Post-op recurrence of Crohns disease

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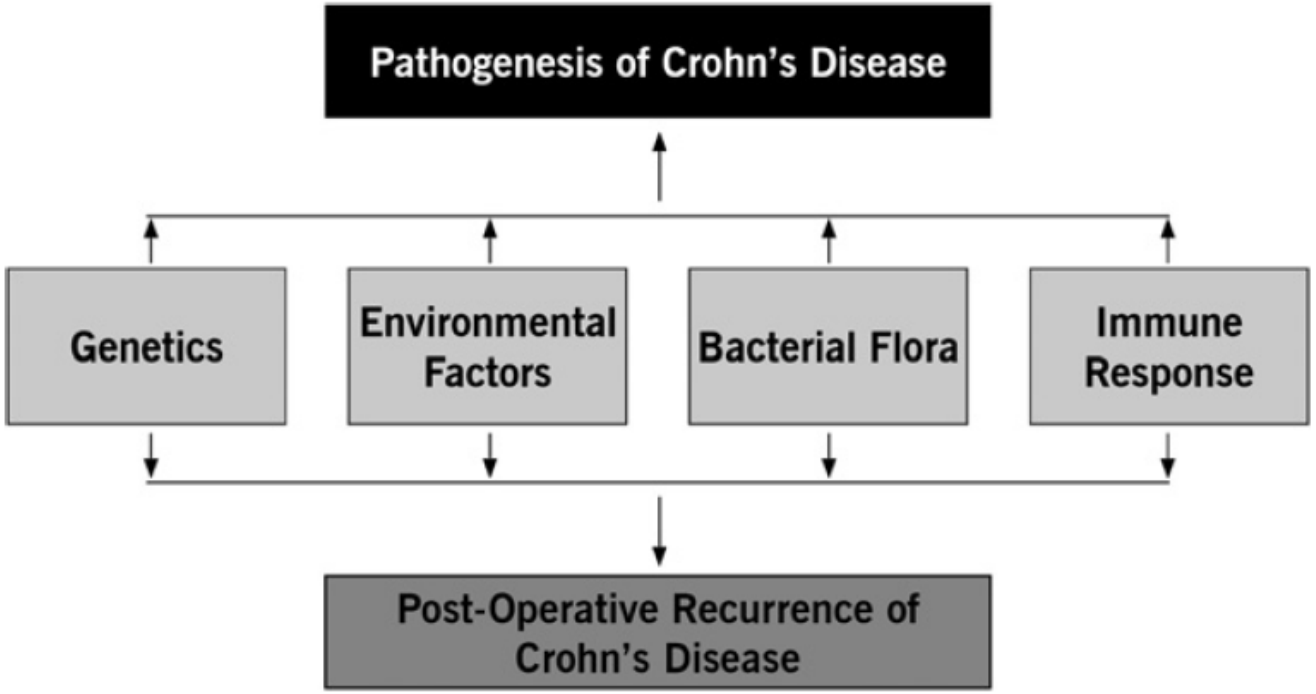
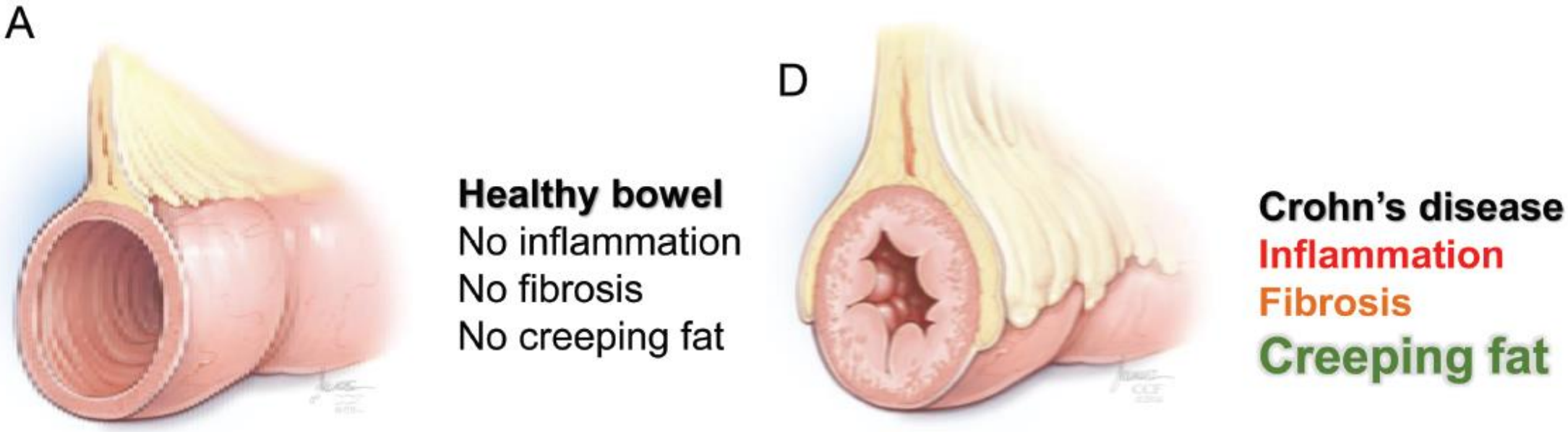
Pathophysiology



