

The logo graphic consists of a green semi-circle at the top, followed by a horizontal line of green dots, a solid green horizontal line, and another horizontal line of green dots below it.

IBDHorizons

A panoramic view of a city skyline at sunset, with a purple and pink sky and a river in the foreground. The buildings are silhouetted against the bright sky.

Fibrotic Crohn's Disease: Present and Future

ARS QUESTION 1

Which is TRUE regarding strictures in Crohn's Disease:

- A. Longstanding Crohn's strictures should be biopsied to check for malignancy
- B. Concomitant intra-lesional steroid injection improves endoscopic balloon dilation outcomes
- C. Anti-TNF intralesional injection is routinely indicated
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Which feature is a contraindication to endoscopic balloon dilation:

- A. Stricture length of < 4 cm
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- C. Absence of ulceration near or within the stricture
- D. Presence of adjacent fistula or deep ulceration

Clinical Case 5

21-year-old with newly diagnosed with isolated 12cm ileal Crohn's disease characterized by ulcers, stenosis that cannot be traversed. She is currently on no treatment and reports abdominal pain, nausea, and decreased stool output.

Fibrostenotic Crohn's Disease: Present and Future

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Acknowledgement:

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#WetheFibrosisLab @IBD_FloMD

<https://www.lerner.ccf.org/immuno/rieder/>

Disclosures

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- Pfizer
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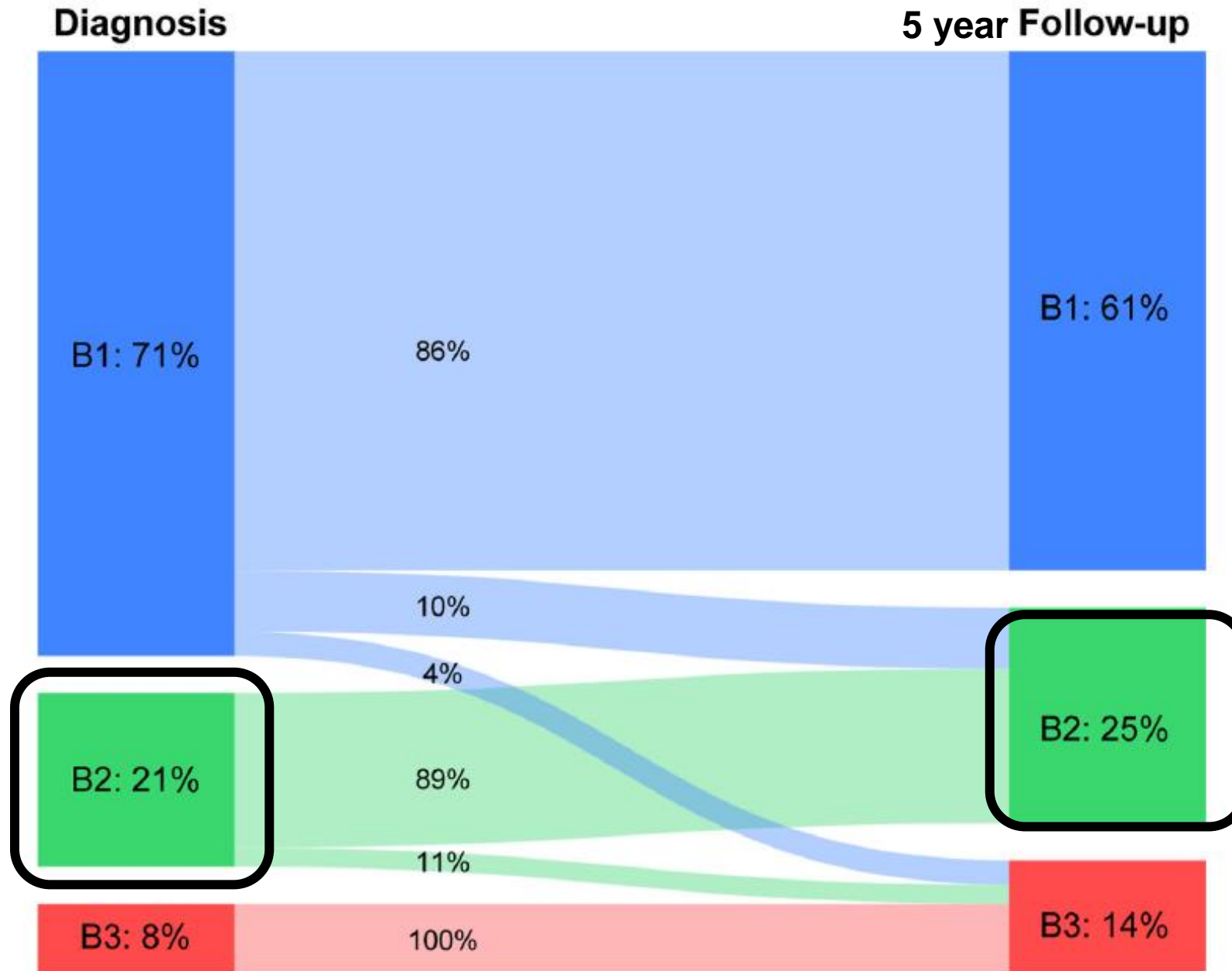
Advisory Board/Consultant:

