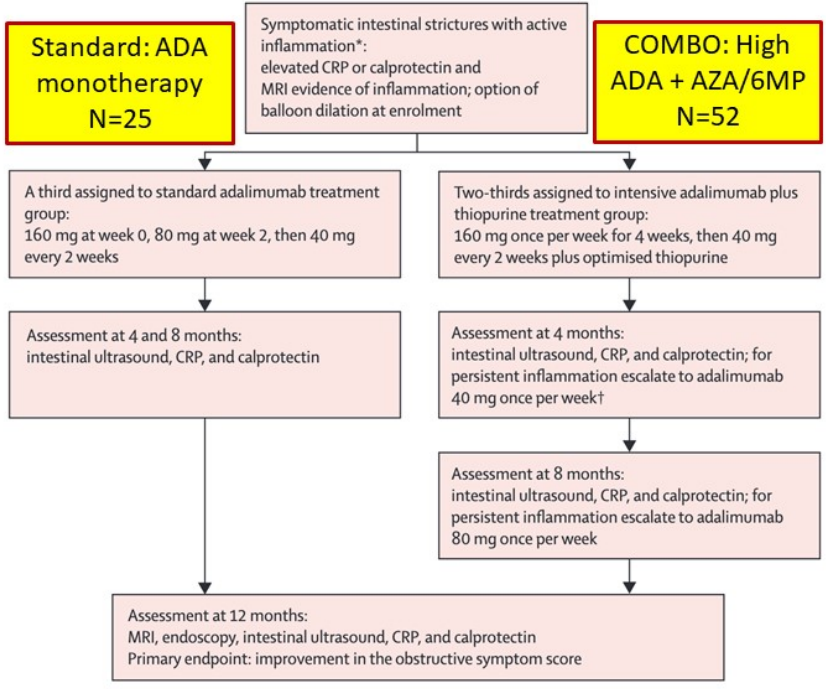
https://riskcalc.org/CrohnsDiseaseSmallBowelStricture/



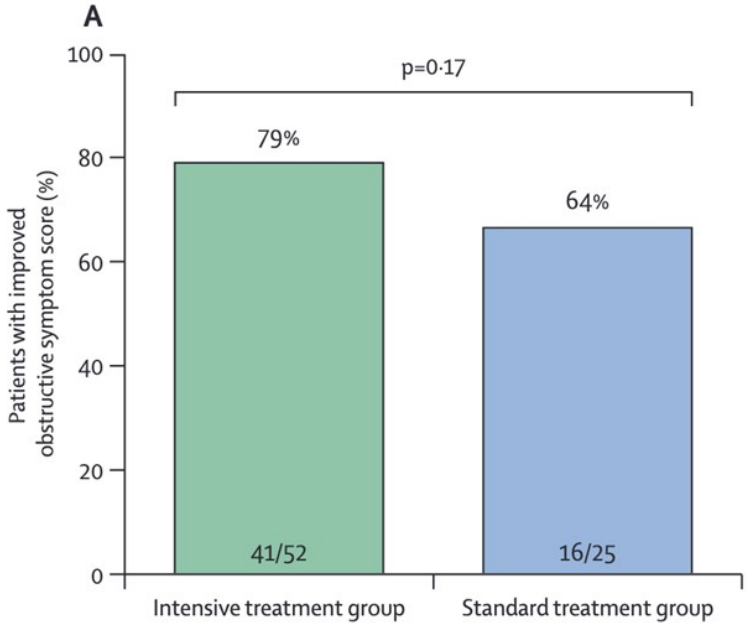
Ouali, S. *et al. United Eur Gastroent* **10**, 958–972 (2022).

Is there a room for intensive therapy in stricturing CD? Data from STRIDENT

- Single center trial in Australia in adult CD patients
- **Primary endpoint**
  Improvement (decrease) in the 14-day obstructive symptom score at 12 months by one or more points compared with baseline.



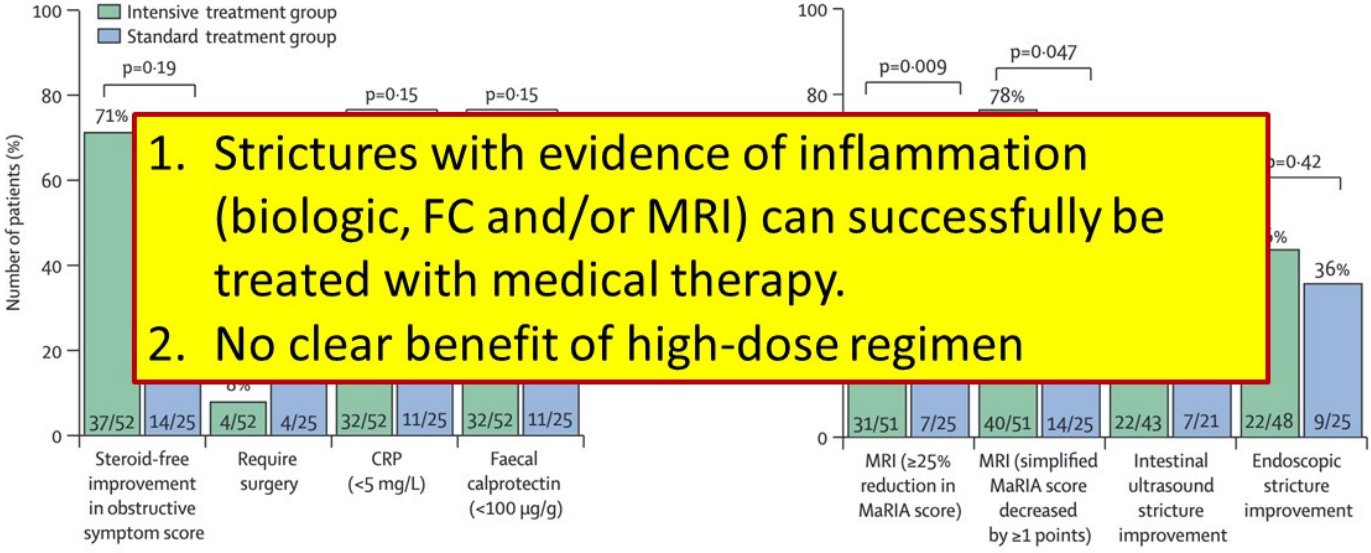
Schulberg, J. D. *et al. Lancet Gastroenterology Hepatology* **7**, 318–331 (2022).