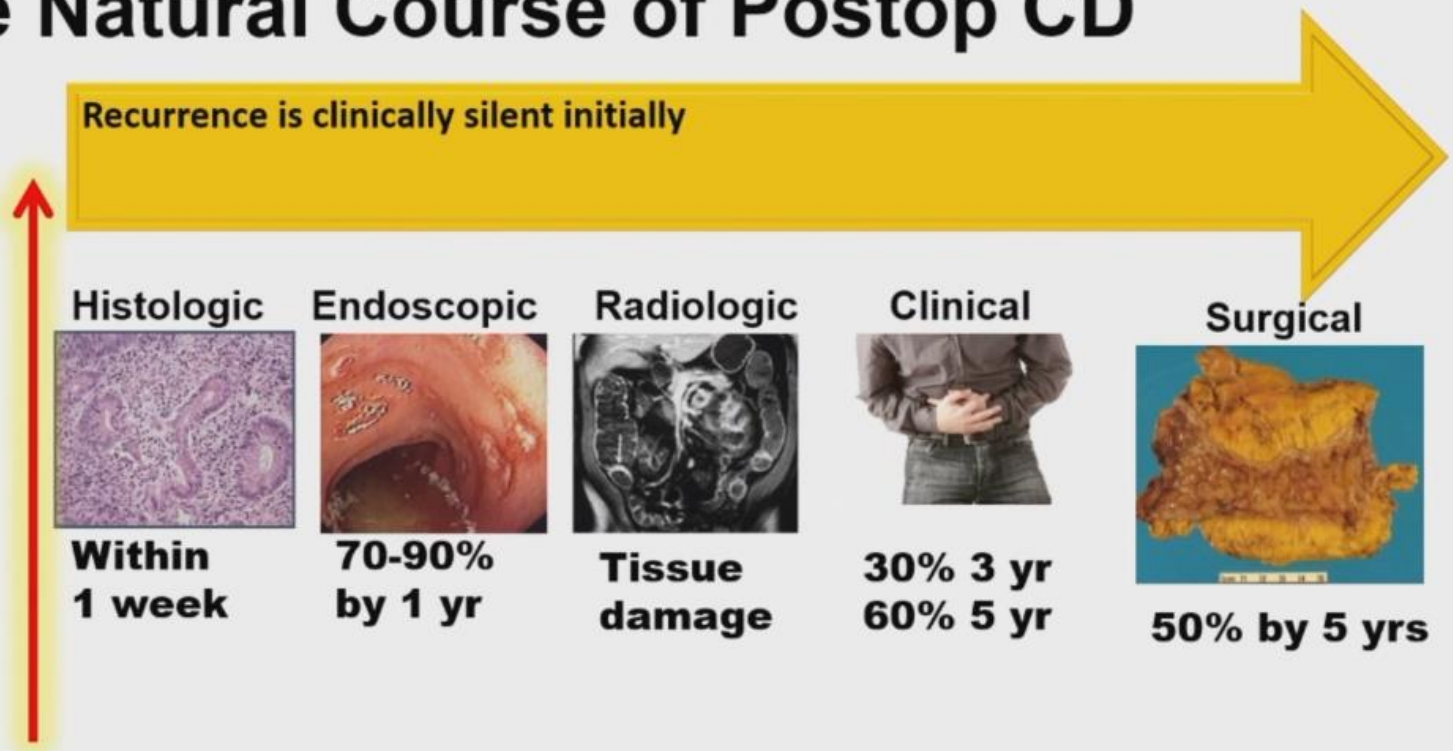
Pathogenesis of postoperative recurrence in Crohn's disease Tasneem Ahmed et al 2010

Mesenteric involvement in Crohns



Mao R et al Creeping Fat Influencing Stricture Formation in Crohn's Disease. Inflamm Bowel Dis. 2019 Feb 21;25(3):421–6.

The Natural Course of Postop CD



D'Haens GR, et al. *Gastroenterology*. 1998;114(2):262-267. Olaison G, et al. *Gut*. 1992;33(3):331-335. Rutgeerts P, et al. *Gastroenterology*. 1990;99(4):956-963. Sachar DB. *Med Clin North Am*. 1990;74(1):183-188.

Predictors of Recurrence

Patient related

- Tobacco smoking
- Female > male

Disease related

- Prior surgery
- Penetrating and perforating disease
- Young age- younger than 30 years old
- Shorter duration of disease before surgery (<10y)
- Use of steroids
- Multisite disease
- Family history

Jana Hashash, Expert Review Gastro-hep, 2012

Risk stratifying recurrence

High Risk Factors:

- Current smoking
- History of perforating or penetrating phenotype
- History of perianal phenotype
- History of at least 2 prior surgeries
- Younger age (<30 y)

Clinical Gastroenterology and Hepatology 2020;18:1356–1366

Moderate Risk factors:

- Longer segment of diseased bowel at the time of resection (>10 cm)
- Shorter time to initial surgery (<10 y)

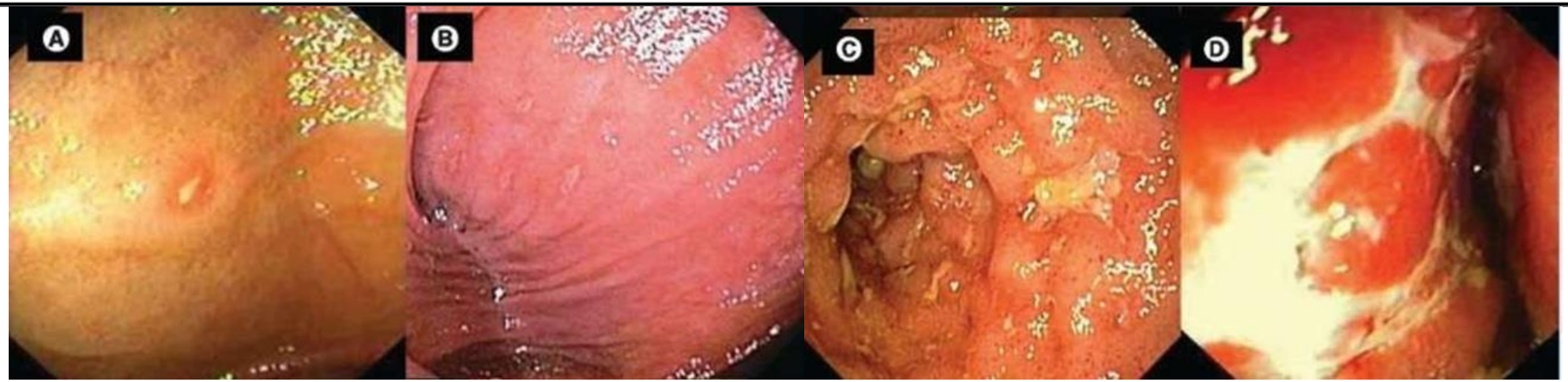
• Low Risk Factor:

- The absence of an identifiable risk factor

Assessing Recurrence

- Endoscopy
- Video Capsule endoscopy
- Faecal Calprotectin and Faecal Lactoferin
- MRI

