"Post-Operative Management in Pediatric Crohn’s Disease: How Should the Pediatric Gastroenterologist Approach This in 2015?"

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Disclosures
In the past 12 months, I have had the following financial relationships:

Consultant: Abbott Laboratories and AbbVie

Objectives
- Describe the natural history of post-operative recurrence in patients with Crohn’s disease
- Review different methods for defining, and monitoring for, post-operative recurrence
- Review the data on efficacy of different treatment regimens
- Discuss therapeutic approaches for effective management post-operatively
- Next steps?
Pediatric Crohn's Disease Progression to Complicated Phenotypes

- n = 9114
- 34% surgery by 5 yrs

Incidence and Risk for Surgery in Pediatric Crohn's Disease

- Gupta, et al. 2006. Gastroenterology

Children With Crohn's Disease Do Not Progress to Surgery As Quickly As Adults

How Can We Predict Which Patients Will Have Post-Operative Recurrence?

- Disease-Related Factors
- Patient-Related Factors
- Medications

The Natural History of Post-Operative Crohn's Disease

Recurrence initially clinically silent

<table>
<thead>
<tr>
<th>Histologic</th>
<th>Endoscopic</th>
<th>Clinical</th>
<th>Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 1 week</td>
<td>70-90% by 1 year</td>
<td>30% 3 year 60% 5 year</td>
<td>50% by 20 years</td>
</tr>
</tbody>
</table>

Rutgeerts, et al. 1990. Gastroenterology

What Are Predictive Factors for Post-Operative Recurrence in Pediatric Crohn's?

- Retrospective review; multivariate analyses of 79 children undergoing 100 surgeries
- Clinical recurrence rates: 17% at 1 yr; 38% at 3 yrs, and 60% at 5 yr.
- Shorter post-op recurrence free interval:
  - Colonic Crohn's (median 1.2 yr) vs. ileocecal (median 4.4 yr) or diffuse disease (median 3.0 yr) (p = 0.01).
  - High PCDAI at the time of surgery (p = 0.01)
  - Preoperative 6-MP (p < 0.005)

**Post - Op Recurrence in Adult vs. Pediatric Onset Crohn’s Disease**
- Retrospective review: patients with ileocecectomy or hemicolectomy
- Onset of disease: \(\leq 16\) yrs (n=34), >16 yrs (n=108)
  - Pediatric - onset† pre-op immunomodulators
- Recurrence: 37% at 1 yr; 65% at 3 yrs; 78% at 5 yrs
  - *No difference between groups
- Predictors of delayed time to recurrence
  - Adult - onset: Post - op prophylaxis \(\leq 4\) weeks
  - Pediatric - onset: None

**Outcome After Resection in Pediatric CD**
- Retrospective study of French population – based cohort (n=130)
- Increased risk of 2\(^{nd}\) resection
  - Age < 14 years
  - Strictures or fistulizing disease
  - Upper GI disease

<table>
<thead>
<tr>
<th>Risk of Disease Relapse</th>
<th>Cumulative Probability of 2(^{nd}) Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Years</td>
<td>18%</td>
</tr>
<tr>
<td>5 Years</td>
<td>34%</td>
</tr>
<tr>
<td>10 years</td>
<td>47%</td>
</tr>
</tbody>
</table>

**High Post - Op Recurrence in Children**
- Danish National Patient Registry
  - N = 1545 (1978 – 2007); n = 422 (27%) underwent surgery
  - Post – op recurrence defined as PGA and as need for step up or surgical therapy
  - Cumulative recurrence rates: 50% at 1 yr, 73% at 5 yrs, and 77% at 10 yrs
  - *No significant difference in post – op AZA for time to 2\(^{nd}\) resection/operation
**Improved Growth Post - Operatively**

- 1st surgery ≤ 3 yrs from dx
- Better catch-up growth and weight
- Age of patient: < 16 years
- Pubertal or bone age delay

Bouall et al. 2013. Inflamm Bowel Dis
Hojahj et al. 2015. J Ped Surg

**How Do You Evaluate for Post-Op Recurrence?**

- Ileocolonoscopy is the gold standard
- Endoscopic inflammation correlates with clinical recurrence by Rutgeerts’ score
- Evaluation within 1 yr post – op recommended in ECCO guidelines

Rutgeerts, et al. 1990. Gastroenterology
De Cruz, et al. 2012. Inflamm Bowel Dis

**Evaluating for Endoscopic Recurrence**

<table>
<thead>
<tr>
<th>Score</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No lesions</td>
</tr>
<tr>
<td>1</td>
<td>≤ 5 aphthous lesions</td>
</tr>
<tr>
<td>2</td>
<td>5 aphthous lesions with normal mucosa between lesions, or skip areas of larger lesions, or lesions confined to ileocolonic anastomosis</td>
</tr>
<tr>
<td>3</td>
<td>Diffuse aphthous ileitis with diffusely inflamed mucosa</td>
</tr>
<tr>
<td>4</td>
<td>Diffuse inflammation with already larger ulcers, nodules, and/or narrowing</td>
</tr>
</tbody>
</table>

0 and 1: Low likelihood of progression
3, 3, 4: Higher likelihood of progression to surgery

Rutgeerts, et al. 1990. Gastroenterology
Capsule Endoscopy

- Capsule endoscopy (WCE) vs. colonoscopy
  - 6 months post-op (n=32)
  - WCE inferior (sensitivity 62-76%) at anastomosis
  - WCE revealed more proximal disease
- WCE vs. Small intestinal contrast USN (SICUS) vs. colonoscopy
  - 12 months post-op (n=22)
  - 5/22: Could not have WCE due to narrowing
  - 16/17: Recurrence detected by colonoscopy and WCE
  - 17/17: Recurrence detected by SICUS (1 false positive)