- AbbVie
- Bristol Myers Squibb
- Genentech
- InDex Pharmaceuticals
- Janssen
- Organon
- Pfizer
- Takeda

Objectives

- Summarize the role of medications in CD patients with stricture
- Highlight the indications for endoscopic stricture interventions
- Review the surgical approach to stricturing Crohn's disease
- Review new developments in reversing fibrosis

Crohn's disease behavior at presentation



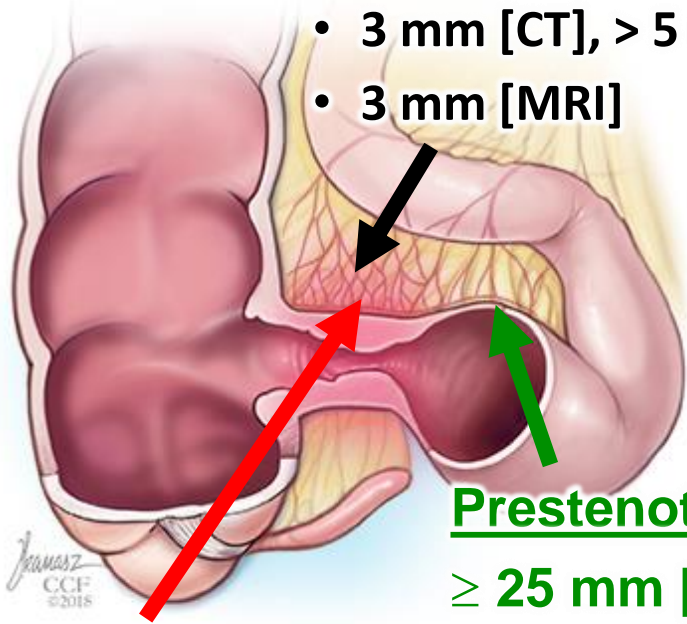
At 5 years:

- 22% required surgery
- 36% hospitalizations
- 10% progressed from B1 to B2

Stricturing Crohn's disease:

Radiologic definitions

- Wall thickness
- 3-5 mm [US]
- 3 mm [CT], > 5 mm [CT]
- 3 mm [MRI]



Prestenotic dilation

≥ 25 mm [US]

≥ 25-40 mm [CT]

Luminal diameter

4 mm [US]

< 6-12 mm [CT]

	Inflammation	Fibrosis
Wall thickness	X	X
T2 hypersignal	X	X
Delayed hyperenhancement	X	
Layered enhancement	X	
Comb sign	X	X
Fistula	X	X

SLIDE Modified from FLORIAN RIEDER MD

Factors associated with higher rate of success with medical therapy

- On immunosuppressive treatment
- CD Obstructive score ≥ 4
 - rated 0-6 based on abdominal pain, N/V, hospitalization, dietary modifications)
- Duration obstructive symptoms (weeks) ≤ 5
- Length of stricture $< 12\text{cm}$
- Maximal small bowel diameter proximal to stricture (18-29 mm)
- Marked enhancement on delayed T1 weighted sequence
- No fistula

