Prevention & management of post-operative recurrence in Crohn's disease

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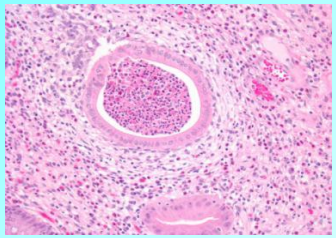
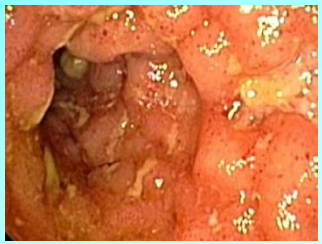
Post-operative recurrence

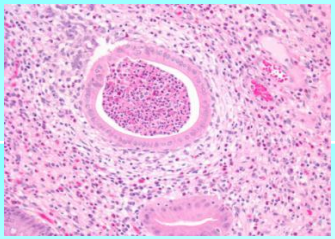
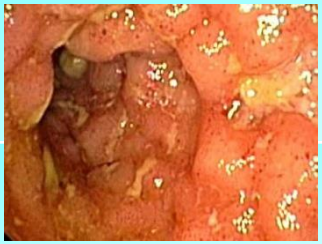
- Very common complication of CD (almost ubiquitous)
- Typically at the site of anastomosis or proximal to it

Histologic	Endoscopic	Clinical	Surgical
			
Within 1 week	90% by 1 year	50% at 5 years	25% at 5 years

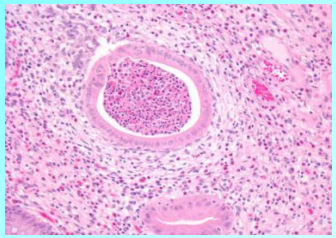
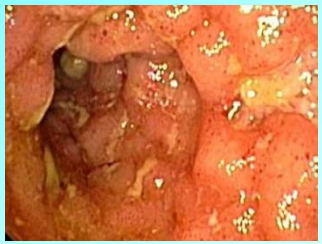
Post-operative recurrence

- Early endoscopic recurrence is typically asymptomatic
- Failure to treat subclinical inflammation:
- May result in progressive damage
- By the time symptoms occur this is often irreversible

Prophylaxis Endoscopy (6-12 months)
Rx based on severity

Histologic	Endoscopic	Clinical	Surgical
			

Prophylactic medication

Histologic	Endoscopic	Clinical	Surgical
			
Within 1 week	90% by 1 year	50% at 5 years	25% at 5 years

Prophylaxis vs. placebo

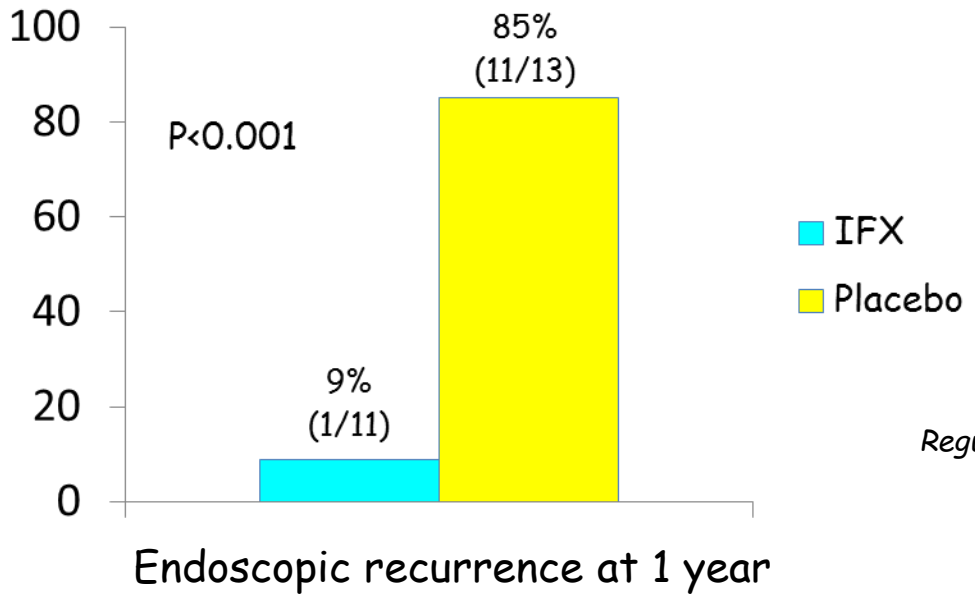
Medication	Endoscopic recurrence	Clinical recurrence
Probiotics	NS	NS
Budesonide	NS	NS
5-ASA	NNT=8	NNT=12
Imidazole antibiotics	NNT=4	NNT=4
AZA/6-MP	NNT=4	NNT=7

