MEDICAL PERI-OPERATIVE AND SURGICAL PERSPECTIVES IN IBD

A. Hillary Steinhart, MD MSc FRCP(C)
Medical Lead, Centre for Inflammatory Bowel Disease
Mount Sinai Hospital
Professor of Medicine
University of Toronto
# Financial Interest Disclosure

*(over the past 24 months)*

<table>
<thead>
<tr>
<th>Commercial Interest</th>
<th>Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbvie, Takeda, Janssen, Pfizer, Genentech, Roche, Amgen, Lycera, Red Hill Biopharma, Arena</td>
<td>Research Grant / Research Support</td>
</tr>
<tr>
<td>Abbvie, Janssen, Takeda, Shire, Novartis, Ferring, Pfizer</td>
<td>Speaker</td>
</tr>
<tr>
<td>Abbvie, Shire, Janssen, Pfizer, Merck, Takeda</td>
<td>Advisory Board Member</td>
</tr>
</tbody>
</table>
Objectives

• Reflect on the medical optimization of Crohn’s disease patients undergoing surgical resection

• Review evidence on the effect to drug therapy on surgical complications and outcomes in Crohn’s disease

• Consider strategies to minimize the risk of recurrence of Crohn’s disease after surgery

• Discuss the combined medical and surgical management of fistulizing perianal Crohn’s disease
Case 1

- 28 year old woman presenting with 3 year history of CD – ileal involvement
- Multiple courses of prednisone over first 2 years; azathioprine started 1 year after diagnosis
- Infliximab started 6 months before presentation
- Now presents with increased RLQ pain and 30 pound weight loss
- CT – 30 cm of thickened TI with 5 cm segment luminal narrowing; prestenotic dilatation; associated phlegmon/abscess
Surgery for Luminal Crohn’s Disease

- Surgical rates have decreased over past 60 years but are still significant\(^1\)
  - 16% at 1 year
  - 33% at 3 years
  - 46% at 10 years
- Increased mortality in CD is primarily due to deaths within 30 days of surgery\(^2\)
- High risk of recurrence following resection
- Risk of short bowel with multiple resections

1. Frolkis AD et al. Gastroenterology 2013;145:996-1006
What factors impact risk of surgical complications in luminal CD?

- Patient age
- Nutritional status
- Cardiopulmonary/general medical condition (ASA Class)
- Sepsis
- Obstruction (dilated bowel)
- Medications
  - Steroids
  - Immune suppression?
  - Biologic therapy?
- Surgical factors
Pre-operative Management of Luminal CD

- Disease staging
- Control of sepsis
  - percutaneous drainage of abscesses
  - antibiotics
- Nutritional support
- Decompression of obstruction
- Optimize general medical condition (treatment of anemia, thromboembolic prophylaxis)
- Medical therapy of CD
  - wean steroids
  - immune suppression and biologic therapy (?)
- Timing of surgery
Pre-operative Nutritional Support

- Multiple definitions of malnutrition:
  - low BMI (<18.5 kg/m²)
  - >10% unintentional weight loss
  - anthropometric measurement abnormalities
  - reduced grip strength

- Approximately 75% of CD patients undergoing surgery are malnourished

- Retrospective studies suggest reduced post-operative complications when pre-operative nutritional support is provided¹,²

- Relative merit of PN vs. EN has not been studied

Pre-operative CD Management: Outcomes

- 78 patients with penetrating ileal CD (37 with abscess) undergoing first ileocecal resection
- Nutrition support (n=50), abscess drainage (n=11), broad spectrum antibiotics and weaning of steroids, immunosuppressives and anti-TNF
- Uncomplicated operative course (n=58; 74%); major complication (n=4; 5%); minor complications (n=10; 13%)

Pre-operative CD Management: Effect of Optimization

• Retrospective study of 237 CD patients undergoing surgery at 3 centres
• No difference between patients who did and did not receive optimization (nutrition support for ≥1 week and/or optimization of medication*) with respect to:
  - overall complications
  - surgical site infections
  - re-operation
  - intra-abdominal septic complications
  - length of stay

*D/C steroids, immunosuppressives and anti-TNF

No difference in major complications, infectious complications, non-infectious complications or surgical complications

Xu YY, et al. Inflamm Bowel Dis 2018 July 24 (Epub)
Impact of Pre-operative Vedolizumab on Post-operative Complications in CD

Overall, the odds of developing complications in IBD patients exposed preoperatively to vedolizumab vs those not given biological agents were not significantly different (OR, 0.88; 95% CI, 0.34–2.26); the results were similar in patients with UC (OR, 0.6; 95% CI, 0.31–1.13) and CD (OR, 1.24; 95% CI, 0.21–7.52) (Fig. 2B).

Infectious Complications

Vedolizumab vs anti-TNFs

The odds of infectious complications were not significantly different in IBD patients exposed preoperatively to vedolizumab in comparison with anti-TNFs (OR, 0.92; 95% CI, 0.35–2.43). The results were similar in patients with UC (OR, 0.75; 95% CI, 0.24–2.37) and CD (OR, 1.00; 95% CI, 0.07–13.86) (Fig. 3A).

Vedolizumab vs no biologics

The odds of infectious complications were not significantly different when comparing IBD patients exposed to vedolizumab vs those not given biological agents (OR, 0.72; 95% CI, 0.19–2.74). Results were similar in patients with UC (OR, 0.62; 95% CI, 0.26–1.49) and those with CD (OR, 0.84; 95% CI, 0.04–15.88) (Fig. 3B).