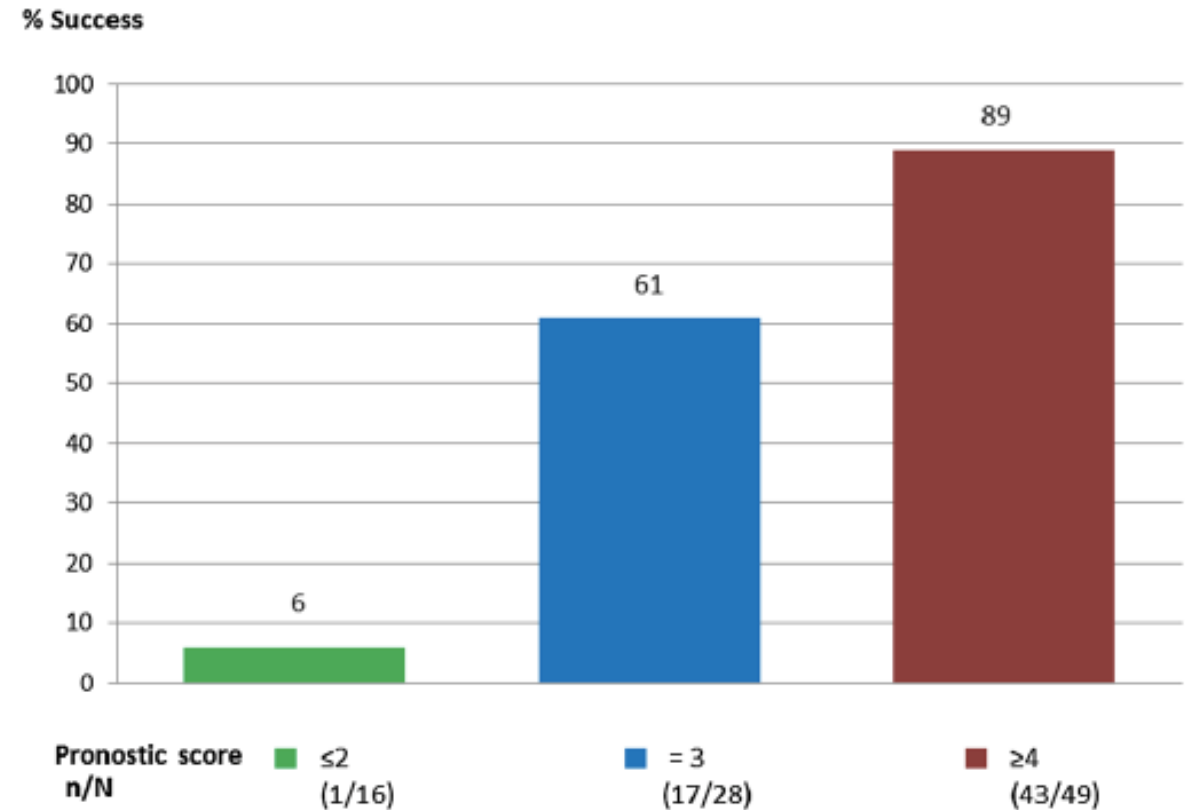
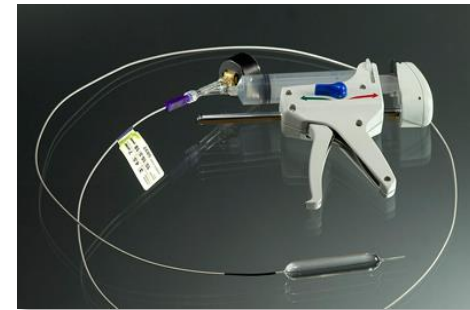
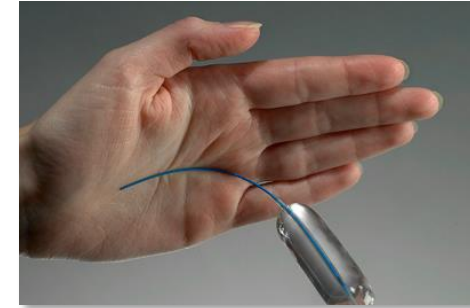


Figure 1 The observed probability of success at week 24 in 93* patients with Crohn's disease and symptomatic small bowel stricture(s) according to the clinicoradiological prognostic score†. *93 of 97 patients had a delayed T1 weighted sequences; †for details see table 3.