Rutgeerts Score		Endoscopic Findings at IC
Grade i0	Endoscopic Post-operative Remission	Normal mucosa
Grade i1		<5 Aphthous ulcers
Grade i2	Endoscopic Post-operative Recurrence (EPOR)	>5 Aphthous ulcers with normal intervening mucosa or large lesions confined to the anastomosis
Grade i3		Diffusely inflamed mucosa with aphthous ileitis
Grade i4		Diffuse inflammation, large ulcers/nodules/narrowing



Rutgeerts, Gastroenterology 1990

Video Capsule Endoscopy

- Sensitivity and Specificity for POR 50-79% and 94- 100% respectively
- Risk of impaction in strictures

Bourreille A, Gut, 2006

MRE

Classification of findings:

- MR -0 – No abnormality
- MR 1 – minimal mucosal changes
- MR 2 – diffuse aphthoid ileutis
- MR 3 – Severe recurrence – trans and extramural changes

Compared with Rutgeerts – Kappa value – 0.67

MR2 & MR3 – Sensitivity and specificty – 89 & 100% for i3 & i4

Limited access and cost

Koilakou, IBD 2010

Faecal Calprotectin and Faecal lactoferrin(FL)

- Cut-offs for POR – FC - >50 U, FL.7.5 U(µg/g)
- Increase to 2X ULN – disease flare
- Both were better than CRP in POR prediction, better sensitivity

A Buisson, Digestive and Liver Dis, 2012

- Correlates well with Rutgeert's score
- Can be utilized to monitor for POR and response to Rx
- Predicts POR with greater accuracy than CRP/CDAI
- Levels > 100 mg/g appear to be the optimal cut off
- - NPV 90%

Wright E, et al. Gastroenterology 2015;148:938–947

Predicting Recurrence

- Who?
- When?
- Prophylaxis?

Landmark Studies

- POCER
- PREVENT

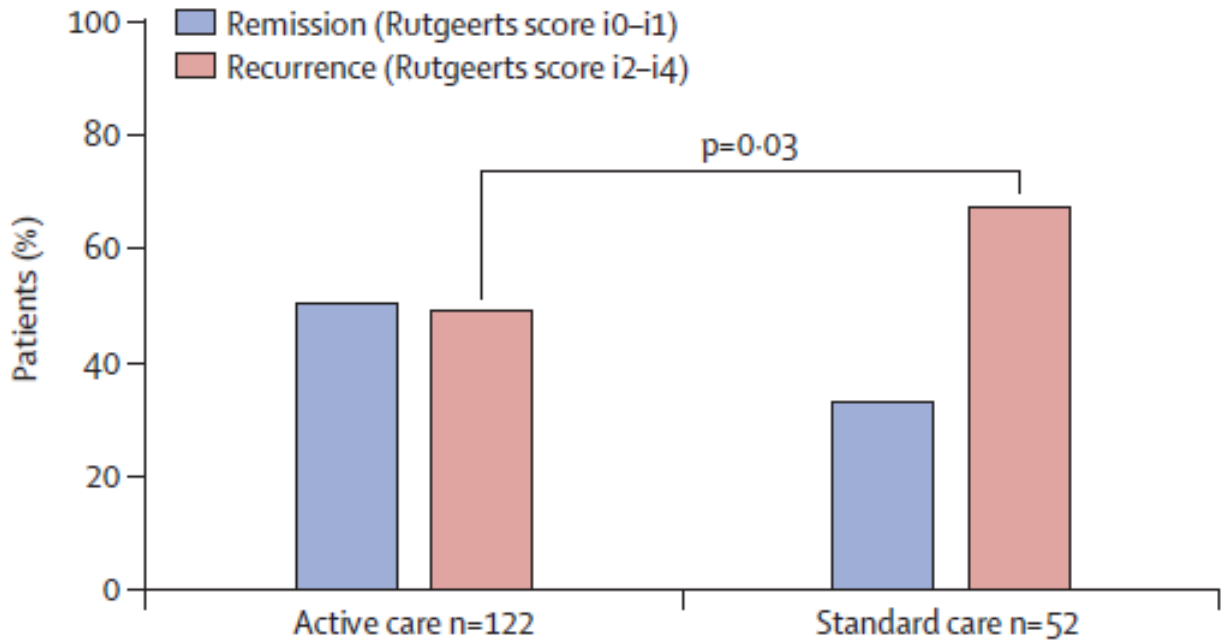
POCER

- The study included 174 patients post -operatively
- Patients were labelled ‘high’ risk or ‘low’ risk
- High risk if ≥1 of the following factors:
- - Smoking
- - Perforating disease (abscess, enteric fistula)
- Previous resection
- High risk patients received AZA/6-MP or adalimumab (if AZA/6-MP intolerant)
- Low risk patients received no treatment

De Cruz P, et al. Lancet 2015; 385: 1406–17

- The aim of the study was to follow patients up over an 18 month period with the primary aim being recurrence at 18months
- Patients were randomised into 2 groups
- The active group had colonoscopy to assess for endoscopic recurrence at 6 months.
- If recurrence was found then treatment would be altered appropriately
- The standard group did not have colonoscopy at 6 months to assess for recurrence
- All patients were treated with metronidazole for 3 months unless not tolerated

Results


Remission (Rutgeerts score i0–i1)
Recurrence (Rutgeerts score i2–i4)
p=0·03
Patients (%)
100
80
60
40
20
0
Active care n=122
Standard care n=52

Imadazole antibiotic studies

- Original placebo controlled trials
- Metronidazole (20mg/kg/day) vs placebo for 3 months
- Ornidazole (500mg BD) vs placebo for 1 year
- Both trials showed less recurrence of disease compared to placebo
- Stopping Antibiotics resulted in recurrence