FIGURE 2.

Forest plots showing OR of all complications, comparing the vedolizumab treatment group with (A) the anti-TNF group and (B) patients not given biologics.

Yung DE, et al. Inflamm Bowel Dis 2018;24:2327-2338
Prevention of Post-operative Recurrence of Crohn’s Disease
Post-operative Crohn’s Disease: Endoscopic Recurrence Following Primary Ileocolic Resection

The cumulative probability of CR was 8, 13, and 27 % at 1, 2, and 5 years, respectively (see Fig. 2). The median time to CR was 12.1 years (95 % CI 9.5–14.6). The median time to clinical recurrence differed based upon the Rutgeerts score (i-1 = 10.0 years, i-2 = 5.5 years, i-3 = 2.8 years, and i-4 = 3.6 years) on the initial post-operative endoscopy (see Fig. 3).

Predictors of Endoscopic and Clinical Recurrence

In a univariate model, the only significant predictor of ER was the absence of postoperative medical prophylaxis (see Table 3). In a multivariate model, both penetrating disease behavior (HR 1.50; 95 % CI 1.00–2.10; \( P = 0.05 \)) and postoperative medical prophylaxis (HR 0.66; 95 % CI 0.46–0.95; \( P = 0.03 \)) were independent predictors of ER. Exposure to biologics preoperatively had no effect on ER (HR 1.00; 95 % CI 0.63–1.59; \( P = 0.99 \)).

In a univariate analysis, age less than 16 years, smoking, and upper gastrointestinal (GI) tract involvement were found to be predictors of CR (see Table 4). In a multivariate model, only perioperative smoking (HR 2.25; 95 % CI 1.27–4.01; \( P = 0.006 \)) and upper GI tract involvement (HR 4.00; 95 % CI 1.82–8.33; \( P < 0.0006 \)) were independent predictors of CR. There was a non-significant trend toward earlier CR in patients with an age at diagnosis less than 16 years (HR 1.61; 95 % CI 0.93–2.86; \( P = 0.09 \)).

Patients with i-1 and i-2 endoscopic recurrence on their initial postoperative endoscopy were examined. Interestingly, the cumulative probability of clinical recurrence was significantly higher in the i-2 subgroup when compared to the patients with i-1, HR 2.5 (95 % CI 1.2–5.9), \( P = 0.013 \) (see Fig. 4). Moreover, in patient with endoscopy within 3 years postoperatively, there was a non-significant trend toward a shorter clinical relapse-free survival in patients with i-3 or i-4 compared to i-1 or i-2 endoscopic recurrence (median time to clinical relapse 2.8 vs. 9.2 years, \( P = 0.08 \)).

The Natural History of Mild Endoscopic Recurrence

A total of 46 patients were found to have i-1 on their initial postoperative endoscopy documenting recurrence (see Table 5). Of these patients, we examined 11 patients who had not been exposed to any postoperative medical therapy and who underwent repeat endoscopic evaluation. During study follow-up, 6 patients actually regressed to an i-0 on subsequent endoscopy and only 3 patients displayed endoscopic progression (see Fig. 5).

Fig. 1 Survival analysis of endoscopic recurrence after primary ileocolic resection

Fig. 2 Survival analysis of clinical recurrence after primary ileocolic resection

Fig. 3 Survival analysis of clinical recurrence based upon Rutgeerts score from initial postoperative endoscopy
Post-operative Crohn’s Disease: Clinical Recurrence Following Primary Ileocolic Resection

The cumulative probability of CR was 8, 13, and 27 % at 1, 2, and 5 years, respectively (see Fig. 2). The median time to CR was 12.1 years (95 % CI 9.5–14.6). The median time to clinical recurrence differed based upon the Rutgeerts score ($i-1 = 10.0$ years, $i-2 = 5.5$ years, $i-3 = 2.8$ years, and $i-4 = 3.6$ years) on the initial postoperative endoscopy (see Fig. 3).

Predictors of Endoscopic and Clinical Recurrence

In a univariate model, the only significant predictor of ER was the absence of postoperative medical prophylaxis (see Table 3). In a multivariate model, both penetrating disease behavior (HR 1.50; 95 % CI 1.00–2.10; $P = 0.05$) and postoperative medical prophylaxis (HR 0.66; 95 % CI 0.46–0.95; $P = 0.03$) were independent predictors of ER.

Exposure to biologics preoperatively had no effect on ER (HR 1.00; 95 % CI 0.63–1.59; $P = 0.99$).

In a univariate analysis, age less than 16 years, smoking, and upper gastrointestinal (GI) tract involvement were found to be predictors of CR (see Table 4). In a multivariate model, only perioperative smoking (HR 2.25; 95 % CI 1.27–4.01; $P = 0.006$) and upper GI tract involvement (HR 4.00; 95 % CI 1.82–8.33; $P < 0.0006$) were independent predictors of CR. There was a non-significant trend toward earlier CR in patients with an age at diagnosis less than 16 years (HR 1.61; 95 % CI 0.93–2.86; $P = 0.09$).

Patients with $i-1$ and $i-2$ endoscopic recurrence on their initial postoperative endoscopy were examined. Interestingly, the cumulative probability of clinical recurrence was significantly higher in the $i-2$ subgroup when compared to the patients with $i-1$, HR 2.5 (95 % CI 1.2–5.9), $P = 0.013$ (see Fig. 4). Moreover, in patient with endoscopy within 3 years postoperatively, there was a non-significant trend toward a shorter clinical relapse-free survival in patients with $i-3$ or $i-4$ compared to $i-1$ or $i-2$ endoscopic recurrence (median time to clinical relapse 2.8 vs. 9.2 years, $P = 0.08$).