Indications for endoscopic dilation

- **Symptomatic** ileal or ileocecal valve strictures
 - CAUTION RE: **Colonic strictures** → **dysplasia or cancer in 3.5%** of IBD patients with colonic strictures
- **Isolated** anastomotic strictures
- Upper GI strictures → if technically feasible
- Ulcerated stenosis/inflamed stenosis → not an absolute contraindication



Cross sectional imaging is important to exclude penetrating complications, length and angulation

Efficacy of endoscopic balloon dilation

Systematic review: n=1463 with n=3213 dilatations

Dilation	Median %	95% CI %
Technical success	89	87 - 91
Clinical efficacy	81	75 – 85
Major complications*	2.8	2.1 – 3.9

*Perforation, bleeding, dilation related surgery

- Stricture <5cm associated with surgery free outcome
- Each 1cm increase = 8% increase in hazard for surgery
- Duodenal stricture 5x risks for surgery
- Active disease **NOT** associated with increased risk
- Anastomotic and primary strictures → similar surgical, re-dilation rates

Considerations for endoscopic interventions for stricturing disease

1.1 Computed tomography enterography or magnetic resonance enterography, with or without retrograde contrast enema, should be done before the endoscopic intervention **Recommend imaging before endoscopy**

1.2 Optimal bowel preparation should be done before colonoscopy, pouchoscopy, and ileoscopy **Good prep is key**

1.3 Monitored anaesthesia care or general anaesthesia is recommended for patients undergoing deep enteroscopy, anticipated long-lasting or technically challenging endoscopic procedures, or for those with significant comorbidities **Use MAC**

1.7 Prophylactic antibiotics can be considered in patients who are at risk for procedure-associated bacterial translocation (at the discretion of the endoscopist) **Antibiotics for higher risk patients**

1.8 Systemic corticosteroid exposure is associated with an increased risk of complications from endoscopic interventions **Steroids increase complications**

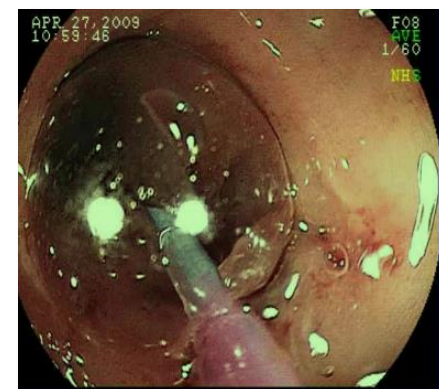
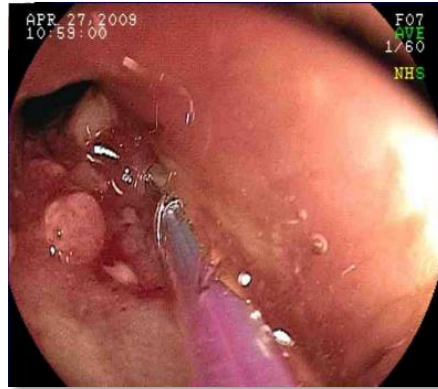
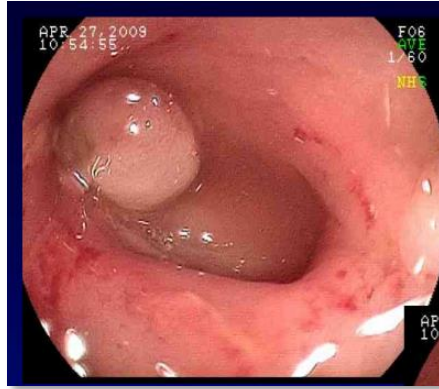
1.9 Biologics can be safely continued in patients undergoing endoscopic intervention **No need to hold biologics**

2.14 To rule out malignancy, a biopsy of the stricture should be taken at the index EBD, or a diagnostic endoscopy should be done **Check for malignancy in longstanding strictures**

2.15 Concurrent intralesional steroid injection following EBD is not recommended **No role for steroid injections**

2.16 There is no substantial evidence of benefit from intralesional injection of anti-tumour necrosis factor biologics alone or in combination with EBD† **No role for intralesional biologic injections**