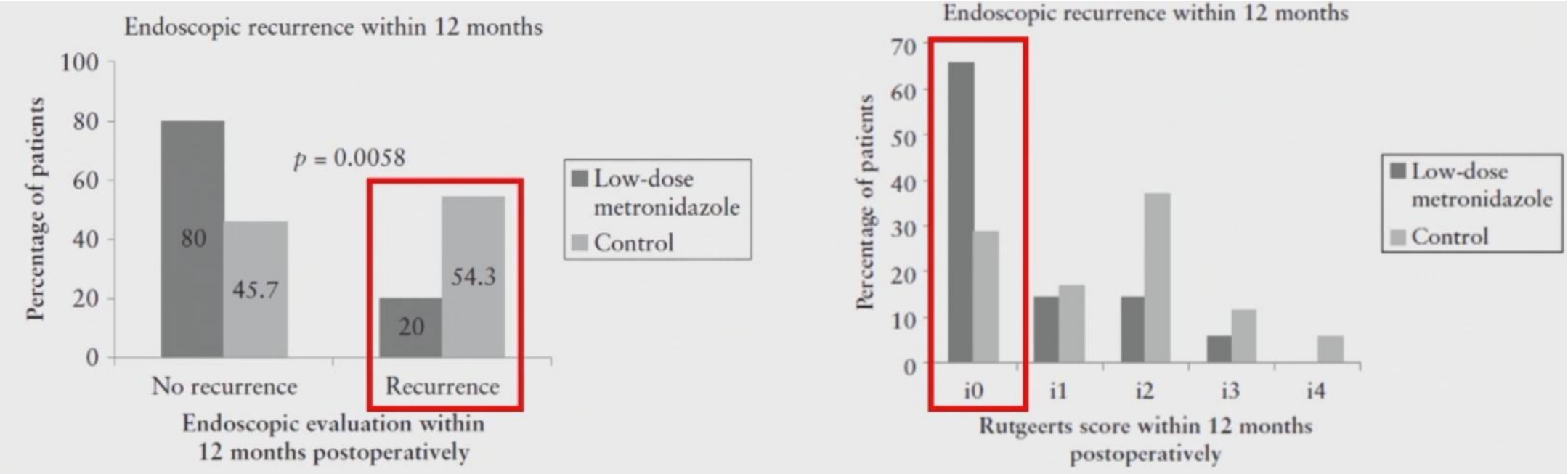
(Rutgeerts P, Hield M, Geboes K, et al. Gastroenterology 1995; 108:1617-1621); (Rutgeerts P, Van Assche G, Vermeire S. et al. Gastroenterology 2005; 128: 856-861)

Low dose Metronidazole vs placebo

- 250mg TDS for 3 months
- Primary outcome: endoscopic recurrence within 12 months (greater than or equal to i2)
- 23% AE, 8% stopped due to AE
- There was a prevention of post operative recurrence however there was recurrence once stopped

Glick et al Journal of Crohn’s and Colitis 2019

Low dose Metronidazole vs placebo



PREVENT Study

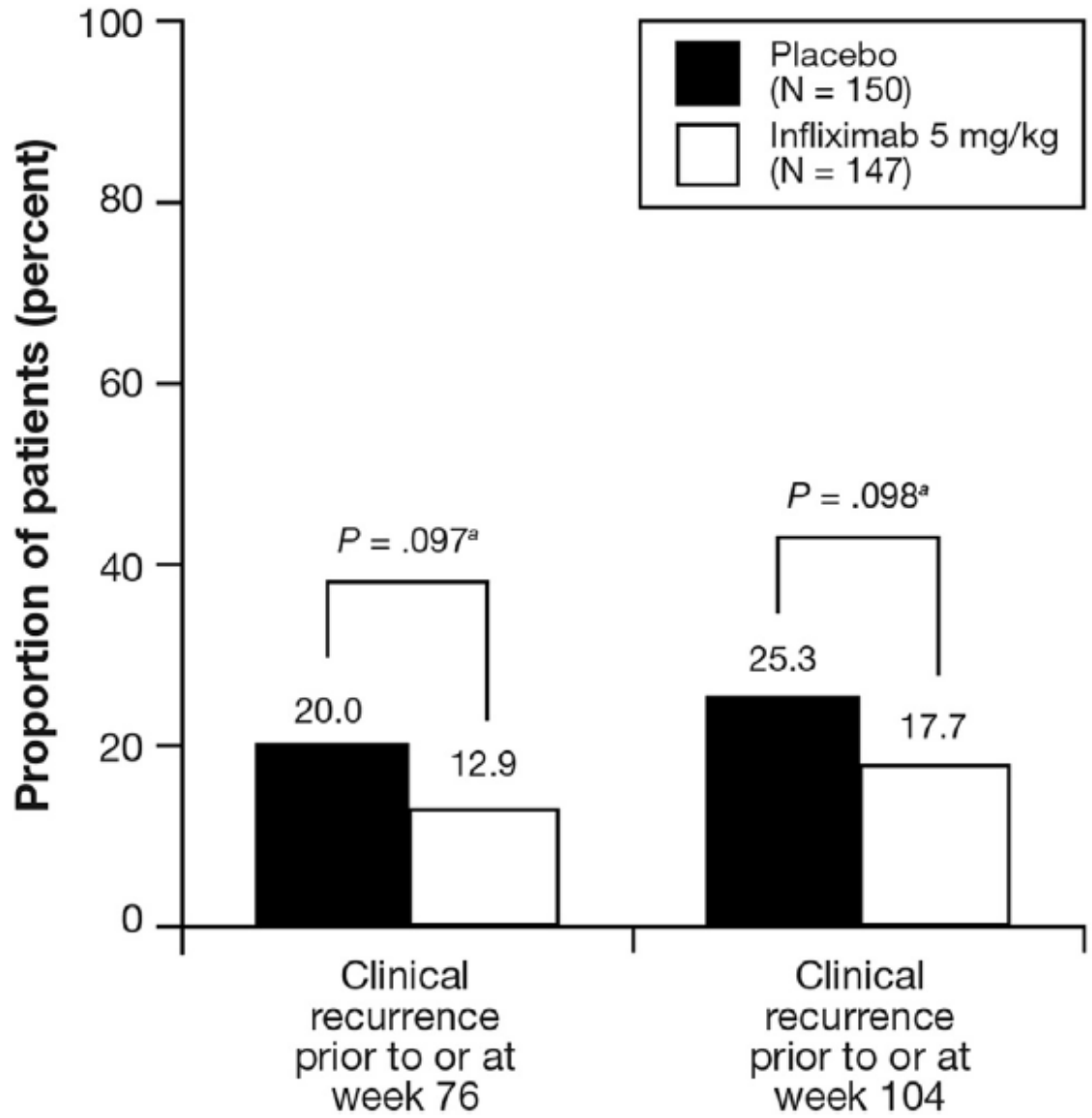
- Randomized trial to compare the ability of infliximab vs placebo to prevent post operative Crohns disease recurrence
- Study was conducted between November 2010 and May 2012
- 104 sites worldwide
- 297 patients were included