Doherty G, et al. Cochrane Database Syst Rev 2009;CD006873

- Metronidazole
- Effective but often poorly tolerated
- Benefits disappear rapidly on discontinuation

- Thiopurines
- Many side effects, slow onset of action

Anti-TNFs as prophylaxis



Regueiro M, et al. Gastroenterology 2009;136:441

- Small numbers and in reality not as impressive
- After this trial several others were published

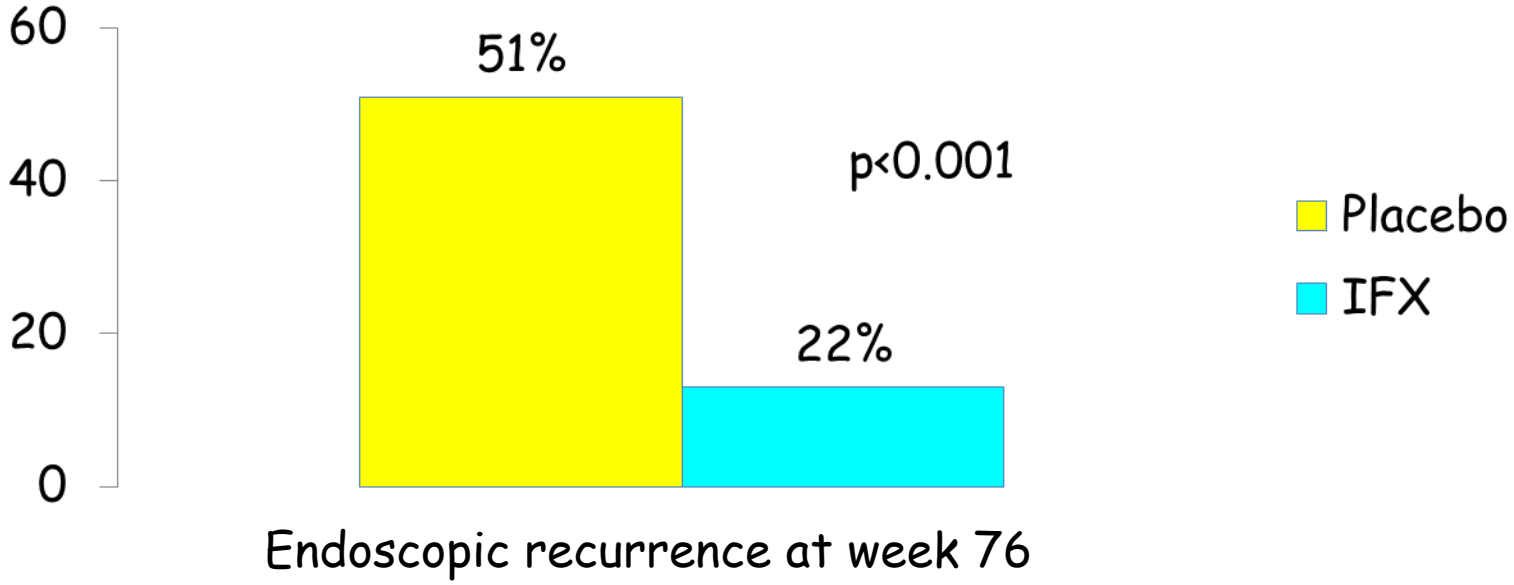
- Mostly observational (IFX and ADA)
- Rates of Endoscopic POR at year ± 20%

Infliximab Reduces Endoscopic, but Not Clinical, Recurrence of Crohn's Disease After Ileocolonic Resection