Suggested endoscopic balloon dilation technique

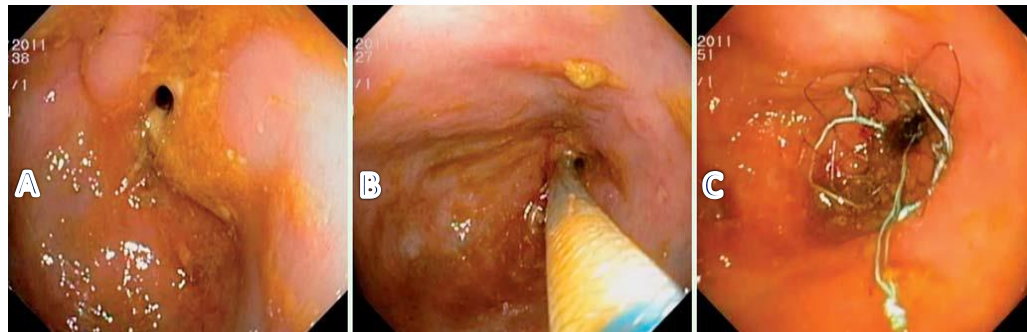
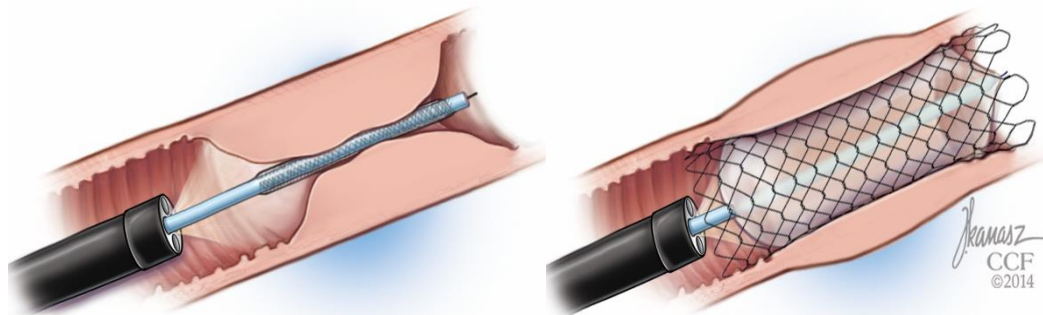


1. Choose the right balloon size depending on stricture severity
2. Use the guidewire to stabilize the balloon
3. Inflate to 1st diameter on hold for 60 seconds
4. Deflate, and re-inflate to higher diameter and hold for 60 seconds
5. Careful when 'pulling' the scope with balloon through stenosis
6. Insufficient data to recommend steroid or other injectable therapies (e.g. anti-TNF)

Other potential endoscopic techniques for strictures

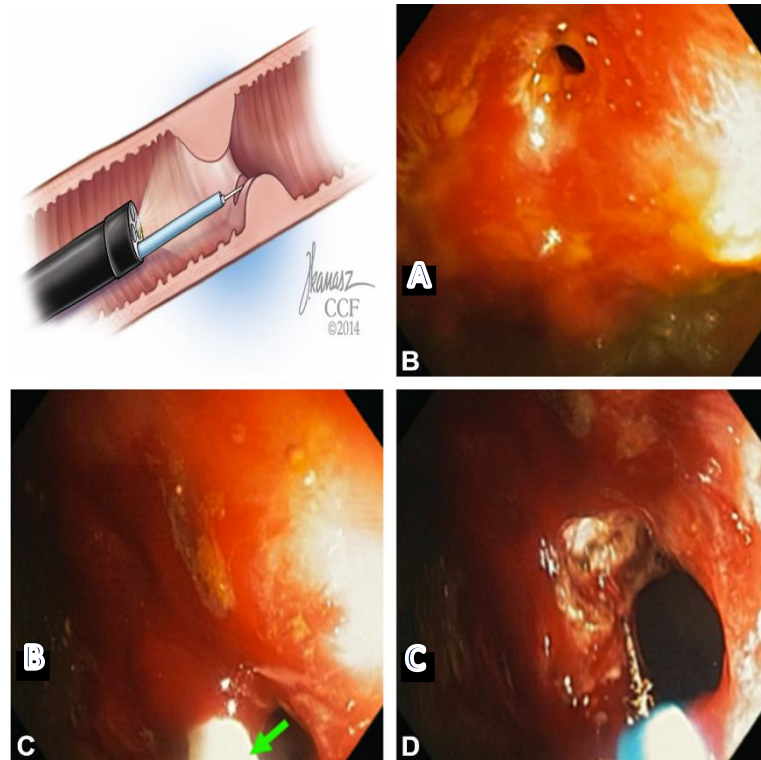
Stent placement:

- Observational data only
- Short-term success rates variable
- Complications: stent migration, fistulae
- Fully covered metal stents may be considered for refractory strictures



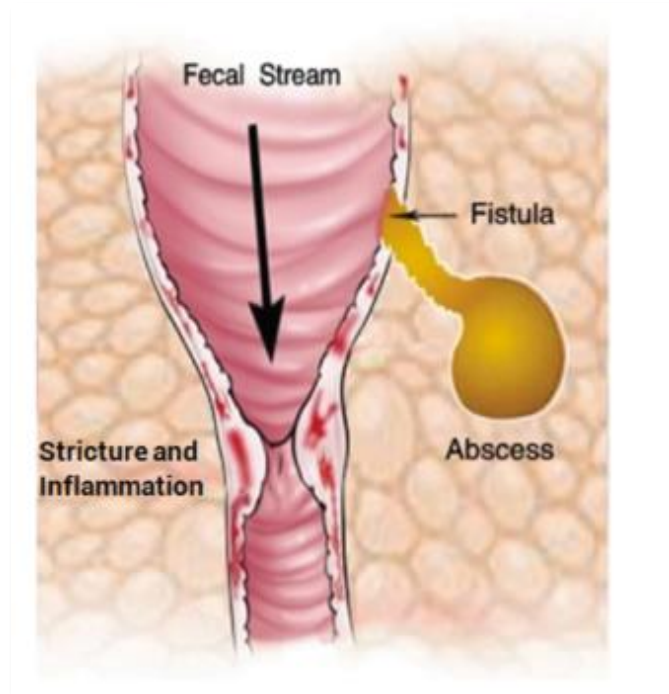
Electroincision

- Potential use for anorectal strictures
- Reserve for refractory strictures
- Refer to centers with experience
- 10% complications → mostly bleeding



Contraindications to endoscopic treatment

- Abscess, fistula, phlegmon, high grade dysplasia or malignancy
- Strictures > 5cm
- Technically unfeasible due to angulation/position, inaccessible
- Serial dilatation – is feasible, but consider symptoms free interval, technical feasibility, patient preference, QoL, dietary restrictions



Endoscopic vs Surgical management of Strictureing Crohn's Disease

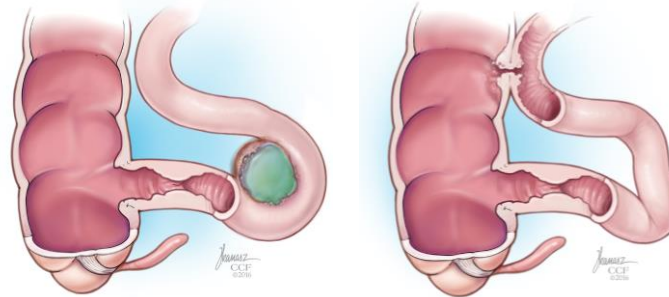
Location, length, accompanying features, technical feasibility, symptom free interval and patient preference (EL3)

Endoscopic dilation

- Short strictures $\leq 5\text{cm}$ (EL2)
- Serial dilation feasible (EL3)
- Inflammation not a contraindication (EL3)
- Anastomotic strictures
- Concomitant techniques not routinely recommended (EL3)
- Intermittent obstructive episodes
- Long interval prior surgery

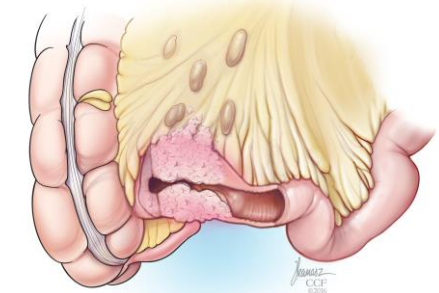
Strictureplasty

- Multiple strictures
- Prior extensive bowel resections (EL4)



Resection

- Long strictures
- Abscess, fistula, phlegmon
- Dysplasia, malignancy (EL3)



Future directions: Anti-fibrotics

Potential targets:

- TGF- β – transforming growth factor \rightarrow involved in fibrogenesis through activation of mesenchymal cells
- IL-36 – interleukin-36 \rightarrow induces gene expression for fibrogenesis
- Rho-kinase inhibition \rightarrow may prevent/reverse fibrosis in animal models

List of potential anti-fibrotic agents that have been tested in murine or human intestinal models.