The Natural History of Mild Endoscopic Recurrence

A total of 46 patients were found to have $i-1$ on their initial postoperative endoscopy documenting recurrence (see Table 5). Of these patients, we examined 11 patients who had not been exposed to any postoperative medical therapy and who underwent repeat endoscopic evaluation. During study follow-up, 6 patients actually regressed to an $i-0$ on subsequent endoscopy and only 3 patients displayed endoscopic progression (see Fig. 5).
Post-operative CD Recurrence

- Endoscopic recurrence occurs in 35 – 80% by 1 year
- Endoscopic recurrence frequently precedes clinical recurrence
- Clinical recurrence:
  - 28 to 36% at 5 years
  - 45 to 61% at 10 years
- Length of recurrent segment is correlated with the length of resected segment
- Severity of endoscopic lesions is predictive of need for another resection

What factors affect risk of post-operative CD recurrence?

- Smoking
- Penetrating or stricturing disease type
- Family history of IBD
- Genetics
- Microbiome
- Time from CD diagnosis to resection
- Number of prior resections
- Surgical technique and pathologic findings
- Medical prophylaxis\textsuperscript{2,3}

Figure 1. Pairwise meta-analysis of different pharmacological interventions for the prevention of (A) clinical recurrence and (B) endoscopic recurrence after surgical resection in patients with CD. In the forest plot, "experimental" refers to the first treatment group and "control" refers to the second treatment group. For the comparison between 5-ASA and placebo for the outcomes of clinical and endoscopic recurrence, random effects meta-analysis was used, with a corresponding OR and 95% CI of 0.59 (0.43 – 0.81) and 0.65 (0.33 – 1.28), respectively.

### 5-ASA vs Placebo

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Odds Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>Wencken 1978</td>
<td>4</td>
<td>32</td>
<td>2.9%</td>
<td>0.40 [0.11, 1.45]</td>
</tr>
<tr>
<td>Caprilli 1994</td>
<td>3</td>
<td>47</td>
<td>3.5%</td>
<td>0.26 [0.07, 1.01]</td>
</tr>
<tr>
<td>Brignola 1995</td>
<td>7</td>
<td>44</td>
<td>3.2%</td>
<td>0.62 [0.21, 1.83]</td>
</tr>
<tr>
<td>McLeod 1995</td>
<td>27</td>
<td>87</td>
<td>8.6%</td>
<td>0.65 [0.34, 1.24]</td>
</tr>
<tr>
<td>Lochs 2000</td>
<td>36</td>
<td>152</td>
<td>13.8%</td>
<td>0.72 [0.44, 1.19]</td>
</tr>
<tr>
<td>Hanauer 2004</td>
<td>28</td>
<td>44</td>
<td>5.0%</td>
<td>0.42 [0.16, 1.09]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>406</strong></td>
<td><strong>407</strong></td>
<td><strong>37.1%</strong></td>
<td><strong>0.59 [0.43, 0.81]</strong></td>
</tr>
<tr>
<td>Total events</td>
<td>103</td>
<td>141</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity Chi²</td>
<td>2.97</td>
<td>df = 5</td>
<td>P = .70; I² = 0%</td>
<td></td>
</tr>
<tr>
<td>Test for overall effect</td>
<td>Z = 3.25</td>
<td>(P = .001)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Budesonide vs Placebo

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Odds Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ewe 1999</td>
<td>8</td>
<td>43</td>
<td>3.5%</td>
<td>0.60 [0.21, 1.70]</td>
</tr>
<tr>
<td>Hellers 1999</td>
<td>20</td>
<td>63</td>
<td>5.3%</td>
<td>1.00 [0.47, 2.09]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>106</strong></td>
<td><strong>106</strong></td>
<td><strong>8.8%</strong></td>
<td><strong>0.84 [0.46, 1.55]</strong></td>
</tr>
<tr>
<td>Total events</td>
<td>28</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity Chi²</td>
<td>0.60</td>
<td>df = 1</td>
<td>P = .44; I² = 0%</td>
<td></td>
</tr>
<tr>
<td>Test for overall effect</td>
<td>Z = 0.57</td>
<td>(P = .57)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Antibiotics vs Placebo

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Odds Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rutgeerts 1995</td>
<td>9</td>
<td>29</td>
<td>3.7%</td>
<td>0.45 [0.15, 1.33]</td>
</tr>
<tr>
<td>Rutgeerts 2005</td>
<td>11</td>
<td>37</td>
<td>4.6%</td>
<td>0.52 [0.20, 1.32]</td>
</tr>
<tr>
<td>Hellath 2013</td>
<td>2</td>
<td>11</td>
<td>0.6%</td>
<td>1.00 [0.11, 8.73]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>77</strong></td>
<td><strong>79</strong></td>
<td><strong>8.9%</strong></td>
<td><strong>0.52 [0.27, 1.02]</strong></td>
</tr>
<tr>
<td>Total events</td>
<td>22</td>
<td>34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity Chi²</td>
<td>0.42</td>
<td>df = 2</td>
<td>P = .81; I² = 0%</td>
<td></td>
</tr>
<tr>
<td>Test for overall effect</td>
<td>Z = 1.89</td>
<td>(P = .06)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Immunomodulator vs Placebo