Strictures respond adequately to therapy regardless of regimen

Schulberg, J. D. *et al. Lancet Gastroenterology Hepatology* **7**, 318–331 (2022).

Medical therapy has a significant impact on stricture outcome



1. Strictures with evidence of inflammation (biologic, FC and/or MRI) can successfully be treated with medical therapy.
2. No clear benefit of high-dose regimen

Schulberg, J. D. *et al. Lancet Gastroenterology Hepatology* **7**, 318–331 (2022).

Endoscopic ballon dilation

- Indicated in strictures <5cm, straight, endoscopically accessible
- technical success rate of the EBDs: 89%
- clinical efficacy. 81%.
- Complications in 3% per procedure.
- Up to 52%: repeat dilation
- 30% surgery at 12- month follow-up after initial EBD.

TABLE 2. 6-, 12-, and 24-Month Rates of Events

	% (95% CI)		
Outcome	6-month	12-month	24-month
Symptoms	35.9 (4.8–56.9)	62.1 (27.6–80.2)	75.9 (31.0–91.6)
Redilation	36.5 (24.6–45.9)	51.8 (36.0–63.6)	73.5 (56.8–83.8)
Surgery	17.5 (11.8–22.9)	30.1 (17.4–40.9)	42.9 (23.7–57.4)

Estimates obtained from the Cox proportional hazards frailty models. Models for redilation and surgery account for stricture location, de novo versus postsurgical stricture, maximal caliber of dilation, steroid injection, and use of concomitant techniques for redilation and surgery. Model for symptoms accounts for stricture location, de novo versus postsurgical stricture, maximal caliber of dilation, and steroid injection.

Bettenworth, D. *et al. Inflamm Bowel Dis* **23**, 133–142 (2016).
Ismail, M. S. & Charabaty, A. *Frontline Gastroenterology* **13**, 524–530 (2022).

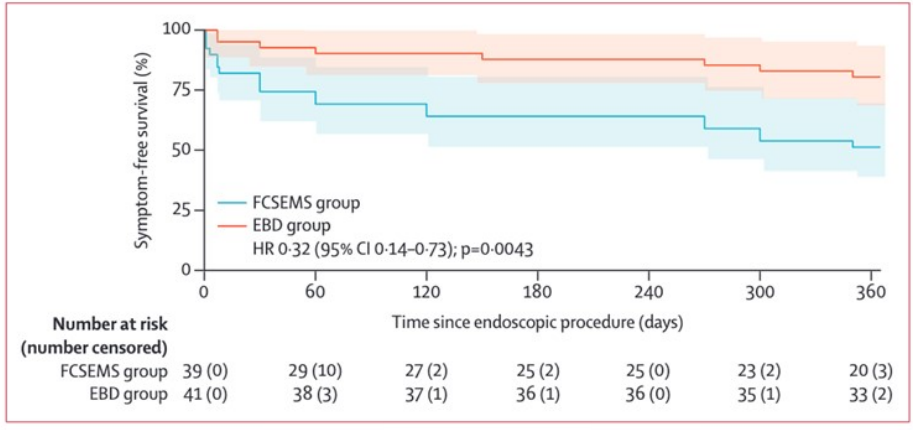
Other approaches

- **Intralesional steroid (triamcinolone) injection**: Conflicting data. Marginal improvement in dilation-refractory cases
- **Needle-knife stricturotomy**
- **Endoscopic stent placement:** high risk of stent migration. Consider for pre-op decompression.

Bharadwaj, S., Fleshner, P. & Shen, B. *Inflammatory Bowel Diseases* **21,** 2194–2213 (2015).
Loras, C. *et al. Lancet Gastroenterology Hepatology* **7**, 332–341 (2022).

Self-expandable metal stents for stricturing CD: The protDilat prospective study (Spain)

- 92% technical success.
- **Stent migration in 35 of 36 patients**
- Median time that the FCSEMS remained in the stricture was 2 days (IQR 2–7).
- In seven (19%) patients a colonoscopy was done for stent removal



Loras, C. *et al*. *Lancet Gastroenterology Hepatology* **7**, 332–341 (2022).

Conclusion and perspectives

- The best way to manage complications is to avoid them!!
- Prevention is key: Tight control and tight monitoring (Stride II guidelines)
- IBD flares can be triggered by infections
- Beware of steroids in patients undergoing surgery and don't underestimate nutritional status
- Strictures: Inflammation can efficiently be fought with drugs but mechanical options are usually necessary

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