The Management of Complicated and Refractory Crohn's Disease

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Complex Crohn’s Disease: Medical

- **What is it?**
  - “I know it when I see it…”
  - Patients who are:
    - Steroid dependent
    - Refractory or intolerant to standard therapies
    - Have extensive disease or disease outside of GI tract (lung, skin)
    - Have had multiple surgeries in past (>1) and/or at risk of short bowel
    - At high risk of recurrence after resection (short disease duration, smokers, etc)
    - Significant co-morbid medical conditions such as PSC, HBV, Pregnancy, cancer, HIV, etc
  - Patients with strictures, fistulas or abscesses
Complex / Refractory Crohn’s Disease : Medical

• What is it?
  – “I know it when I see it…”
  – Patients who are:
    • Steroid dependent
    • Refractory or intolerant to standard therapies
    • Have Intra-abdominal abscess
    • Have had multiple surgeries in past (>1) and /or at risk of short bowel
    • At high risk of recurrence after resection (short disease duration, smokers, etc)
    • Significant co-morbid medical conditions such as PSC, HBV, Pregnancy, cancer, HIV, etc

  – Patients with strictures, fistulas or abscesses
Patient #1
45 yo Male with Intra-Abdominal Abscess

- 45 yo male presents with history ileocolic resection 10 years before. No maintenance medication post-op.
- Presents now with 3 month history of abdominal pain after eating. 20# wt loss during this time.
- FH: positive for Crohn’s
- PE: Some RLQ tenderness and possible fullness...
- Colonoscopy and Imaging show.....
Severe right-sided colitis  Stricture at anasomosis
Initial Management

- Patient admitted for IV antibiotics
  - Use ones that have Gram negative and anaerobic coverage

- Abscess needs to be drained especially if > 3 cm. (poor penetration of antibiotics)
  - Perc drainage successful in 77% of the time in largest study. 1

1-Golfieri et al. Tech Coloproct 2006
Drainage is achieved.... Now what?

• Continue antibiotics. Wait for patient to be afebrile for 48-72 hrs and reimage.
  – If wbc remains elevated and/or fever persists re-interrogate the drain
  – Consider scope (if one has not been done recently to help guide treatment)

• Decisions to make at this point?
  – TPN vs. resuming diet
  – Early Surgery (with diverting stoma) vs. trial of medical treatment
TPN vs. Diet

- Retrospective report of the use of short-term TPN in pts with penetrating disease
  - 78 pts given pre-op nutritional treatment (median 23 days) and weaned off steroids, immunosuppressives

- Need for stoma was only 8%
  - major complications 5%

1- Zerbib, APT 2010
Early Surgery vs. Attempt at Medical Treatment

• 1\textsuperscript{st} determine if abscess related to stricture /fistula and if stricture is fibrotic vs. inflammatory
• If stricture is present (especially if fibrotic) treatment is largely Surgical
• No prospective trial to look specifically at internal fistulas.
  – In general, internal fistulas less likely to respond to Anti-TNF treatment.

1- Parsi, Am J Gastro 2004
In general, if fistula present chance of non-surgical success is low.

- Sahai et al. found in retrospective study of 27 pts with intra-abd abscess that associated fistulas was associated with need for surgery within 30 days despite drainage\(^1\)

- Golfieri et al, found in a study of 70 patients that all failures of perc drainage were associated with a fistula to the bowel\(^2\)

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\(^1\) Sahai et al. Am J Gastro 1997
\(^2\) Golfieri et al. Tech Coloproct 2006
Early Surgery vs. Attempt at Medical Treatment

If no stricture present or stricture is inflammatory can consider medical treatment.

**Pros:**
- Largest study from Mayo Clinic shows equivalent outcomes
- May delay or prevent surgery
- Decrease length of stay

**Cons:**
- Use of anti-TNF may be associated with increased post-op complications
- May delay inevitable
- May “handicap” anti-TNF agents as disease is at an irreversible stage
- Patients failing aggressive therapy unlikely to respond
Early Surgery vs. Attempt at Medical Treatment

• How about the rest of the patients? Can we treat medically?
  – Retrospective review of 95 patients from Mayo Clinic (1999-2006) (55 had perc drainage)\(^1\)
  – 5 year recurrence was 31% (med) vs. 20% (surg) \(p=0.25\)
  – Median LOS was less for med treated pts 15.5 days vs. 5 days \((p<0.001)\)

Anti-TNF Associated with an Increased Risk of Post-Operative Infection

• 325 surgeries at UMB in 211 CD patients
• 150 had anti-TNF ≤ 8 weeks before surgery
• Anti-TNF group had higher rates of surgical site (32% v. 22%) and infectious complications (36% v. 25%) compared to controls
• After adjustment for confounding,
  - OR 2.84 (1.1-3.1) for surgical site
  - OR 2.02 (1.2-3.4) for infectious complications

Summary

• Initial treatment should focus on draining abscess and treating infection
• Risk stratify based on size of abscess, presence of fistulas, strictures and nature of the process (inflammatory vs. fibrotic)
• Use bowel rest and TPN to help bridge to definitive treatment
• Medical treatment reserved for those with a primary inflammatory process (ie those with higher chance of success)
Patient # 2
28 yo with Refractory Disease

• 28 yo male comes to office for 2nd opinion with 6 year history of Crohn’s ileocolitis.