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Odds Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanauer 2004</td>
<td>24</td>
<td>47</td>
<td>6.3%</td>
<td>0.35 [0.14, 0.85]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>47</strong></td>
<td><strong>44</strong></td>
<td><strong>6.3%</strong></td>
<td><strong>0.35 [0.14, 0.85]</strong></td>
</tr>
<tr>
<td>Total events</td>
<td>24</td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect</td>
<td>Z = 2.32</td>
<td>(P = .02)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Anti-TNF vs Placebo

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Odds Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regueiro 2009</td>
<td>0</td>
<td>10</td>
<td>1.8%</td>
<td>0.07 [0.00, 1.53]</td>
</tr>
</tbody>
</table>
Post-operative Management of CD: ECCO Guidelines

ECCO statement 8B
The following are considered predictors of early post-operative recurrence after ileocolonic resection: smoking, prior intestinal surgery, absence of prophylactic treatment [EL1], penetrating disease at index surgery, perianal location [EL2], granulomas in resection specimen [EL2], and myenteric plexitis [EL3]

ECCO statement 8G
Prophylactic treatment is recommended after ileocolonic intestinal resection in patients with at least one risk factor for recurrence [EL2]. To prevent post-operative recurrence the drugs of choice are thiopurines [EL2] or anti-TNFs [EL2]. High dose mesalazine is an option for patients with an isolated ileal resection [EL2]. Imidazole antibiotics have been shown to be effective after ileocolic resection but are less well tolerated [EL1]

Post-operative Management of CD: One Size Does Not Fit All

- Risk of Recurrent CD
- Potential Impact of CD Recurrence
- Potential Impact of Post-operative Therapy
- Patient Preference
- Access to Therapy
Post-operative Management of CD: One Size Does Not Fit All

• Risk of recurrent CD:
  - patient age
  - number of previous resections
  - smoking
  - presence of residual disease (macroscopic)
  - time from diagnosis to first resection
Post-operative Management of CD: One Size Does Not Fit All

- Potential Impact of CD Recurrence:
  - patient age
  - co-morbidities
  - number, length and location of previous resections

- Potential Impact of Post-op Therapy:
  - patient age
  - co-morbidities
  - response to prior therapy
    - efficacy
    - side effects and complications
Post-operative Management of CD: One Size Does Not Fit All

- **Patient Preference:**
  - minimization or fear of medication risk
  - experience with previous medical therapy
  - concerns about specific classes of therapy
  - minimization or fear of recurrence risk
  - monitoring procedures
    - clinical
    - lab (e.g. CRP, fecal calprotectin)
    - endoscopic
    - radiologic
Post-operative Management of CD: One Size Does Not Fit All

- Access to Therapy:
  - ability to pay
  - insurance coverage
  - prior therapy and response to therapy
Post-operative Management of CD: AGA Guidelines

1. In patients with surgically induced remission of CD, the AGA suggests early pharmacological prophylaxis over endoscopy-guided pharmacological treatment. *Conditional recommendation, very low quality of evidence.*

2. In patients with surgically induced remission of CD, the AGA suggests using anti-TNF therapy and/or thiopurines over other agents. *Conditional recommendation, moderate quality of evidence.*

3. In patients with surgically induced remission of CD, the AGA suggests against using mesalamine (or other 5-aminosalicylates), budesonide, or probiotics. *Conditional recommendation, low quality of evidence and very low quality of evidence.*
Risk Stratification of Post-operative Crohn’s Disease Patients

- **Low risk**
  - 1st resection
  - short segment resected
  - non-perforating
  - non-smoker
  - older age (definition)
  - long duration from diagnosis to resection

- **High risk**
  - 2 or more resections
  - long segment(s) resected
  - perforating disease
  - smoker at time of OR
  - younger age
  - short duration from diagnosis to resection (+ exposure to potentially effective medical therapy)
Risk Stratification of Post-op CD: Use of Endoscopy
Ileocolic Anastomosis

Anastomotic line friability and erosions

Rutgeerts i0

6% risk of clinical recurrence at 5 years
Post-surgical CD Recurrence

Rutgeerts i1

6% risk of clinical recurrence at 5 years
Post-surgical CD Recurrence

Rutgeerts i2

27% risk of clinical recurrence at 5 years
Post-surgical CD Recurrence

Rutgeerts i3

63% risk of clinical recurrence at 5 years
Post-surgical CD Recurrence

Rutgeerts i4

100% risk of clinical recurrence at 5 years
Post-surgical CD Recurrence

Rutgeerts i4
Crohn’s disease management after intestinal resection: a randomised trial

Impact of 6 Month Post-op Endoscopic Risk Stratification

Impact of 6 Month Post-op Endoscopic Risk Stratification

Additional adalimumab, and three (50%) of six patients who stepped up to weekly adalimumab. Stepping up treatment at 6 months brought 38% of patients with endoscopic recurrence into remission 1 year after stepping up treatment. 75 (61%) of 122 patients in the active care group were in endoscopic remission at 6 months and did not step up therapy. These patients comprised 13 (62%) of 21 patients at low risk, 40 (55%) of 73 patients at high-risk treated with a thiopurine, and 22 (79%) of 28 high-risk adalimumab-treated patients. In these patients, endoscopic recurrence was seen at 18 months in four (31%) of 13 patients at low risk, 18 (45%) of 40 patients at high risk treated with a thiopurine, and nine (41%) of 22 patients treated with adalimumab. In total, remission at 6 months was associated with endoscopic recurrence in 31 (41%) of 75 of patients 1 year later.