Molecules	Mechanism of action	Model system	Outcome relevant to the gastrointestinal tract	References
AMA0825	Rho-associated protein kinase inhibitor	Murine intestinal fibrosis	Prevention and reversal of intestinal fibrosis	[106]
Tranilast	Reduction of TGF- β activity	Pilot study in human CD patients	Reduced rate of symptom occurrence in asymptomatic strictures	[102]
GED-0507-34 Levo	PPAR γ Receptor agonist	Murine intestinal fibrosis	Prevention of intestinal fibrosis	[107]
IL-36R antibody	Interleukin 36 receptor inhibition	Primary human cells and murine intestinal fibrosis	Prevention and reversal of intestinal fibrosis and reduction in profibrotic gene signatures in human fibroblasts	[104]
Thalidomide	Regulates multiple inflammatory and fibrosis pathways	Murine intestinal fibrosis	Regulation and reversal of intestinal fibrosis	[108]
Andrographolide sulfonate	Inhibits activation of macrophages, suppresses Th1/Th17 response, and down-regulates MAPKs and NF- κ B pathways	Murine intestinal fibrosis	Prevention of intestinal fibrosis	[109,110]
EW-7197	Transforming growth factor- β type I receptor kinase inhibitor	Murine intestinal fibrosis	Prevention of intestinal fibrosis	[111]
TMS275	PAI-1 inhibition	Murine intestinal fibrosis	Reversal of intestinal fibrosis	[112]
Pirfenidone	Inhibits cell proliferation and collagen I production	<i>In vitro</i> primary human intestinal fibroblasts.	Inhibition of fibroblast growth and suppression of collagen production	[113]
Mouse p40 peptide-based vaccines	Sustained Blockage of IL-12 and IL-23	Murine intestinal fibrosis	Prevention and reduction of intestinal fibrosis	[114-116]
Wu-Mei-Wan, a classic traditional Chinese herb medicine	Inhibition of colon fibroblast activation	Murine intestinal fibrosis	Prevent intestinal fibrosis	[117]
ICG-001	TGF- β / WNT signaling inhibition	Intestinal fibroblasts	Inhibition of β -catenin and collagen I production	[118]
Melanin-concentrating hormone antibody	Melanin-concentrating hormone blockage	Murine intestinal fibrosis	Reduction of collagen production and reduction of fibrosis	[119]
Daikenchuto (Da-Jian-Zhong-Tang)	Activating myofibroblast transient receptor potential ankyrin 1 channel	Murine intestinal fibrosis	Prevention of intestinal fibrosis	[120]
Losartan	Downregulation of TGF- β 1 expression	Murine intestinal fibrosis	Prevention of intestinal fibrosis	[121]
Triptolide (PG490)	Anti-inflammatory and immunomodulatory activities	Murine intestinal fibrosis	Prevention and reversal of intestinal fibrosis	[122]
BGB324	AXL Receptor tyrosine kinase inhibitor	Human colonic fibroblasts, murine intestinal fibrosis, Human intestinal organoid culture, colon resections of patients with CD	Prevention and reversal of intestinal fibrosis	[123]

CD: Crohn's disease; TGF- β : Transforming growth factor beta; PPAR γ : Peroxisome Proliferator Activated Receptor Gamma; MAPK: mitogen-activated protein kinase; NF- κ B: Nuclear factor kappa B.