Miguel Regueiro,[1] Brian G. Feagan,[2] Bin Zou,[3] Jewel Johanns,[3] Marion A. Blank,[4] Marc Chevrier,[3] Scott Plevy,[3] John Popp,[4] Freddy J. Comillie,[5] Milan Lukas,[6] Silvio Danese,[7] Paolo Gionchetti,[8] Stephen B. Hanauer,[9] Walter Reinisch,[10,11] William J. Sandborn,[12] Dario Sorrentino,[13,14] and Paul Rutgeerts,[15] for the PREVENT Study Group

Gastroenterology 2016;150:1568–1578

Assess efficacy of prophylactic TNFs in preventing POR



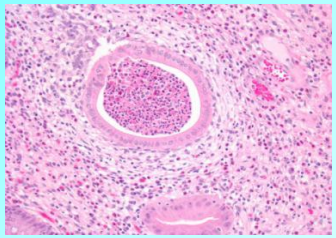
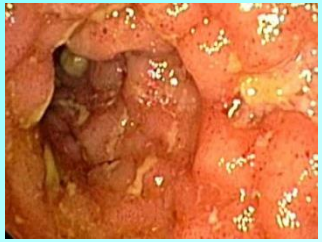
Endoscopic recurrence at week 76

Risk stratifying CD patients

- Who should have immediate postoperative prophylaxis
- One size does not fit all

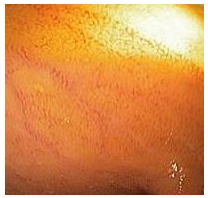
Low risk	Intermediate risk	High risk
> 50 years of age	30 – 50 years of age	Age < 30
Short segment CD (< 20cm)	Longer fibrotic stricture	Myenteric plexitis
Fibrotic stricture	Inflammatory disease	Penetrating or perianal CD
Disease duration > 10 years	Disease duration < 10 years	1 previous surgery
Non-smoker	Non-smoker	Smoker
No prophylaxis	Consider prophylaxis	Prophylaxis

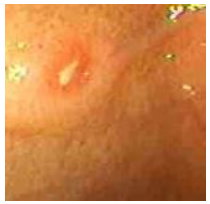
Endoscopy guided treatment

Histologic	Endoscopic	Clinical	Surgical
			
Within 1 week	90% by 1 year	50% at 5 years	25% at 5 years

Early endoscopy to guide therapy

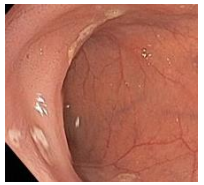
- Colonoscopy 6-12 months post surgery
- Therapy initiated/escalated based on severity of POR

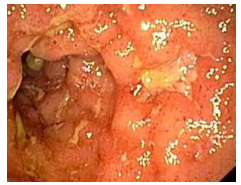
i0 

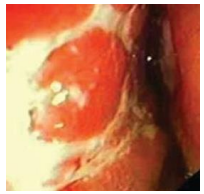
i1 

"Remission"
Low likelihood of progression

Rutgeert's score

i2 

i3 

i4 

"Recurrence"
Likely to progress to another surgery

Early endoscopy to guide therapy

POCER study: 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

POCER study

- 50%: no endoscopy at 6/12 (standard care group)