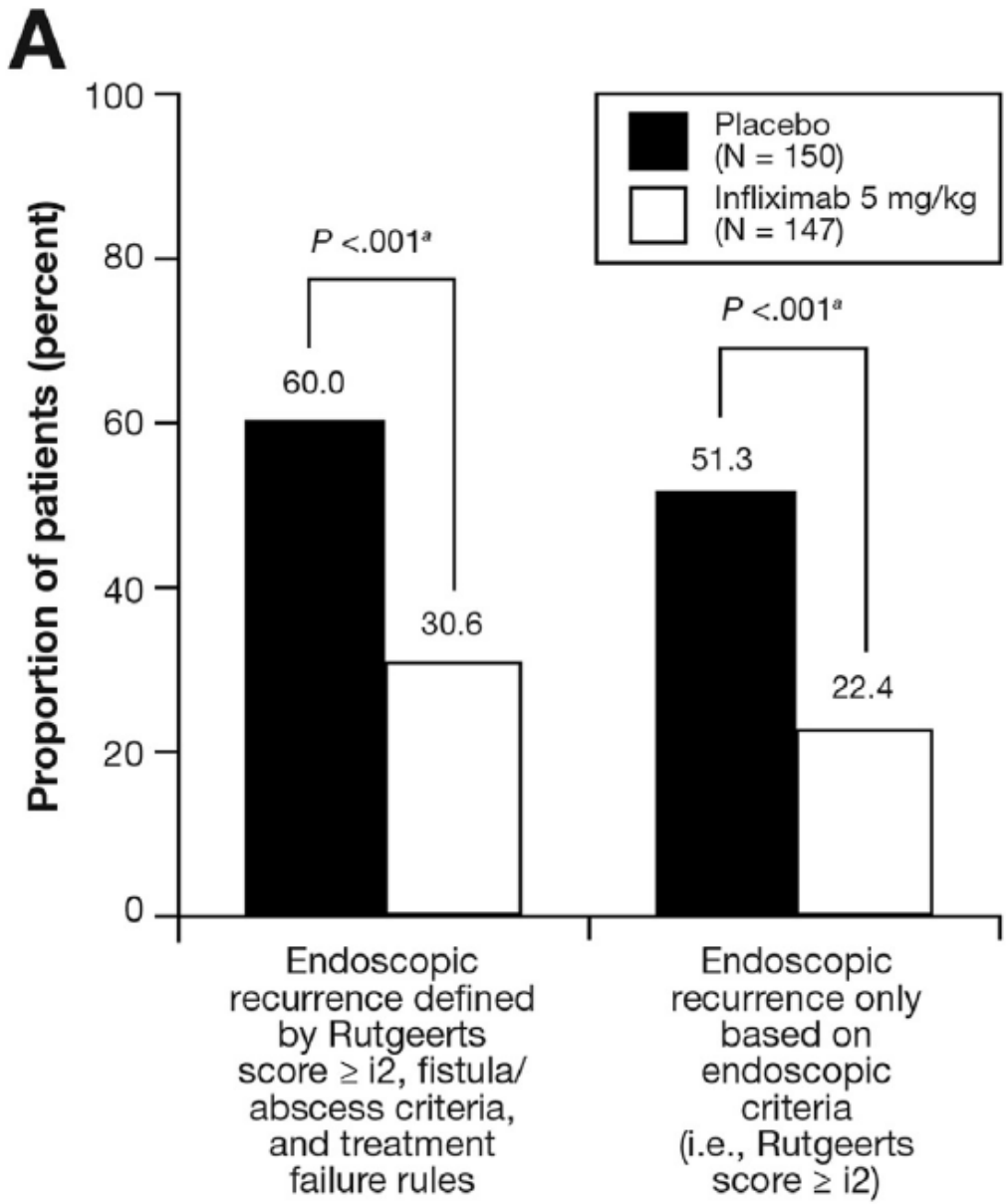
- Gastroenterology 2016;150:1568–1578

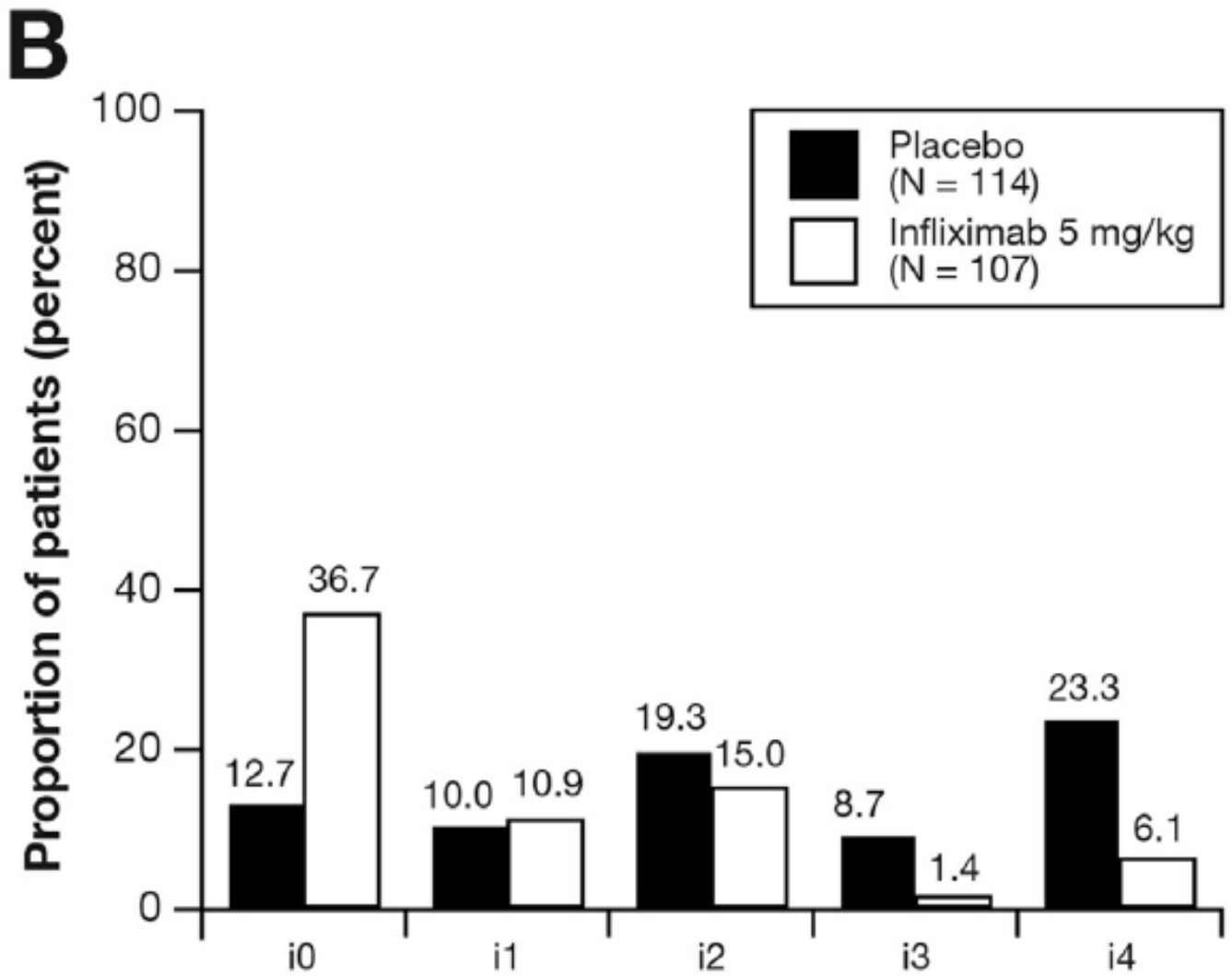
- Primary endpoint was clinical recurrence
- Secondary endpoint was endoscopic recurrence

Outcomes

- Infliximab was not superior when compared to placebo in preventing clinical recurrence
- Infliximab was superior in preventing endoscopic recurrence


Proportion of patients (percent)
100
80
60
40
20
0
Placebo
(N = 150)
Infliximab 5 mg/kg
(N = 147)
P = .097a
P = .098a
20.0
12.9
25.3
17.7
Clinical recurrence prior to or at week 76
Clinical recurrence prior to or at week 104


A
Proportion of patients (percent)
100
80
60
40
20
0
Placebo
(N = 150)
Infliximab 5 mg/kg
(N = 147)
P <.001a
P <.001a
60.0
30.6
51.3
22.4
Endoscopic recurrence defined by Rutgeerts score ≥ i2, fistula/ abscess criteria, and treatment failure rules
Endoscopic recurrence only based on endoscopic criteria (i.e., Rutgeerts score ≥ i2)


B
Proportion of patients (percent)
100
80
60
40
20
0
Placebo
(N = 114)
Infliximab 5 mg/kg
(N = 107)
12.7
36.7
10.0
10.9
19.3
15.0
8.7
1.4
23.3
6.1
i0
i1
i2
i3
i4

Reprevio

- First results of study presented at ECCO this year
- Multicentre randomised controlled trial in high risk patients
- Patients were randomised to receive Vedolizumab vs placebo
- Primary end point of the study was endoscopic recurrence
- 77.8% of patients had a lower Rutgeert's score as compared to placebo
- Initial results are promising