Summary:

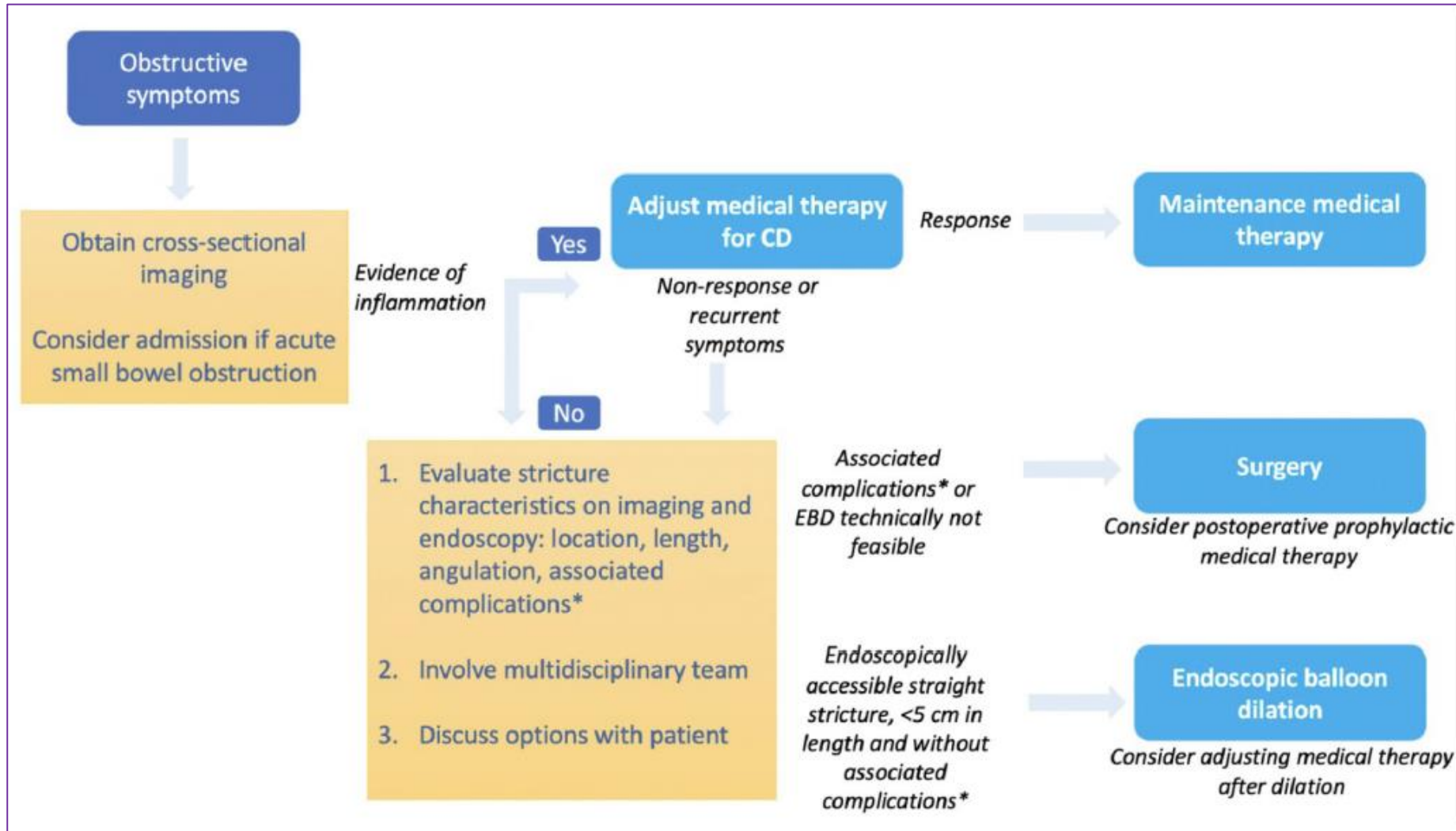
- Strictures most amenable for dilation are:
 - “Short” (< 5cm)
 - “Straight” (can easily pass the TTS dilator + guidewire without resistance)
 - “Safe” (no evidence of penetrating disease, deep ulceration)
- Recommend surgical resection for severe endoscopic disease (e.g. deep ulcers, I4 disease)
- Start or optimize treatment:
 - Inflammatory strictures
 - Post-endoscopic dilation
 - Post-operatively – higher risk patients

CD High-Risk features



Age at diagnosis	< 30 years
Anatomic involvement	Extensive
Perianal and/or severe rectal disease	YES
Ulcers	Deep
Prior surgical resection	YES
Strictureing and/or penetrating behavior	YES

Recommended approach to Crohn's disease strictures



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Panel Discussion

Moderator: Scott Lee, MD

Christina Ha, MD

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Timothy Ritter MD

Brian Feagan, MD

Feza Remzi, M.D.

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