• He has abdominal pain and diarrhea (10-12x / day) with urgency and 10# wt loss. Despite being on infliximab for last 3 years. Now on 10 mg/kg q5 weeks
  – Had initial response to IFX but requiring more over time

• He is also on 2.5 mg /kg/day of azathioprine

• He is a non-smoker

• No previous h/o surgery
28 yo with Refractory Disease (Part B)

- On exam he looks thin, afebrile. Tender to palpation in RLQ. HR is 100
  - Labs: WBC= 10k, Hgb 11, Plt 600, CRP 20
  - Stool studies negative
28 yo with Refractory Disease (Part C)

• What is your approach to this patient?

  – Rule out other causes for symptoms
    • Infection
    • Bile salt diarrhea
    • Stricture / EC fistula
    • IBS

  – Make sure there is active luminal disease

  – Make sure current therapy is maximized
    • If currents meds optimized then consider alternative treatment options (another TNF, meds with alternative mechanism of action)
Increasing Impact of *Clostridium difficile* on IBD

Increasing Proportion of Clostridium difficile Patients with IBD

Optimizing Meds: 6-TG Levels and Clinical Response

Dubinsky et al, *Gastroenterology* 2000
Optimizing Meds: Infliximab Levels

By Trough IFX Concentration at Week 26

Primary Endpoint

Patients (%)

IFX Concentration (mg/ml) at Week 30

19/32
57
73
74
72

Optimizing Meds: Measurement of IFX Levels and ATIs
Test results impacted treatment in 73% of patients

<table>
<thead>
<tr>
<th>IFX Status</th>
<th>Treatment</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtherapeutic IFX</td>
<td>Dose escalation</td>
<td>Complete or partial response - 86%</td>
</tr>
<tr>
<td>Subtherapeutic IFX</td>
<td>Switch anti-TNF</td>
<td>Response - 33%</td>
</tr>
<tr>
<td>Therapeutic IFX</td>
<td></td>
<td>No evidence of active inflammation in 62% of the patients</td>
</tr>
<tr>
<td>ATIs + patients</td>
<td>Switch anti-TNF</td>
<td>Response - 92%</td>
</tr>
<tr>
<td>ATIs + patients</td>
<td>Dose escalation</td>
<td>Response - 17%</td>
</tr>
</tbody>
</table>

“Increasing the infliximab dose in patients who have HACAs is ineffective, whereas in patients with subtherapeutic infliximab concentrations, this strategy may be a good alternative to changing to another anti-TNF agent.”

• Colonoscopy shows ulcerations, friability, and muco-purulence involving the whole colon. There is also active ileitis.

• **CTE:** Active ileitis in distal 8 cm without stricture

• **Lab testing**
  – CRP 20
  – 6-TG 300, 6-mmp 5800
  – IFX trough < 1mcg / ml
  – ATI 29 U/ml
Response and Remission Rates for PRECiSE 4:

**PRECiSE 4:**

Origin: PRECiSE 2 CZP arm

- **HBI Response**
  - Week 4: 28/49 (57%)
  - Week 24: 21/49 (43%)
  - Week 52: 19/49 (39%)

- **HBI Remission**
  - Week 4: 14/49 (29%)
  - Week 24: 17/49 (35%)
  - Week 52: 17/49 (35%)

Time in P4

Serious and sometimes fatal side effects have been reported with CIMZIA, including tuberculosis and other serious infections. Please see important safety information on slide 41 and accompanying prescribing information.
Micro-Reinduction with Adalimumab for loss of response

N=87
Pts given 80 mg x 2 doses

Ligler, Schwartz et al. Advances 2011
Switching to Another TNF

Adalimumab for IFX Failures at Wk 4

Certolizumab pegol for IFX Failures at Wk 6 (open label)

2- Sandborn, Clin Gastro Hep 2010
Alternate Scenarios: Primary Non-responders

- Primary Non-Responders:
  - Switch to 2\textsuperscript{nd} Anti-TNF: Subsets of 2 studies show remission rates of 18-36\% at ~ week 20 with adalimumab\textsuperscript{1-2}
  - Add azathioprine or methotrexate if not already on
  - Switch to Natalizumab
  - Surgery

\textsuperscript{1}\textsuperscript{Lofberg, J Crohn’s Colitis 2012}
\textsuperscript{2}\textsuperscript{Pannaccione, Can J Gastro 2011}
Induction of Remission with Natalizumab: ENCORE* Trial

* All randomized patients (secondary end point).

** $P \leq 0.001$ vs placebo.

~ 99,600 pts have received natalizumab
264 cases of progressive multifocal leukoencephalopathy (PML)
  Only 2 case with CD (1 in clinical trial, 1 post-trial after 35 doses)
All PML cases > 8 months of natalizumab therapy
Rate approximately 2.36 per 1000 treated patients
Summary

• Rule out other causes of for symptoms (infections, etc)

• Document active disease

• For secondary non-responders check levels if available and optimize meds

• For patients who are primary non-responders consider adding anti-metabolite, trying a 2nd anti-TNF, or switching to natalizumab
Thank you for your time!