Management of Postoperative Crohn’s Disease

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Despite IBD medications

60%-75% of Crohn’s disease patients require intestinal resection at some point in their lifetime,

and surgery is not a cure....
The Natural Course of postop CD

Recurrence is clinically silent initially

Histologic
Within 1 week

Endoscopic
70-90% by 1 yr

Radiologic
Tissue damage

Clinical
30% 3 yr
60% 5 yr

Surgical
50% by 5 yrs

Surgery

Endoscopic Recurrence Score

**Endoscopic Remission**
- **i0**: no lesions
- **i1**: ≤ 5 aphthous lesions

**Endoscopic Recurrence**
- **i2**: > 5 aphthous lesions with normal intervening mucosa
- **i3**: diffuse aphthous ileitis with diffusely inflamed mucosa
- **i4**: diffuse inflammation with large ulcers, nodules, and/or narrowing

>70% of Pts Have i2,3,4 Recurrence 1 Year after Surgery – Rutgeerts et al Gastro 1990

i0 and i1 remission
-low likelihood of progression

i2, i3, i4 recurrence
-Likely progression to another surgery
Algorithm for post-op CD management

More Questions than Answers

5-ASA?  Antibiotics?  Steroids?  6MP/AZA?

What about anti-TNFs/Biologics?

How should we follow these patients?

When to Colonosocope?

Are there predictors of disease recurrence?
What would you do postop?

- 59 yo male, 30 yr h/o CD only rx prednisone 25 yr ago – 10 cm stricture
- 32 yo female, 5 yr h/o CD only rx with occ pred and entocort – 15 cm inflam stenosis
- 42 yo female, 1 yr h/o CD only rx with pred and AZA – multiple abd fistula/phlegmon
- 27 yo male, 3 yr h/o CD rx’d AZA 2.5mg/kg/d, 6TG 320 – 15cm inflam stenosis
Medications for Preventing Postoperative Crohn’s Disease
# Summary of Postop RCTs

5ASA, Nitroimidazoles, AZA/6MP

<table>
<thead>
<tr>
<th>Postop Prevention RCTs</th>
<th>Clinical Recurrence</th>
<th>Endoscopic recurrence</th>
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<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>
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Regueiro M. *Inflammatory Bowel Diseases*. 2009
Limitation of the studies: the best we can expect are endoscopic recurrence rates of ~45%.

This means that despite postop meds, nearly half of CD pts will have also have a clinical recurrence and require future surgery.
What about Postop antiTNF?

Recently: A lot of discussion and focus on postop antiTNFs – is it worth the hype?
RCT: Infliximab Prevents Crohn’s Disease Recurrence after Ileal Resection

Regueiro M, Schraut W, Baidoo L, Kip KE, Sepulveda AR, Pesci M, Harrison J, Plevy SE.

• Randomized, two-armed, double-blind, placebo-controlled trial

• Sample size power calculation
  – Assuming 80.0% recurrence in placebo group, 20.7% recurrence in infliximab group
  
  24 total pts needed (2-sided type I error rate of 0.05)

• 24 patients randomly assigned to infliximab 5mg/kg or placebo within 4 weeks of surgery (0, 2, 6, and every 8 weeks for one year)
Endoscopic Recurrence Score

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Endoscopic Recurrence Reduced in Infliximab Treated Patients

Endoscopic Recurrence defined as endoscopic scores of i2, i3, or i4.
Endoscopic Grade by Individual Scores

% patients

Infliximab (n=11)  
Placebo (n=13)

Endoscopic grade 1 year after surgery

0 1 2 3 4
...but this is only one small study, should we really initiate postop antiTNF based on this?

Are there other postop antiTNF studies?
# Endoscopic Recurrence: antiTNF

- **antiTNF** started within 4 wks of surgery

<table>
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<tr>
<th>Study</th>
<th>antiTNF</th>
<th>Placebo/5ASA</th>
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<tr>
<td>Sorrentino¹ (2 yr) (MTX/INF v 5ASA)</td>
<td>0%</td>
<td>100%</td>
</tr>
<tr>
<td>Regueiro² (INF vs PBO RCT 1 yr)</td>
<td>9%</td>
<td>85%</td>
</tr>
<tr>
<td>Yoshida³ (INF vs PBO Open 1 yr)</td>
<td>21%</td>
<td>81%</td>
</tr>
<tr>
<td>Fernandez-Blanco ⁴ (ADA 1 yr)</td>
<td>10%</td>
<td>N/A</td>
</tr>
<tr>
<td>Mantzaris⁵ (ADA 6mos)</td>
<td>0%</td>
<td>N/A</td>
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2. Regueiro et al. Gastroenterol 2009
4. Fernandez-Blanco et al. Gastroenterol 2010A
5. Mantzaris et al. Gastroenterol 2011A
But what about cost... is postop anti-TNF worth it?

Two Studies:


Doherty GA, et al. Inflamm Bowel Dis 2011; epub
Upfront INF: most effective, most expensive (beyond 1 yr INF may be more cost effective)
Infliximab: most effective, most expensive
AZA most cost effective (by IECR)
Is post-op antiTNF safe?

Postoperative infliximab is not associated with an increase in adverse events in Crohn's disease.