In the active care arm, of the two of 21 low risk, 17 of 73 thiopurine treated, and 15 of 28 adalimumab treated patients with complete mucosal healing (i0) at 6 months, zero of two, eight of 17, and seven of 15, respectively, had complete mucosal healing at 18 months.

Figure 1: Endoscopic outcomes at 18 months postoperatively. Modifi  ed intention-to-treat analysis. (A) Remission (Rutgeerts endoscopic score of i0 or i1) and recurrence (Rutgeerts score i2, i3, or i4) in the active care versus standard care groups. (B) Rutgeerts scores in the active versus standard care arms. (C) Complete mucosal healing (Rutgeerts score i0) in patients in the active versus standard care groups. (D) Severe endoscopic recurrence (Rutgeerts score i3 and i4) in the active versus standard care arms. (E) Rutgeerts scores in patients treated with adalimumab alone immediately postoperatively and in patients receiving a thiopurine immediately postoperatively and stepping up to a thiopurine plus adalimumab at 6 months.

Active care n=122
Standard care n=52
p=0·03

Patients (%)

18 Month Outcome

Suggested Post-operative CD Management Algorithm

Small bowel resection

1st resection

Ileocolonoscopy at 6 (to 12) months

i2 disease in neo-TI

i0 – i1 disease in neo-TI

eosscopic follow-up

i3 – i4 disease in neo-TI

biologic therapy +/- thiopurine therapy

≥ 2nd resection

biologic therapy and/or thiopurine therapy

Ileocolonoscopy at 6 months

i0 – i1 disease in neo-TI

eososcopic follow-up

i2 – i4 disease in neo-TI

optimize or change therapy

*long length resection, short time from diagnosis, smoking, penetrating disease behavior
Surgical Management of Ileocolic Crohn’s Disease

November 2, 2018

Erin Kennedy, MD, PhD
Associate Professor
Department of Surgery
University of Toronto
Surgical management of ileocolic Crohn’s disease

- Role and timing of surgery
- Surgical considerations
  - Type of anastomosis
  - Extent of mesenteric resection
  - Microbiome
LIR!C Study

- RCT, 29 hospitals
  - Short segment ileocolic CD
  - Failed 3 months conventional therapy (steroids, thiopurines, methotrexate)
  - No previous resection
  - No evidence of obstruction on imaging
- Infliximab versus laparoscopic ICR
- Primary outcome QoL on IBDQ @ 12 months
- Endoscopic recurrence @ 12 months

## LIR!C Results

<table>
<thead>
<tr>
<th></th>
<th>IFX (n=70)</th>
<th>ICR (n=73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBDQ @ 1 year</td>
<td>178.1</td>
<td>172.0</td>
</tr>
<tr>
<td>Endoscopic remission @ 1 year</td>
<td>84% (38/45)</td>
<td>79% (49/53)</td>
</tr>
<tr>
<td>Readmission</td>
<td>21% (15)</td>
<td>18% (13)</td>
</tr>
<tr>
<td>Time spent in hospital per patient, days (range)</td>
<td>7.0 (3.0-11.0)</td>
<td>5.0 (3.5-10.0)</td>
</tr>
<tr>
<td>Not able to participate in social life, days (SD)</td>
<td>1.1 (4.5)</td>
<td>1.8 (6.3)</td>
</tr>
<tr>
<td>Days on sick leave, days (SD)*</td>
<td>1.4 (4.7)</td>
<td>3.4 (7.1)</td>
</tr>
</tbody>
</table>

*p<0.05
LIR!C Study

- 20% (13/65) IFX → ICR
- 4% (3/73) ICR → IFX
- ICR excellent option for short segment ileocolic CD
- Similar quality of life both options
- Consider offering surgery early(ier)
- Cost effective

Type of Anastomosis – does it matter?

- Relationship between anastomosis and recurrence
  - Proctocolectomy
  - Pre-anastomotic location
  - Stasis
- Types of Anastomoses
  - Side to Side
  - End to End
  - End to Side
  - Kono S
Side to Side Anastomosis
End to End Anastomosis
Kono S Anastomosis

- Supporting column

- 0.5cm-1cm

- 7cm-8cm
# Side to Side vs End to End

<table>
<thead>
<tr>
<th>N of studies</th>
<th>N</th>
<th>Post-Op Complications</th>
<th>Anastomotic Leak</th>
<th>Recurrence</th>
<th>Re-operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>He, 2014</td>
<td>8</td>
<td>0.54 (0.32-0.93)</td>
<td>0.45 (0.20-1.0)</td>
<td>0.20 (0.07-0.55)</td>
<td>0.18 (0.07-0.45)</td>
</tr>
<tr>
<td>Guo, 2013</td>
<td>11</td>
<td>Favours SSTA</td>
<td>No difference</td>
<td>No difference</td>
<td>No difference</td>
</tr>
<tr>
<td>Simillis, 2007</td>
<td>8</td>
<td>No difference</td>
<td>Favours SSTA</td>
<td>No difference</td>
<td>No difference</td>
</tr>
</tbody>
</table>

He. Dig Dis Sci 2014:59;1544-1551  
Guo. World J Surg 2013:37;893-901  
Simillis. DCR 2007:50;1674-1687
CAST Study

- RCT, 16 centres
- Stapled side to side (STS) versus hand-sewn end to end (ETE)
- Endoscopic recurrence @ 12 months
- Colonoscopy by gastroenterologist
- Recurrence assessed by adjudication committee