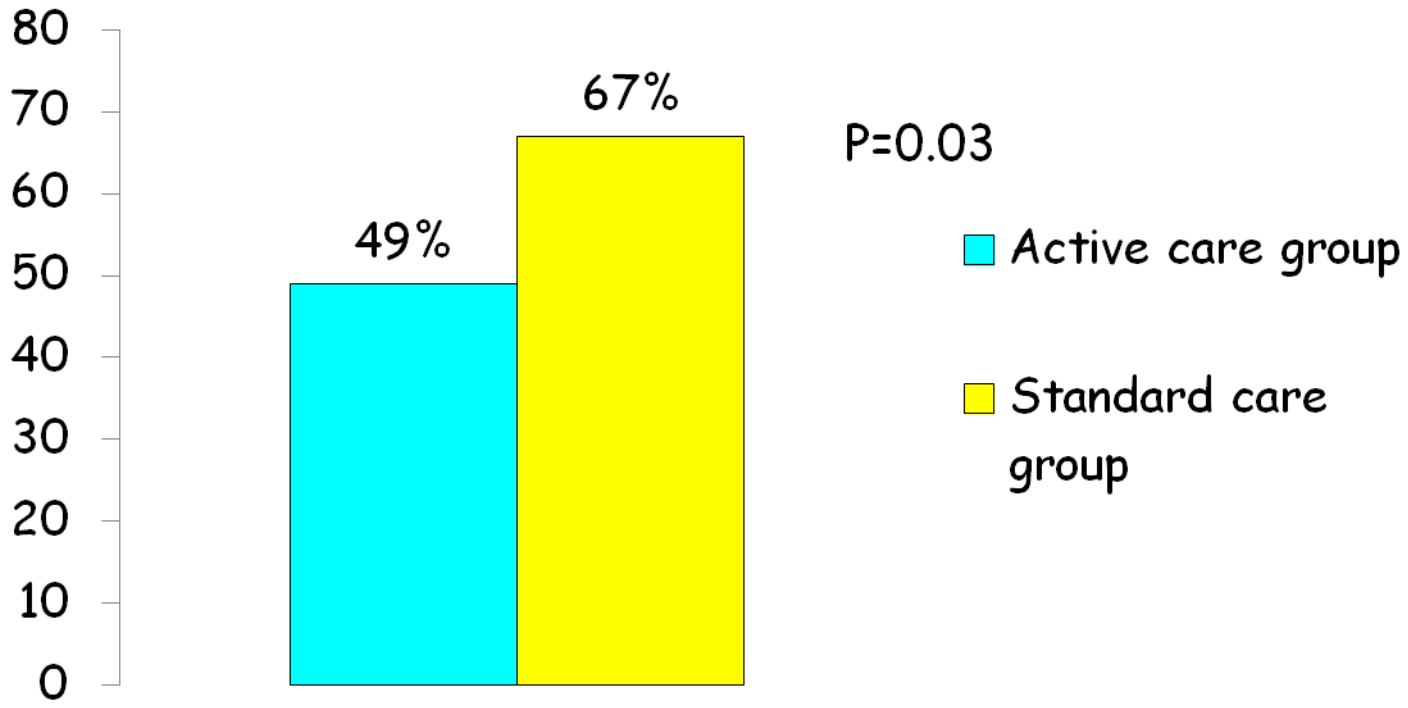
- 50%: had endoscopy at 6/12 (active care group)

- Treatment escalated depending on Rutgeert's score
- Even if asymptomatic
- No treatment → AZA/6-MP
- AZA/6-MP → Adalimumab
- Adalimumab → Decrease dosage interval