No Difference in Adverse Events between Placebo and Infliximab (started within 4 wks of surgery)
Why not delay therapy until there is endoscopic recurrence?

Insights into mucosal healing in Crohn’s ds – Med Tx trials vs postop prevention vs rx of postop recurrence.
<table>
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<th><strong>Endoscopic Remission (i0,i1)</strong></th>
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<td>Yamamoto¹ (after 6 mos- INF)</td>
<td>38%</td>
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<td>Regueiro² (after 1 yr- INF)</td>
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<td>Mantzaris (within 1 yr ADA)³</td>
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<tr>
<td>Sorrentino (after 6 mos- INF)⁸</td>
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6. Colombel Am J Gastroenterol 2008A  
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<th>Endoscopic Remission (i0,i1)</th>
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<td>44%</td>
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<td><strong>ACCENT 1⁵ (INF)</strong></td>
<td>18% (5mg/k)</td>
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Anti-TNF therapy is most effective in early disease.

Disease duration (years)

Remission at 1 year (%) 0 20 40 60 80 0 1 2 3 4 5 6 7 8 9 10

SUTD  REACH  SONIC  CHARM  ACCENT I

If Healing the Mucosa is Important – The Mucosal Healing Awards

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<th>Medal</th>
<th>Timing of antiTNF</th>
<th>Endoscopic Remission (mucosal healing)</th>
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<td>Gold</td>
<td>Immediately after Surgery</td>
<td>90% - 100%</td>
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<td>Silver</td>
<td>Delay until endosc recurrence</td>
<td>38% - 61%</td>
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<tr>
<td>Bronze</td>
<td>Delay until CD dx (2yrs to many yrs)</td>
<td>11% – 44%</td>
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My Approach – Almost All of my patients start a med after surgery

...but NOT necessarily an antiTNF
- take into account Risk Factors for Recurrence
Risk Factors Associated with Postoperative CD Recurrence

• Relative Risk Factors
  – Early age of surgery (<30)
  – Short time to first surgery
  – Ileocolonic disease

• Active cigarette smoking

• Progressed to surgery despite immunomodulators

• Penetrating (fistulizing) disease

• History of prior resection
Risk of Post-Op Recurrence

Low
- No Meds
  - Colonoscopy 6-12 months post-op
    - No Recurrence
      - Colonoscopy every 1-3 yrs
    - Recurrence
      - Immunomodulator or anti-TNF

Moderate
- 6MP or AZA ± metronidazole
  - Colonoscopy 6-12 months post-op
    - No Recurrence
      - Colonoscopy every 1-3 yrs
    - Recurrence
      - Immunomodulator or anti-TNF
      - Colonoscopy every 1-3 yrs
      - ↑ anti-TNF or Δ biologics

High
- Anti-TNF
  - Colonoscopy 6-12 months post-op
    - No Recurrence
      - Colonoscopy every 1-3 yrs
    - Recurrence
      - ↑ anti-TNF or Δ biologics

Penetrating disease, > 2 surgeries

Long-standing CD, 1st surgery, short stricture
<10 yrs CD, long stricture or inflammatory CD
Penetrating disease, > 2 surgeries
What I would do for these pts postop

- 59 yo male, 30 yr h/o CD only rx with pred yrs ago – 10 cm stricture
- No postop meds and colonoscopy 6 months postop
- 32 yo female, 5 yr h/o CD only rx with occ pred and entocort – 15 cm inflam stenosis
- Azathioprine 2.5 mg/kg/day and rescope 6 mos postop
- 42 yo female, 1 yr h/o CD only AZA – multiple abd fistula/phlegmon
- antiTNF and AZA and rescope 6 months
- 27 yo male, 3 yr h/o CD rx’d AZA 2.5mg/kg/d, 6TG 320 – 15cm inflam stenosis
- Add antiTNF and rescope at 6 months
Future Direction

- Post-op CD provides a unique model for natural course of disease study
  - “Wipe slate clean” and explore the genetics, immunology, and microbiome
- Extrapolate to undiagnosed or newly dx’d: clinically silent until complication develops
- Potential to evaluate true top-down Rx with induction of very deep remission
- International postop trial (PREVENT) underway (USA PI- Regueiro, Europe PI- Rutgeerts)
- Treatment initiated in response to endoscopic recurrence vs. prophylaxis?
Acknowledgements and thank you

Leonard Baidoo, MD
Arthur “Tripp” Barrie, MD, PhD
David Binion, MD
Richard Duerr, MD
Sandra El Hachem, MD
Jennifer Holder-Murray, MD
David Medich, MD
Janet Harrison, MD
Miguel Regueiro, MD
Wolfgang Schraut, MD, PhD
Marc Schwartz, MD
Jason Swoger, MD, MPH
Andrew Watson, MD
James Celebrezze, MD

Beth Rothert RN, BSN
Linda Kontur RN
Jennifer Rosenberry, RN
Diane Sabilla, RN
Joann Fultz
Kristy Rosenberry, RN
Paula Conwell
Linda Nelson
Katie Weyant, CRNP
Elena Infante
Amy Kulus, RN
Annie Kudlac, RN
Karen Beck