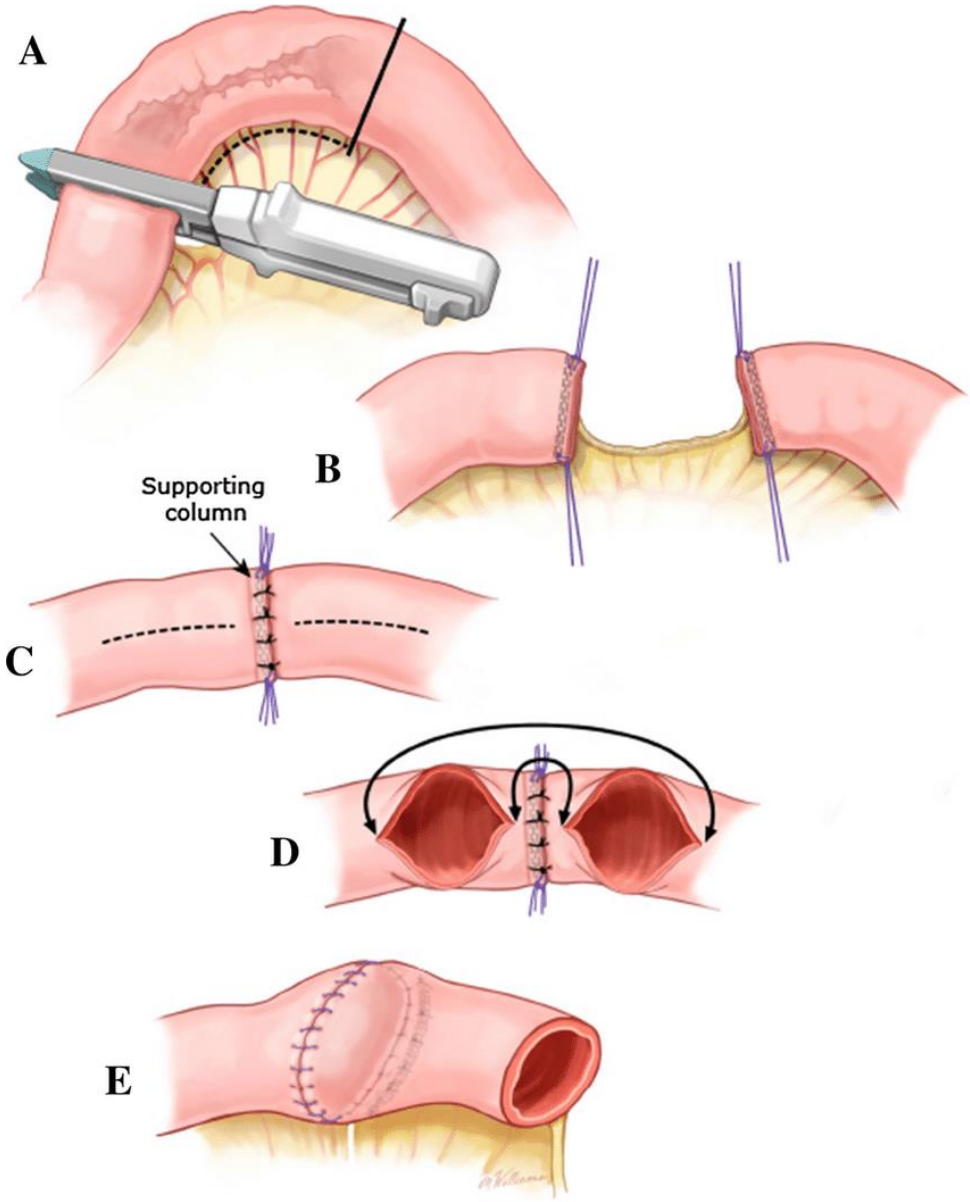
Ustekinumab

- The comparative efficacy of ustekinumab against anti-TNF agents in the prevention of POR is still unclear
- Ustekinumab is comparative to Vedolizumab in preventing POR in high risk patients
- Larger studies are needed
- Initial results are promising

Gisbert, J. P., & Chaparro, M. (2023). Anti-TNF Agents and New Biological Agents (Vedolizumab and Ustekinumab) in the Prevention and Treatment of Postoperative Recurrence After Surgery in Crohn's Disease. In Drugs (Vol. 83, Issue 13, pp. 1179–1205). Adis.

Macaluso, F. S. Et Al (2023). Ustekinumab is a promising option for the treatment of postoperative recurrence of Crohn's disease. Journal of Gastroenterology and Hepatology (Australia), 38(9), 1503–1509.

Kono S

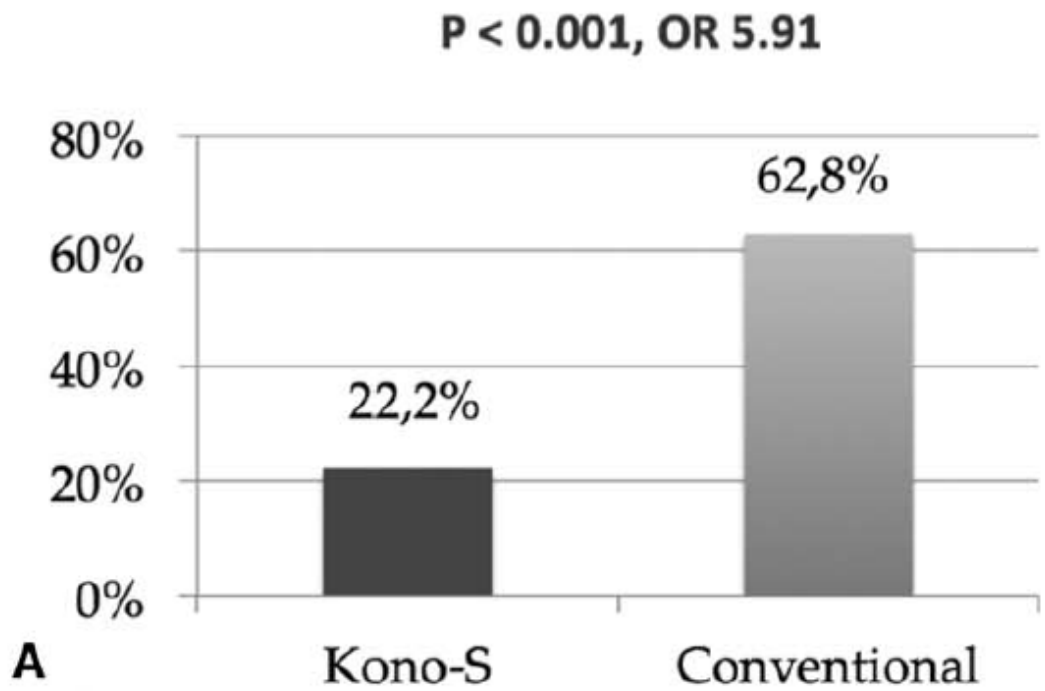


The SuPREMe-CD Study

- Randomised clinical trial
- 79 patients divided randomly between Kono S anastomosis and conventional anastomosis
- Conventional surgery was defined as stapled ileocolic side to-side anastomosis
- The primary endpoint was endoscopic recurrence (Rutgeerts Score greater than or equal to i2) after 6 months
- Secondary endpoints were clinical recurrence after 12 and 24 months [defined as a Crohn's Disease Activity Index (CDAI) >200, endoscopic recurrence after 18 months, and surgical recurrence after 24 months

Luglio G et al. Surgical Prevention of Anastomotic Recurrence by Excluding Mesentery in Crohn's Disease: The SuPREMe-CD Study - A Randomized Clinical Trial. Ann Surg. 2020 Aug 1;272(2):210–7.

Presence of any Endoscopic Recurrence (Rutgeerts ≥ 2)