McLeod RS. Dis Colon Rectum 2009; 52: 919-927
CAST Study

- Baseline characteristics between groups similar

- Endoscopic recurrence @ 12 months
  - 37.9% STS vs 42.5% ETE (95% CI -21.0 to 11.9, p=0.55)

- Symptomatic recurrence @ 12 months
  - 22.7% STS vs 21.9% ETE (95% CI -13.2 to 15.3, p=0.92)

McLeod RS. Dis Colon Rectum 2009; 52: 919-927
## CAST Study

<table>
<thead>
<tr>
<th>Metric</th>
<th>STSA (n=84)</th>
<th>ETEA (n=86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to complete anastomosis, mins (range)</td>
<td>10 (7-15)</td>
<td>26 (20-34)</td>
</tr>
<tr>
<td>Laparoscopic</td>
<td>30%</td>
<td>33%</td>
</tr>
<tr>
<td>Report difficulties with the anastomosis</td>
<td>1%</td>
<td>7%</td>
</tr>
<tr>
<td>Report difficulties with operation</td>
<td>14%</td>
<td>12%</td>
</tr>
<tr>
<td>Median hospital stay, days (range)</td>
<td>6 (5-8)</td>
<td>6 (4-8)</td>
</tr>
<tr>
<td>Anastomotic leak</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Re-operation</td>
<td>7%</td>
<td>7%</td>
</tr>
</tbody>
</table>
## Health Care Utilization in Post-Operative Crohn’s Disease

<table>
<thead>
<tr>
<th></th>
<th>ETE (n=68)</th>
<th>STS (n-60)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endoscopic recurrence</strong></td>
<td>25.4%</td>
<td>39.3%</td>
<td>1.8 (0.8 to 4.2)</td>
</tr>
<tr>
<td><strong>Re-operation</strong></td>
<td>2.9%</td>
<td>6.7%</td>
<td>2.2 (0.4 to 12.6)</td>
</tr>
<tr>
<td><strong>Mean SIBDQ</strong></td>
<td>53.4</td>
<td>47.9</td>
<td>-5.1 (-8.7 to 1.5)</td>
</tr>
<tr>
<td><strong>Median HBI</strong></td>
<td>3</td>
<td>4</td>
<td>0.9 (-0.2 to 2.1)</td>
</tr>
<tr>
<td><strong>Median CRP</strong></td>
<td>0.33</td>
<td>0.26</td>
<td>0.08 (-0.2 to 0.4)</td>
</tr>
<tr>
<td><strong>ED Visit</strong>*</td>
<td>14.7%</td>
<td>33.3%</td>
<td>2.9 (1.2 to 6.9)</td>
</tr>
<tr>
<td><strong>Hospitalization</strong>*</td>
<td>11.8%</td>
<td>30%</td>
<td>3.1 (1.2 to 7.8)</td>
</tr>
<tr>
<td><strong>Abdo CT</strong>*</td>
<td>13.2%</td>
<td>50%</td>
<td>6.5 (2.7 to 15.8)</td>
</tr>
</tbody>
</table>

Gajendran M. Am J Gastroenterol 2018;113:576-583
# Kono S Anastomosis

<table>
<thead>
<tr>
<th></th>
<th>Kono S (n=69)</th>
<th>Other (n=73)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopic recurrence @ 1 year</td>
<td>83</td>
<td>79</td>
<td>NS</td>
</tr>
<tr>
<td>Re-operation</td>
<td>3</td>
<td>26</td>
<td>0.0007</td>
</tr>
<tr>
<td>Stenosis at anastomosis</td>
<td>0</td>
<td>15</td>
<td>0.0013</td>
</tr>
</tbody>
</table>

Mesenteric adipocytes, fibroblasts and lymphocytes play a role in systemic inflammation.

<table>
<thead>
<tr>
<th>Element</th>
<th>Function</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiponectin</td>
<td>Induces IL-10 and IL-1 receptor antagonist</td>
<td>Production of pro- and anti-inflammatory cytokines</td>
</tr>
<tr>
<td>Leptin</td>
<td>Activation of CD4+ and CD8+</td>
<td>Production of pro-inflammatory cytokines</td>
</tr>
<tr>
<td>Resistin</td>
<td>Up regulates TNF-alpha, IL-6 and IL-12</td>
<td>Pro-inflammatory effects; correlate with higher CRP levels in serum</td>
</tr>
<tr>
<td>Fibrocytes</td>
<td>Secretion of IL-13, TGF-beta and TNF-alpha</td>
<td>Pro-inflammatory and pro-fibrotic responses</td>
</tr>
</tbody>
</table>
• “Creeping fat” or fat wrapping correlates with intestinal inflammation

• Affected mesentery infiltrated by inflammatory cells that promote mucosal ulceration and stricturing

• “Outside in” phenomenon that contributes to bowel inflammation and fibrosis
Extent of Mesenteric Resection

A

Conventional – Mesentery retained

B

Mesocolic excision – Mesentery removed
Extent of Mesenteric Resection

- 30 consecutive CD patients undergoing ICR with mesenteric resection
- 34 CD patients with previous ICR and no mesenteric resection as historic controls
- Baseline characteristics similar
- Follow up: 51.7 +/- 20 months versus 69.9 +/- 48.47 months

