Perianal Crohn’s Disease: Current Treatment Approach

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New Diagnosis Patient

• 30 yo female presents with 3-month history of perianal pain and drainage. No change in stool habits.
  • Treated empirically with metronidazole, with only minimal improvement
  • Colonoscopy with TI intubation and bx are normal
• FH: Positive for Crohn’s
• PE: Normal except rectal exam which showed…
Patient asks you if she could have Crohn's disease and does this happen frequently to CD patients or is she just the unlucky one?

She also wants to know what to expect over her lifetime if this is from Crohn's disease?
Cumulative Incidence of Crohn’s Fistulas

- Any fistula: 100%
- Perianal fistula: 60%

Frequency of Perianal Fistulas According to the Anatomic Location of Bowel Involvement

- Colon only: 41%
- Small intestine only: 12%
- Combined ileocolic: 15%
- Rectum only: 92%

**Schwartz et al, Gastro 2002**

**Hellers et al, Gut 1980**
Anatomy

Anatomic Relationships in the Pelvis

- Rectal columns
- Dentate line
- Intersphincteric space
- Internal anal sphincter
- External anal sphincter
Park’s Classification of Perianal Fistulas

A: Superficial
B: Intersphincteric
C: Trans-sphincteric
D: Suprasphincteric
E: Extrasphincteric
Severe PCD Patient

- 50 yo male presents with long history of perianal pain and drainage. Recently started passing air and stool when he urinates. No change in stool habits.
  - Treated in past with antibiotics, immunomodulators and infliximab
  - Several attempts at surgical treatment without success
  - Colonoscopy with TI intubation and biopsies are normal
- FH: positive for Crohn's
- PE: Normal except rectal exam which showed…
What is the best approach to this problem?

What are his treatment options (medical and surgical)?
Why is a precise evaluation important?

The key to successful management is to establish adequate drainage of all abscesses and to control fistula healing. An imaging modality should provide a virtual road map for this purpose.

What Happens When Fistulas are Missed at Time of EUA?

- 52% of patients needed repeat surgery in cases where surgery and MRI disagreed
- Fistula recurrence was always at the site predicted by MRI

Buchanan et al, Lancet 2002
Study Results

• A prospective, triple blinded study compared EUS, MRI and EUA in 32 patients with suspect perianal Crohn’s disease.\(^1\)

• All three methods showed excellent accuracy in assessing these patients
  • EUS – 91% (95% CI 75% - 98%)
  • EUA – 91% (95% CI 75% - 98%)
  • MRI – 87% (95% CI 69% - 96%)

• Combining either of the imaging modalities with EUA increased the accuracy to 100%.

\(^1\) Schwartz et al., Gastro 2001

Options for Therapy
**Does Controlling Fistula Healing Make a Difference?**

Response to Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab Only</td>
<td>83</td>
</tr>
<tr>
<td>EUA Before Infliximab</td>
<td>100</td>
</tr>
</tbody>
</table>

Fistula Recurrence

<table>
<thead>
<tr>
<th>Treatment</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab Only</td>
<td>79</td>
</tr>
<tr>
<td>EUA Before Infliximab</td>
<td>44</td>
</tr>
</tbody>
</table>

*(Requeiro et al. IBD 2003)*

**Comparison of Healthcare Utilization in Patients with CD Perianal Fistulas Treated with Biologics with or without Setons**

**Figure 2.** Mean Number of All-Cause and Fistula-Related Hospitalizations at Baseline and Follow-Up for NSBB and SBB Cohorts

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Follow-Up</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-Cause</td>
<td>0.54</td>
<td>0.21</td>
<td>0.021</td>
</tr>
<tr>
<td>Fistula-Related</td>
<td>0.17</td>
<td>0.18</td>
<td>0.33</td>
</tr>
</tbody>
</table>

**Figure 3.** Mean Total Costs of All-Cause and Fistula-Related Hospitalizations During the Follow-Up Period for NSBB and SBB Cohorts

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Follow-Up</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-Cause</td>
<td>4755</td>
<td>3618</td>
<td>0.0004</td>
</tr>
<tr>
<td>Fistula-Related</td>
<td>1661</td>
<td>1270</td>
<td>0.0017</td>
</tr>
</tbody>
</table>

*(Schwartz, et al. ECCO 2013)*
With & Without Seton

Surgical Treatment
Abscesses

Incision and Drainage

Incision
Fistulas

Perianal Crohn’s Disease – Surgical Treatment Options

- Fistulotomy
- Setons
- Advancement Flap
- Fibrin Glue / Fistula Plug
- Diversion / Proctectomy
**Medical Therapies**

- Antibiotics (metronidazole, ciprofloxacin)
- Immunosuppressives
  - Azathioprine
  - 6-mercaptopurine
  - Cyclosporine
  - Tacrolimus
- Biologic Agents
  - Infliximab
  - Adalimumab
  - Certolizumab

**Antibiotics**
Antibiotics – Fistula Response

Fistula Response at 10 weeks

<table>
<thead>
<tr>
<th></th>
<th>%</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cipro</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>Flagyl</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Placebo</td>
<td>13</td>
<td>8</td>
</tr>
</tbody>
</table>

\[ p=0.43 \]


All patients received adalimumab 160 mg at wk 0, 80 mg at wk 2, and then 40 mg qow. Patients were then randomized to Ciprofloxacin 500 mg bid or placebo.