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

POCER study

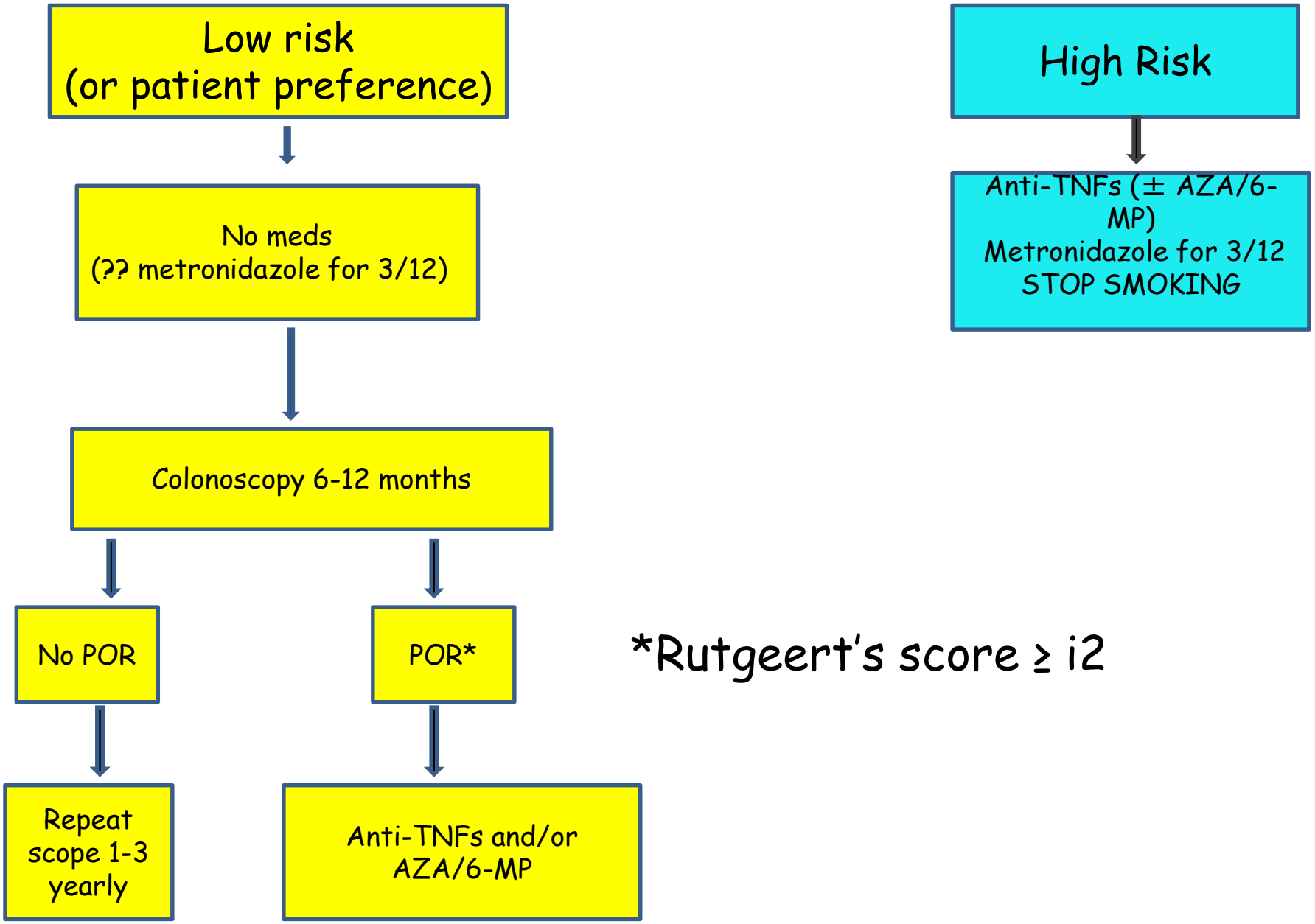
Endoscopic recurrence at 18 months



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

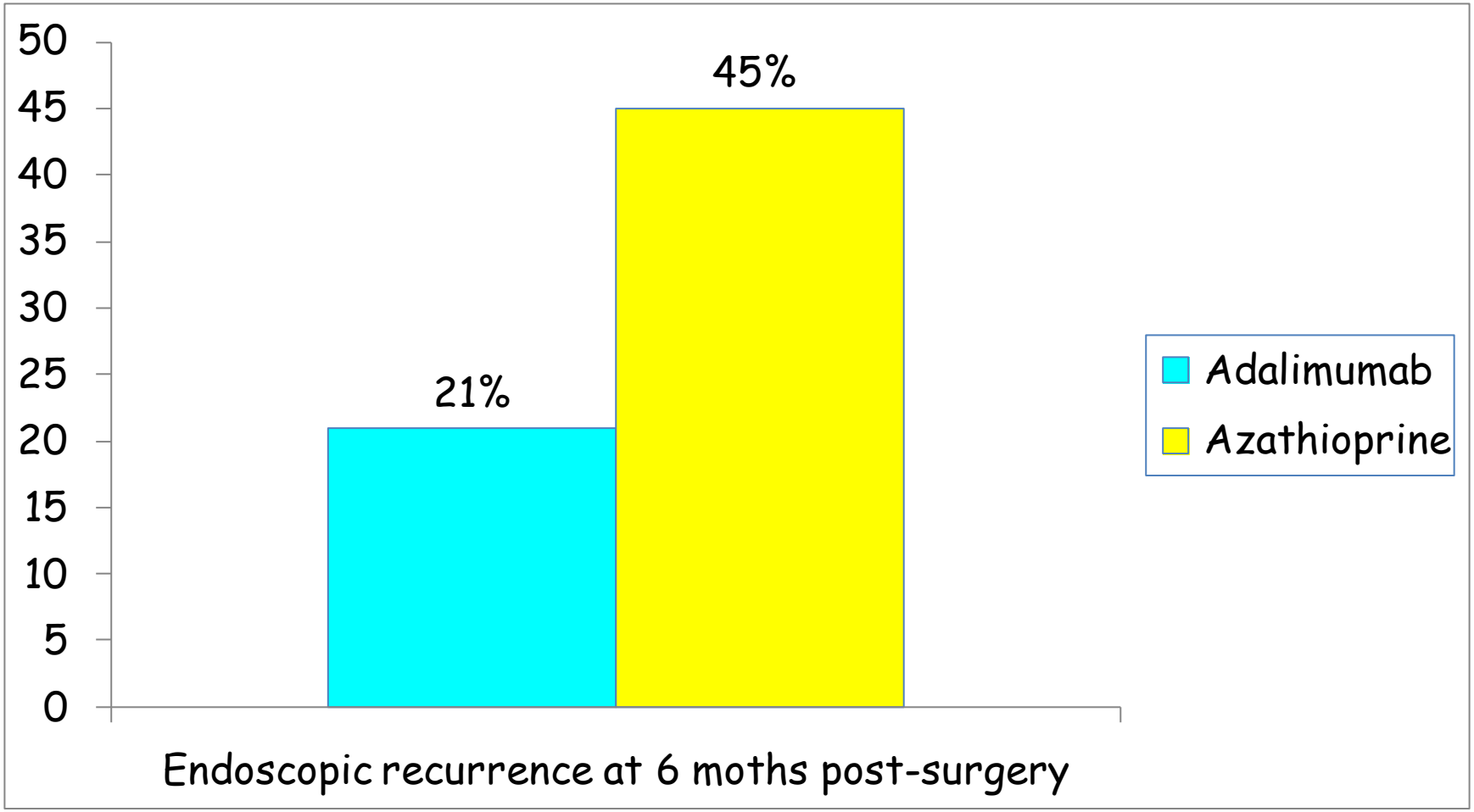
POR in 2017

AGA Guidelines. Gastroenterology 2017;152:271–275

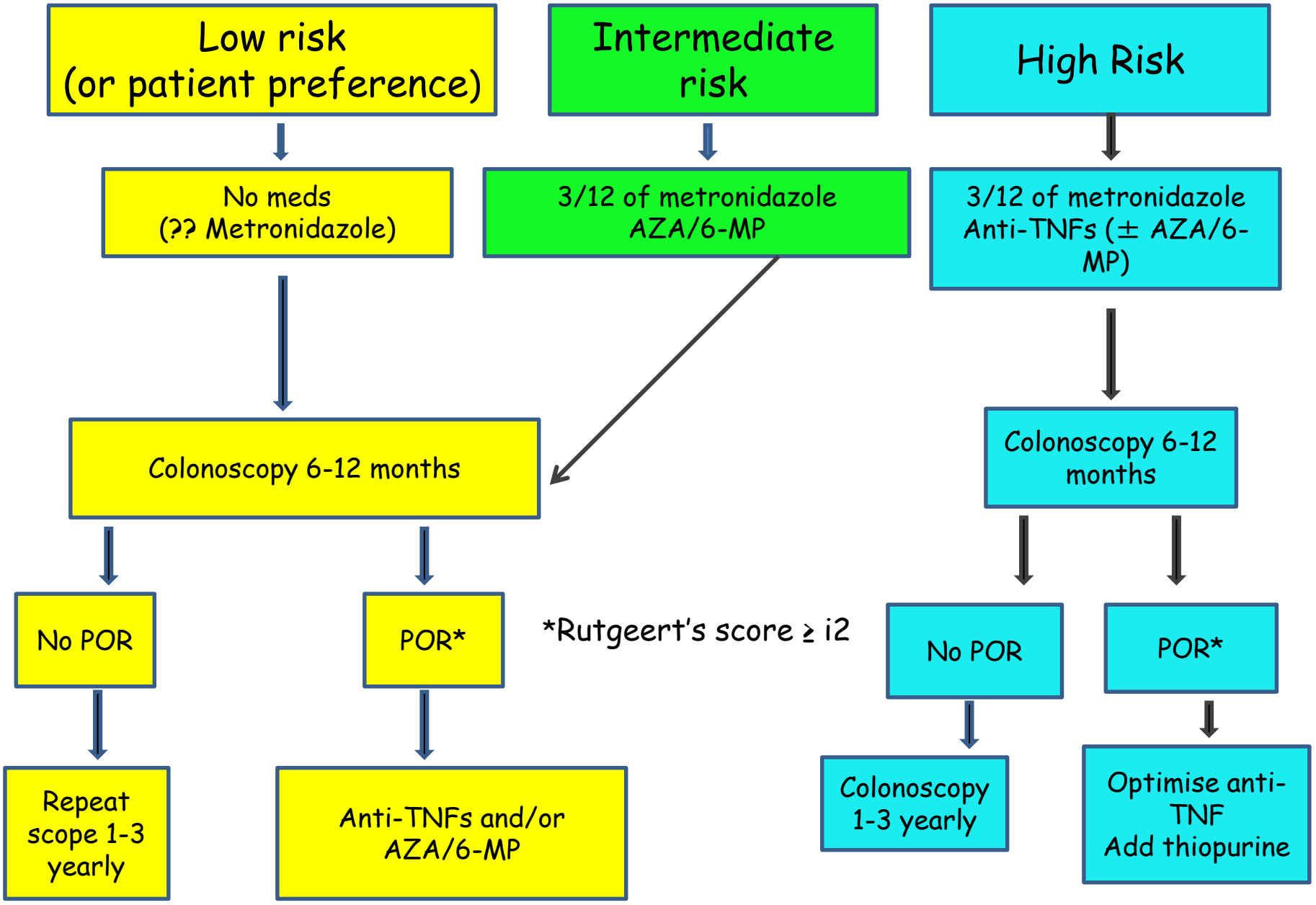


*Rutgeert's score ≥ i2

Anti-TNFs vs. Thiopurines in POR



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


Low risk
(or patient preference)
Intermediate risk
High Risk
No meds
(?? Metronidazole)
3/12 of metronidazole
AZA/6-MP
3/12 of metronidazole
Anti-TNFs (± AZA/6-MP)
Colonoscopy 6-12 months
Colonoscopy 6-12 months
No POR
POR*
*Rutgeert's score ≥ i2
No POR
POR*
Repeat scope 1-3 yearly
Anti-TNFs and/or AZA/6-MP
Colonoscopy 1-3 yearly
Optimise anti-TNF
Add thiopurine

Non-invasive methods to evaluate POR

- Ileocolonoscopy is gold standard
- But it is invasive

ECCO statement 8E

"Calprotectin, trans-abdominal ultrasound, MRE, and CE are emerging as alternative tools for identifying POR"