<table>
<thead>
<tr>
<th>Re-operation for CD</th>
<th>No mesenteric resection (n=34)</th>
<th>Mesenteric resection (n=34)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30% (9/30)</td>
<td>2.9 (1/34)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Coffey C. Journal of Crohn’s and Colitis 2018;1-12
• Surgery leads to changes in the GI microbiome
• Recurrence associated with elevated levels of Proteus and reduced Faecalibacterium
• Smoking associated with elevated levels of Proteus

Wright EK. Journal of Crohn’s and Colitis 2017;191-203
CONSIDER EARLY(IER) SURGICAL CONSULT

Side to side anastomosis preferred

RCT data necessary to show:

- ETEA improves hospital utilization and quality of life
- Kono-S superior to STSA

Future RCT need to consider type of anastomosis, extent of mesenteric resection and microbiome
End to Side Anastomosis
IBDQ Scores

Mean difference at 12 months: 6.1, 95% CI 4.2 to 16.4, p=0.245
SF-36 Physical Component

Mean difference at 12 months: 3.1, 95% CI 4.2 to 6.0, p=0.040
Based on fat wrapping (FW) and mesenteric thickness (MT)

Correlates with CDAI ($r=0.7$, $p<0.0001$)

<table>
<thead>
<tr>
<th>Element</th>
<th>Severity</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal FW, Minimal MT</td>
<td>Mild</td>
<td>1</td>
</tr>
<tr>
<td>FW &lt;25%, MT vascular pedicle only</td>
<td>Moderate</td>
<td>2</td>
</tr>
<tr>
<td>FW &lt;25%, MT pan mesenteric</td>
<td>Severe</td>
<td>4</td>
</tr>
<tr>
<td>FW &gt;25%, MT pan mesenteric</td>
<td>Very severe</td>
<td>6</td>
</tr>
</tbody>
</table>
MEDICAL PERI-OPERATIVE AND SURGICAL PERSPECTIVES IN IBD

A. Hillary Steinhart, MD MSc FRCP(C)
Medical Lead, Centre for Inflammatory Bowel Disease
Mount Sinai Hospital
Professor of Medicine
University of Toronto
Case 2

- 20 year old male with 5 year history of ileocolonic CD presenting with intermittent perianal pain and swelling; now has persistent drainage of yellow-brown fluid
- 3 – 4 soft stools per day
- No abdominal pain
- Presently on MTX maintenance therapy
- Previously on prednisone
Medical Management of Perianal Fistulizing Crohn’s Disease: Key Aspects

- Identification of need for surgical intervention
- Antibiotics for initial symptomatic control
- Optimization of therapy for intestinal disease activity (especially rectal disease)
- Initiation of effective medical therapy for reduction and elimination of fistula drainage and prevention of abscesses and new fistulas
Clinical Practice Guideline for the Medical Management of Perianal Fistulizing Crohn’s Disease: The Toronto Consensus

A. Hillary Steinhart, MD,* Remo Panaccione, MD,† Laura Targownik, MD,‡ Brian Bressler, MD,§ Reena Khanna, MD,¶ John K. Marshall, MD,¶¶ Waqqas Aff, MD,** Charles N. Bernstein, MD,‡‡ Alain Bitton, MD,*** Mark Borgaonkar, MD,†† Usha Chauhan, NP,** Brendan Halloran, MD,§§ Jennifer Jones, MD,¶¶ Erin Kennedy, MD, PhD,¶¶¶ Grigorios I. Leontiadis, MD, PhD,¶ Edward V. Loftus Jr, MD,*** Jonathan Meddings, MD,† Paul Moayyedi, MB, PhD,¶ Sanjay Murthy, MD,†† Sophie Plamondon, MD,‡‡ Greg Rosenfeld, MD,§§§ David Schwartz, MD,¶¶¶¶ Cynthia H. Seow, MBBS (Hons),***** and Chadwick Williams, MD*****
Perianal Fistulizing CD: Identification of Need for Surgical Intervention

- Clinical evidence of abscess
  - local pain
  - swelling
  - fever
  - inflammatory markers

- Imaging studies
CAG Clinical Practice Guidelines:

Perianal fistulizing CD with signs/symptoms of activity

YES

Clinically suspected abscess (pain, fever, leucocytosis)

NO

Antibiotic therapy for initial symptom control

Imaging assessment (EUS or MRI)

Surgical consultation and EUA:
± abscess drainage
± seton placement

Complicated fistulizing CD

Effective Medical Therapy

Uncomplicated fistulizing CD

Statement 3: In patients with Crohn’s disease and evidence of fistulizing disease, we suggest the use of antibiotic therapy for initial management to achieve symptomatic response.

GRADE: Conditional recommendation, very low-quality evidence. Vote: strongly agree, 48%; agree, 48%; uncertain, 5%.

Adapted from: Steinhart AH, et al. Inflamm Bowel Dis 2018 Aug 6 (Epub ahead of print)
Management of Perianal Fistula: Proper Evaluation and Staging of Disease is Critical First Step

- Defining fistula anatomy or classification
- Identifying sepsis/drainable collections
- Evaluation of inflammation in the fistula tracts and the surrounding tissues
- Assessing associated luminal disease
Evaluation of Perianal Fistula with Endoanal Ultrasound

Evaluation of Perianal Fistula with Endoanal Ultrasound

Evaluation of Perianal Fistula with Magnetic Resonance Imaging


Transphincteric fistula
Evaluation of Perianal Fistula with Magnetic Resonance Imaging