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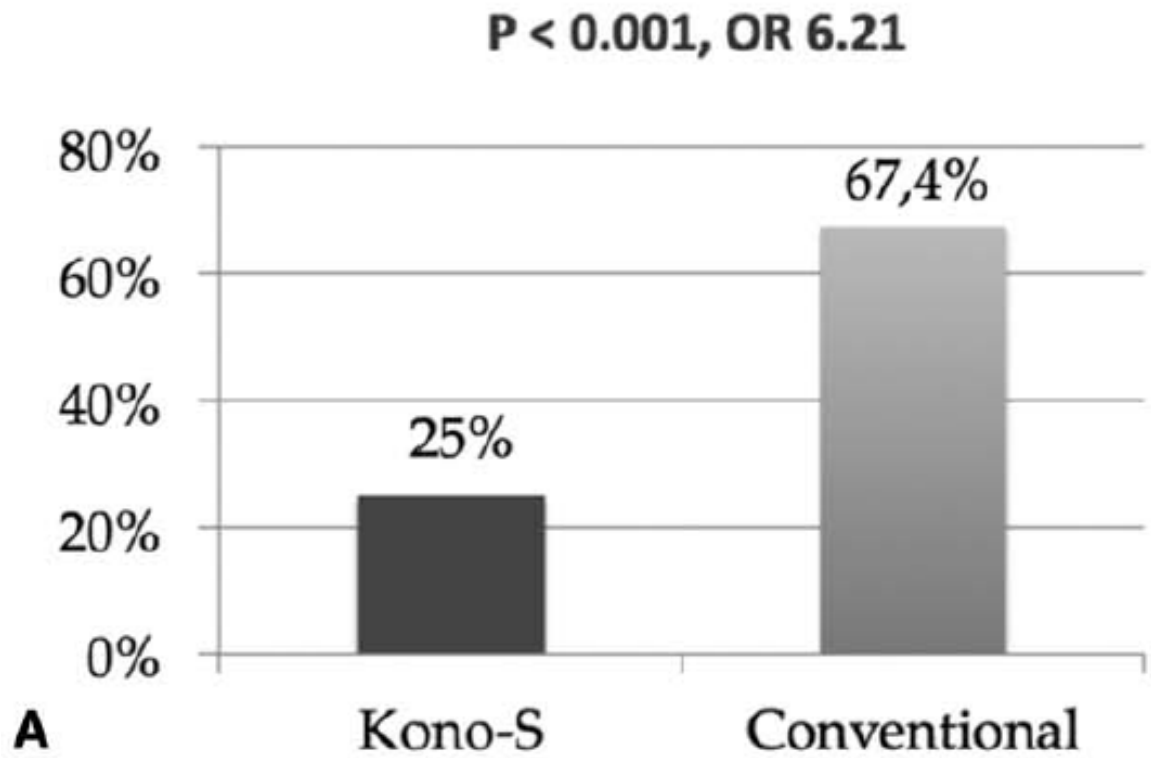
Presence of any Endoscopic Recurrence (Rutgeerts ≥ 2



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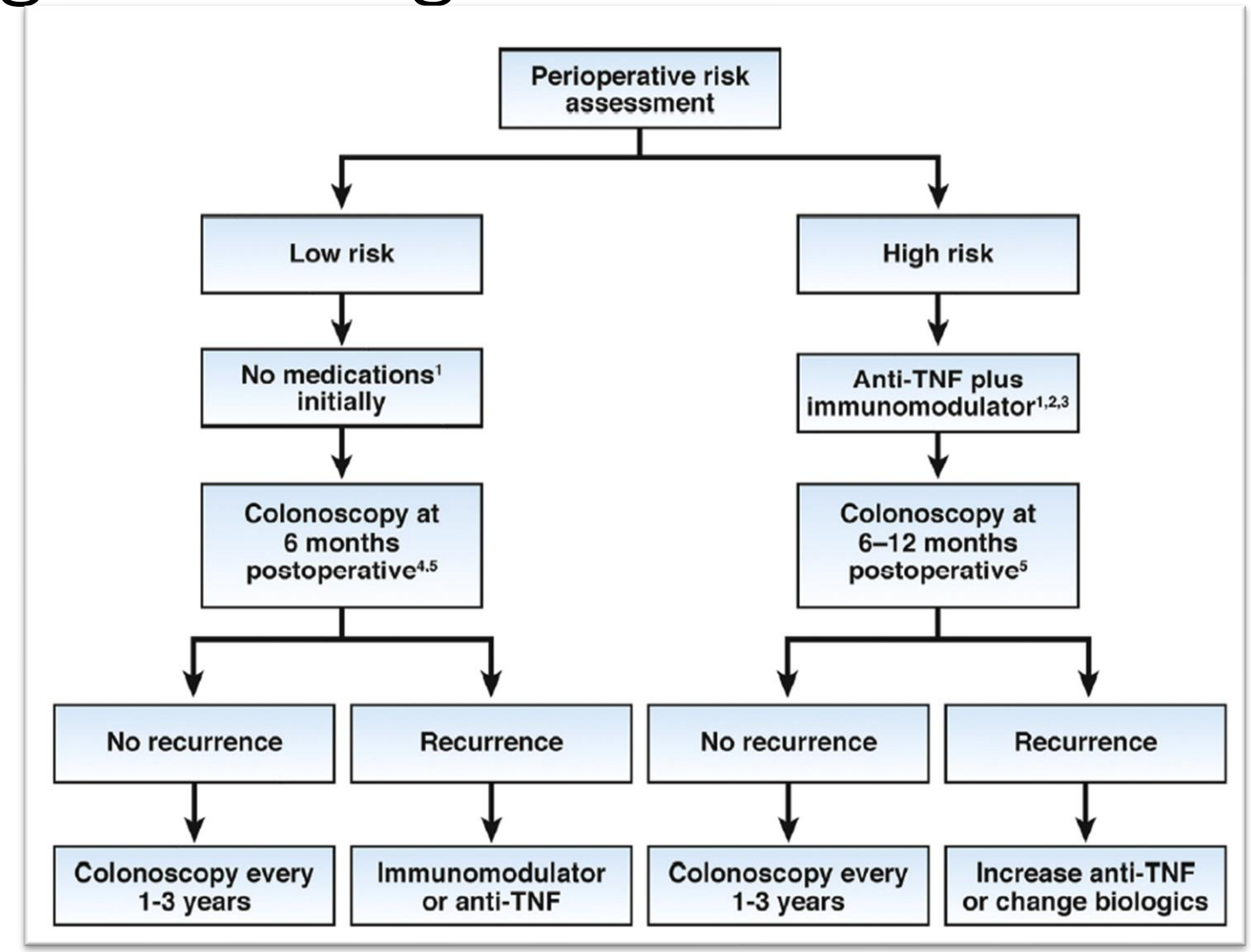
Management Algorithm



Barnes et al Clinical Gastroenterology and Hepatology Vol. 18, No. 6

Conclusion

- Post-op recurrence is predictable
- Risk stratify patients
- Use of non-invasive modalities to monitor recurrence are useful complementary tests
- Endoscopy remains the gold standard to diagnose and affect management
- Escalate treatment based on endoscopy regardless of clinical symptoms
- Anti TNF therapy is the current best therapy
- Ustekinumab and Vedolizumab are good alternative therapies if failing Anti-TNF therapy