Biancone, et al. 2007. Inflamm Bowel Dis

Radiographic Imaging

- MR enterography
  - Sensitivity 100%, specificity 89% in one study
  - MR score correlated well with Rutgeerts score
- Abdominal CT
  - Sensitivity 88%, specificity 97% in one study
  - Not recommended due to radiation exposure
- Ultrasound
  - Sensitivity 79%, specificity 95% in one study
  - Highly operator dependent; improved outcomes with PEG contrast (SICUS)

Kotmale, et al. 2010. Inflamm Bowel Dis
De Cruz, et al. 2012. Inflamm Bowel Dis

Fecal Calprotectin

- Adult study compared FC at time of scope 1 yr post-op (n=30)
  - Poor correlation; variability in patients with diarrhea
  - FC > 600: 6/7 (86%) endoscopic recurrence
  - FC < 100: 6/8 (75%) endoscopic remission

Traditional Adult CD Post-Operative Algorithm

![Algorithm Diagram]

Regueiro, et al. 2009. Inflamm Bowel Dis

Crohn’s Post-Operative Medication Options

<table>
<thead>
<tr>
<th>Medications for Post – Op Prevention (RCT)</th>
<th>Clinical Recurrence</th>
<th>Endoscopic Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>25 – 77%</td>
<td>53 – 79%</td>
</tr>
<tr>
<td>5-ASA</td>
<td>24 – 58%</td>
<td>63 – 66%</td>
</tr>
<tr>
<td>Budesonide</td>
<td>19 – 32%</td>
<td>52 – 57%</td>
</tr>
<tr>
<td>Nitroimidazole</td>
<td>7 – 8%</td>
<td>52 – 54%</td>
</tr>
<tr>
<td>AZA/6MP</td>
<td>34 – 50%</td>
<td>42 – 44%</td>
</tr>
<tr>
<td>Infliximab</td>
<td>0%</td>
<td>9%</td>
</tr>
</tbody>
</table>

Endoscopic recurrence rates almost 50% or greater in all medication classes except anti – TNF agents

Regueiro, et al. 2009. Inflamm Bowel Dis

Crohn’s Post-Operative Medication Options

<table>
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<tr>
<th>Drug</th>
<th>Endoscopic recurrence</th>
<th>Clinical recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesalamine</td>
<td>5 – 51%</td>
<td>50%</td>
</tr>
<tr>
<td>Thiopurines</td>
<td>2 – 22%</td>
<td>50%</td>
</tr>
<tr>
<td>Anti - TNF</td>
<td>0 – 21%</td>
<td>81 – 85%</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>13%</td>
<td>43%</td>
</tr>
<tr>
<td>Probiotics</td>
<td>9 – 21%</td>
<td>15 – 18%</td>
</tr>
<tr>
<td>Budesonide</td>
<td>52%</td>
<td>57%</td>
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</tbody>
</table>

Regueiro, et al. 2009. Inflamm Bowel Dis
**Anti-TNF is More Effective Than Conventional Therapy to Prevent Post-Op Recurrence**

<table>
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<tr>
<th>Clinical Remission &gt; 1 yr</th>
<th>Endoscopic Remission &gt; 1 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Graph" /></td>
<td><img src="image2" alt="Graph" /></td>
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*High risk phenotypes: penetrating disease, smoking, perianal disease, and young age at diagnosis.


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**Endoscopic Recurrence Reduced in Infliximab Treated Patients**

![Graph](image3)


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**Long – Term Effects of Infliximab Therapy Post - Operatively**

- Significant prevention of Crohn’s recurrence or need for surgery when IFX continued > 1yr
- Discontinuation of infliximab in high risk post-op patients resulted in endoscopic recurrence, additional surgery

Adalimumab is More Effective Than Thiopurines in Preventing Early Recurrence

De Cruz, et al. 2015. Aliment Pharm Ther

Long-term Prevention of Adult Post-Op Recurrence with Enteral Nutrition


Traditional Adult CD Post-Operative Algorithm

### Post – Operative Issues in Pediatric Crohn's Disease: Summary
- Patients with Crohn's disease have high recurrence rates post-operatively
- Risk factors include extensive/severe disease, colonic disease, early age at disease onset, smoking
- Choice of post-operative prophylaxis essential, with anti-TNF agents more effective versus thiopurines, 5-ASA, antibiotics, and budesonide
- Surveillance is key, with ileocolonoscopy the gold standard

### Post – Operative Care in Pediatric Crohn's Disease: Recommendations
- All patients with Crohn's disease who have undergone resection should undergo a post-operatively colonoscopy within 6 months after surgery
- Consider placing/continuing patients at high risk (prior IBD-related surgeries; presence of colonic disease; penetrating/perforating disease, tobacco usage) on anti-TNF therapy after resection

### Post – Operative Issues in Pediatric Crohn's Disease: Issues to Consider
- How do we define high risk in the pediatric population?
  - Additional factors: VEOIBD; growth failure
- Should all pediatric patients be started on medication prophylaxis post-operatively?
- Can we change the natural history of the disease?
  - Utilization of anti-TNF agents and other biologics
  - Role of enteral therapy and diet
  - Timing of surgery
What Do We Need to Do Next?

- Leverage/collect data from ongoing collaborative studies
- Develop best practice pathways for post-op management for pediatric Crohn’s disease patients

Prevent post-operative recurrence!