T2-weighted fast spin echo

T1-weighted fat saturated fast spin post iv contrast = granulation tissue

Comparative Accuracy of EUA, MRI and Endoscopic Ultrasound

• 34 patients with suspected CD perianal fistulas underwent EUA, MRI and EUS in blinded fashion
• Consensus gold standard arrived at in all but one patient
• 39 fistulas in 32 patients
• Accuracy:
  - US - 91%
  - MRI - 87%
  - EUA - 91%
  - Combination of any 2 modalities - 100%

Medical Peri-operative Management of Perianal Fistulizing Crohn’s Disease

- Identification of need for surgical intervention
- Antibiotics for initial symptomatic control
- Optimization of therapy for intestinal disease activity (especially rectal disease)
- Initiation of effective medical therapy for reduction and elimination of fistula drainage (\( ? = \) “healing”) and prevention of abscesses and new fistulas
Perianal fistulizing CD with signs/symptoms of activity

Clinically suspected abscess (pain, fever, leucocytosis)

Antibiotic therapy for initial symptom control

Imaging assessment (EUS or MRI)

Complicated fistulizing CD

Surgical consultation and EUA:
± abscess drainage
± seton placement

Uncomplicated fistulizing CD

Effective Medical Therapy

Statement 3: In patients with Crohn's disease and evidence of fistulizing disease, we suggest the use of antibiotic therapy for initial management to achieve symptomatic response.

GRADE: Conditional recommendation, very low-quality evidence. Vote: strongly agree, 48%; agree, 48%; uncertain, 5%.
ACCENT II: Week 54 Results
Complete fistula response on infliximab

Note: Complete response = absence of draining fistulas

Infliximab Maintenance Therapy: Reduced Hospitalization

ACCENT II

CHARM: Week 26 and Week 56 Healing of draining fistulas on adalimumab

Note: Healing = no draining fistulas. Patients with fistulas: draining fistulas at both screening and baseline

Improving efficacy of infliximab by combining with seton placement

Retrospective study (n=23) of IFX (3 doses) +/- seton$$^1$$*
- 100% of pts had complete closure (vs. 83% IFX only, $$p=0.014$$)
- 44% had recurrence (vs. 79% with IFX only, $$p=0.001$$)
- Time to recurrence 13.5 mos (vs. 3.6 with IFX only, $$p=0.0001$$)

Retrospective study (n=21) of IFX**+ immunosupp. + surgery$$^2$$
- Surgery: seton (n=10), drainage (n=2), diversion (n=1)
- At 9 months, 67% of pts had complete closure and 19% of pts had partial response

* All patients had at least 3 months of follow-up after the third dose of infliximab.
** At 0, 2, 6 weeks ± every 8 weeks (mean number of infusions = 3)

In patients with Crohn’s disease and evidence of fistulizing disease, we suggest the use of antibiotic therapy for initial management to achieve symptomatic response.

**Statement 3:**

**CAG Clinical Practice Guidelines: Failure of Medical Therapy**

- Anti-TNF ± thiopurine or MTX

**Surgical management including one or more of the following:**
- abscess drainage
- seton placement
- fistula plug
- ERAF, LIFT
- diversion
- proctectomy

**Loss of symptomatic response**

- Continue anti-TNF ± thiopurine or MTX

**Symptomatic response**

- Inadequate symptomatic response*

- Continue anti-TNF ± thiopurine or MTX

*Medical therapy should be optimized, informed by therapeutic drug monitoring (if needed) before patients are considered refractory to treatment.

GRADE: Conditional recommendation, very low-quality evidence. Vote: strongly agree, 48%; agree, 48%; uncertain, 5%.
Management of Perianal Crohn’s Disease

November 2, 2018

Erin Kennedy, MD, PhD
Associate Professor
Department of Surgery
University of Toronto
IMAGING

- MRI preferred to US
  - Patient comfort
- Not absolutely necessary prior to EUA
- Main indications
  - Assess for undrained collection
  - Assess for complex, branching fistulas
- No need for serial imaging
Goodsalls’ RULE
SURGICAL TREATMENT OPTIONS

1. SETON
2. SETON
3. SETON
4. SETON
5. SETON
6. Diversion
7. Protectomy
GOALS OF SETON

- Keeps fistula tract open; minimal damage to sphincter
- Allows drainage; prevents recurrent abscess
- Reduces chronic inflammation and discomfort
- Allows fistula tract to epithelialize (mature)
- Once tract has matured, it will not close
- Shorter tracts take less time to mature than longer tracts
- Generally 6-12 weeks to mature
SURGICAL TREATMENT OPTIONS

- Fibrin glue
- Mucous plug
- Mucosal advancement flap
- Ligation of the intersphincteric fistula tract (LIFT)
- Stem cell (Cx601, Gastroenterology 2018)
- Fistulotomy
Studies difficult to evaluate due to definitions of “healing”

Fistula will not heal (i.e., close) with seton in place or after tract is mature

Biologic more likely to be successful if taken out “earlier” than “later”

Biologic more likely to be successful if simple rather than complex fistula

Fistula unlikely to heal if active disease (i.e., continued diarrhea)
SUMMARY

- MRI preferred
- Most fistula follow Goodsall’s rule
- Seton preferred treatment
- Seton can stay in indefinitely
- Fistula tract is unlikely to close after it has epithelialized or matured
- Combination biologic and seton is good treatment option
- Future studies on biologics and timing of seton removal are important
Summary

• Communication and coordination between gastroenterologist and surgeon is critical in planning surgery in CD
• Medical optimization can reduce post-op complications
• Post-op prophylaxis can reduce CD recurrence
• Combined surgical and medical management of perianal CD can improve outcomes