Journal of Crohn's and Colitis, 2017, 135–149

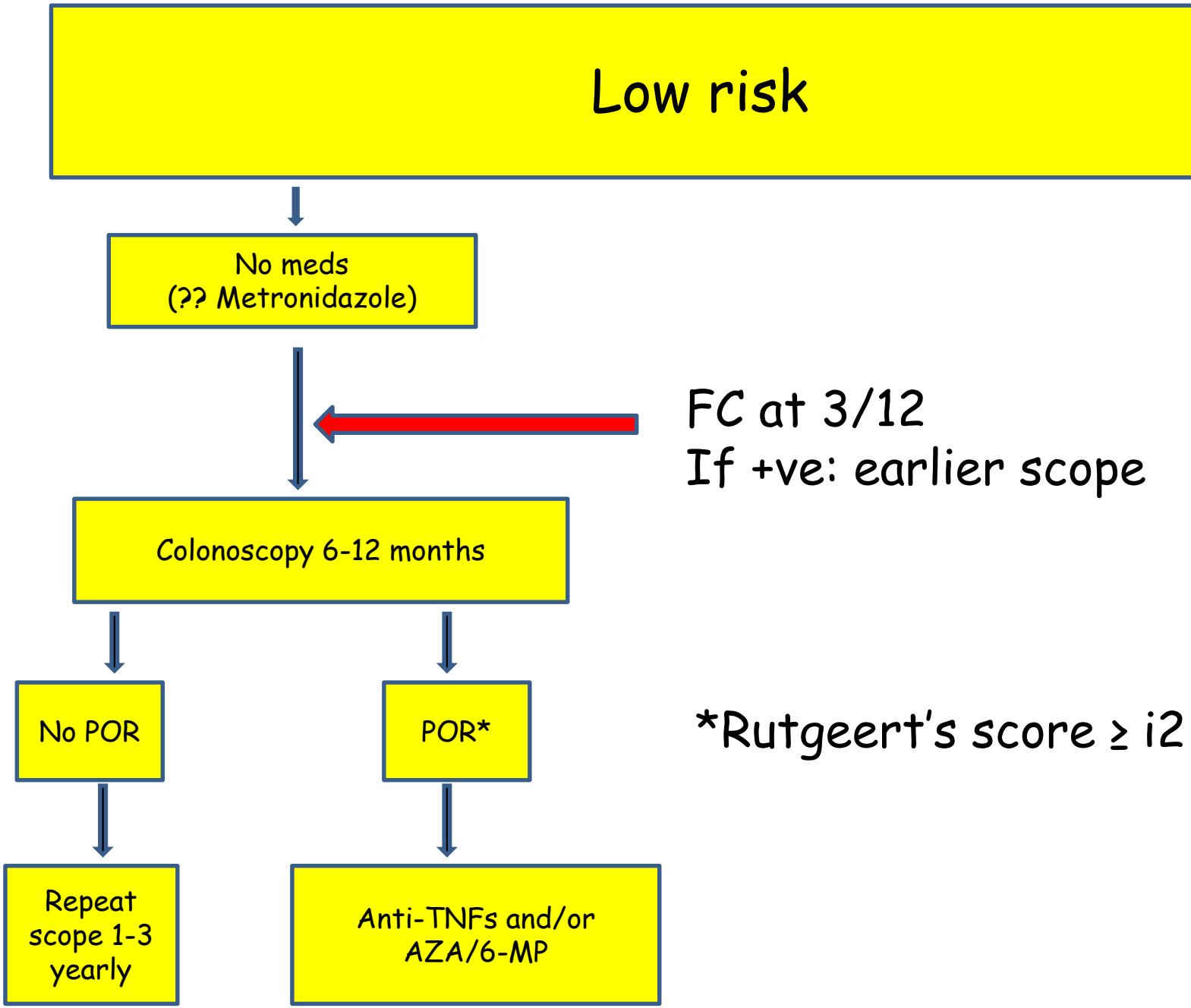
- FC the only one ready for prime time

Faecal calprotectin

- Correlates well with Rutgeert's score
- Can be used 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

- FC does not replace the need for colonoscopy
- Rather serves as a complementary investigation
- Can be measured frequently
- If positive may prompt earlier endoscopy


Low risk
No meds
(?? Metronidazole)
FC at 3/12
If +ve: earlier scope
Colonoscopy 6-12 months
No POR
POR*
*Rutgeert's score ≥ i2
Repeat scope 1-3 yearly
Anti-TNFs and/or AZA/6-MP

The future

- Personalised medicine
- Tailored to the individual
- Not just the fore mentioned risk factors

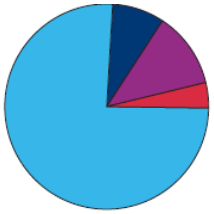
- Predicting POR
- Predicting response to therapy
- Genetics
- Epigenetics
- Microbiome

Microbiome and POR
(POCER study)

- Following ileocaecal resection POR was associated with:
- Elevated *Proteus* in the resection specimen (p = 0.01)
- Reduced *Faecalibacterium prausnitzii* (p< 0.001)
- Smokers had increased *Proteus* (p = 0.01) post-op

Wright E, et al. Journal of Crohn's and Colitis, 2017, 191–203

High Faecalibacterium
Proteus absent



Low Faecalibacterium
Proteus abundant

Remission and non-smoker

Remission and active smoker

Recurrence and active smoker

Recurrence and non- smoker

Take home messages

- POR is very common
- Immediate post-op prophylaxis and early Rx are key
- Stratify patients by risk: STOP SMOKING
- Anti-TNFs are the best therapy to date
- As prophylaxis in high risk patients
- Early endoscopy to guide future treatment is recommended to improve outcomes (6-12 months post-op)
- Escalate Rx based on endoscopic recurrence regardless of symptoms
- The future: personalised approach