Antibiotics Improve Fistula healing in Combination with Anti-TNF Therapy

Fistula Response at Week 12

<table>
<thead>
<tr>
<th></th>
<th>Percent</th>
<th>N=76</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA + PIC</td>
<td>47%</td>
<td></td>
</tr>
<tr>
<td>ADA + Cpr</td>
<td>71%</td>
<td></td>
</tr>
</tbody>
</table>
Azathioprine / 6 - MP

• The 5 controlled trials were summarized in a meta-analysis\(^1\)
  – 22 / 41 (54%) of patients who received AZA / 6-MP responded vs. 6 / 29 (21%) who received placebo.
  – Pooled odds ratio was 4.44 in favor of fistula healing

\(^1\) Pearson et al. *Ann Intern Med*. 1995
Cyclosporine & Tacrolimus (FK-506)


The double blinded placebo study of 48 patients randomized to receive 0.20mg/kg/day for 10 weeks. Primary endpoint was improvement defined as closure of ≥ 50% fistulas and maintenance of closure for ≥ 4 weeks.

Week 10 Results

<table>
<thead>
<tr>
<th></th>
<th>Tacrolimus</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>43</td>
<td>8</td>
</tr>
<tr>
<td>p</td>
<td>0.004</td>
<td></td>
</tr>
</tbody>
</table>

Only 10% had closure of all fistulas.

Anti-TNF α Antibody

Infliximab for Crohn’s Perianal Fistulas

Primary endpoint: > 50% reduction in open fistulas

Initial Fistula Response to Infliximab

- 10mg/kg: 56% (p = 0.041)
- 5mg/kg: 68% (p < 0.001)
- Placebo: 26%

N=94

Present et al., NEJM 1999
David A. Schwartz, MD, FACG

Anti-TNF Maintenance Therapy for CD Related Fistulas

- Infliximab
- Adalimumab
- Certolizumab

1- Sands et al., NEJM 2004
2- Colombel, Gut 2009
3- Schreiber S, et al. APT, 2011

How Can We Improve Outcomes for Patients with Crohn’s Perianal Fistulas?
• 45 yo female presents with 5-year history of Crohn’s disease. Has had perianal fistula that has drained intermittently for 4 years.

• Presents with 2-month history of perianal pain and drainage.
  ▪ Currently on infliximab monotherapy
  ▪ Colonoscopy with TI intubation and biopsies shows active proctitis

• PE: Normal except rectal exam which showed…

She asks what can be done to get increase her chances of healing and get her fistula to stop draining for good?
**The Use of Imaging to Guide Therapy**

MRI to Guide Therapy with Infliximab or Adalimumab

Medical therapy was increased if no or partial response seen on MRI

Ng et al. Am J Gastro 2009
MRI to Monitor Therapy

- 41 pts, serial MRIs, 3 years’ follow-up

- Patients with early response (6 weeks) had 5x ↑ rate of remission (p=0.004)

- All patients (7) who continued the TNF after achieved MRI healing maintained remission

- Improvement plateaued at 1 year

Tozer, et al. IBD 2012.

Utilizing EUS to Improve Fistula Healing

Schwartz et al, IBD 2005
2 Randomized Prospective Studies Looking at EUS to Improve Outcomes

Initial Prospective Pilot Study

Recent Follow-up Prospective Study

Conclusion

1. History and physical exam
2. Endoscopy to assess activity of Crohn’s disease
3. Imaging study (EUS or MRI) to delineate perianal disease process
4. Exam under anesthesia (EUA)

Simple fistula without rectal inflammation
- Antibiotics and AZA/6-MP
- Consider anti-TNF

Simple fistula with rectal inflammation
- Antibiotics, AZA/6-MP & Anti-TNF (consider monitoring healing with repeat imaging study)

Complex fistula
- Seton placement
- Antibiotics, AZA/6-MP, & Anti-TNF (consider monitoring healing with repeat imaging study)

Treatment Failure
- Fistulotomy
- Consider fibrin glue, fistula plug or endorectal advancement flap
- If 1 or 2 fails, treat as complex fistulizing process

Treatment Success
- Continue maintenance AZA/6-MP & Anti-TNF

Treatment Failure
- Treat as complex fistulizing process

Treatment Success
- Continue maintenance AZA/6-MP & Anti-TNF
- Consider Tacrolimus in selected pts

1. Remove seton
2. Continue maintenance AZA 6-MP & Anti-TNF