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

<table>
<thead>
<tr>
<th>Histologic</th>
<th>Endoscopic</th>
<th>Clinical</th>
<th>Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Histologic Image]</td>
<td>![Endoscopic Image]</td>
<td>![Clinical Image]</td>
<td>![Surgical Image]</td>
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<tr>
<td>Within 1 week</td>
<td>90% by 1 year</td>
<td>50% at 5 years</td>
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**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

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<tbody>
<tr>
<td><img src="image1.png" alt="Histologic Image" /></td>
<td><img src="image2.png" alt="Endoscopic Image" /></td>
<td><img src="image3.png" alt="Clinical Image" /></td>
<td><img src="image4.png" alt="Surgical Image" /></td>
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Prophylactic medication

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## Prophylaxis vs. placebo

<table>
<thead>
<tr>
<th>Medication</th>
<th>Endoscopic recurrence</th>
<th>Clinical recurrence</th>
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<tbody>
<tr>
<td>Probiotics</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Budesonide</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>5-ASA</td>
<td>NNT=8</td>
<td>NNT=12</td>
</tr>
<tr>
<td>Imidazole antibiotics</td>
<td>NNT=4</td>
<td>NNT=4</td>
</tr>
<tr>
<td>AZA/6-MP</td>
<td>NNT=4</td>
<td>NNT=7</td>
</tr>
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</table>

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

- **Thiopurines**
  - Many side effects, slow onset of action

Anti-TNFs as prophylaxis

- 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%

Assess efficacy of prophylactic TNFs in preventing POR

Endoscopic recurrence at week 76

- Placebo: 51%
- IFX: 22%

p<0.001
Risk stratifying CD patients

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

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<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
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<tr>
<td>&gt; 50 years of age</td>
<td>30 - 50 years of age</td>
<td>Age &lt; 30</td>
</tr>
<tr>
<td>Short segment CD (&lt; 20cm)</td>
<td>Longer fibrotic stricture</td>
<td>Myenteric plexitis</td>
</tr>
<tr>
<td>Fibrotic stricture</td>
<td>Inflammatory disease</td>
<td>Penetrating or perianal CD</td>
</tr>
<tr>
<td>Disease duration &gt; 10 years</td>
<td>Disease duration &lt; 10 years</td>
<td>1 previous surgery</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>Non-smoker</td>
<td>Smoker</td>
</tr>
<tr>
<td>No prophylaxis</td>
<td>Consider prophylaxis</td>
<td>Prophylaxis</td>
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**Endoscopy guided treatment**

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Early endoscopy to guide therapy

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

Rutgeert’s score

- **i0**
  - “Remission”
  - Low likelihood of progression
- **i1**
- **i2**
- **i3**
  - “Recurrence”
  - Likely to progress to another surgery
- **i4**
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

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

POCER study

Endoscopic recurrence at 18 months

POR in 2017

AGA Guidelines. Gastroenterology
2017;152:271-275
Low risk
(or patient preference)

- No meds
  (?? metronidazole for 3/12)

  Colonoscopy 6-12 months

- No POR

  Repeat scope 1-3 yearly

- POR*

  Anti-TNFs and/or AZA/6-MP

High Risk

- Anti-TNFs (± AZA/6-MP)

  Metronidazole for 3/12

  STOP SMOKING

*Rutgeert’s score ≥ i2
Anti-TNFs vs. Thiopurines in POR

Endoscopic recurrence at 6 months post-surgery

21% Adalimumab
45% Azathioprine

Low risk (or patient preference)

- No meds (?? Metronidazole)
  
  Colonoscopy 6-12 months
  
  No POR
  
  Repeat scope 1-3 yearly

Intermediate risk

- 3/12 of metronidazole AZA/6-MP
  
  Colonoscopy 6-12 months
  
  *Rutgeert’s score ≥ i2

High Risk

- 3/12 of metronidazole
  Anti-TNFs (± AZA/6-MP)
  
  Colonoscopy 6-12 months
  
  No POR
  
  POR*
  
  Optimise anti-TNF
  Add thiopurine

Anti-TNFs and/or AZA/6-MP

Repeat scope 1-3 yearly
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%
  

- 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)

Colonoscopy 6-12 months

No POR

Repeat scope 1-3 yearly

POR*

Anti-TNFs and/or AZA/6-MP

FC at 3/12
If +ve: earlier scope

*Rutgeert’s score ≥ i2
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


![High Faecalibacterium Proteus absent](image1)

![Low Faecalibacterium Proteus abundant](image2)

- 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