Complex Perianal Crohn’s

After EUA and seton placement

Courtesy of David A. Schwartz, M.D.

Long-Term Evolution of Disease Behavior in Crohn’s Disease

Cosnes J et al. Inflamm Bowel Dis. 2002;8:244.
Cumulative Incidence of Fistulas in an Inception Cohort of Crohn’s Disease in Olmsted County, Minnesota (n=169)

![Graph showing cumulative incidence of fistulas over time from diagnosis.]

- **Any fistula**:
  - Cumulative incidence over time.
  - Maximum incidence at 20 years.

- **Perianal fistula**:
  - Cumulative incidence over time.
  - Maximum incidence at 20 years.

**Type of Fistula (n=88)**

- **Perianal** 54%
- **Recto-vaginal** 9%
- **Entero-enteric** 24%
- **Other** 13%

Schwartz DA et al. Gastroenterology 2002;122:875
Number of Any Fistula Episodes (n=88)

<table>
<thead>
<tr>
<th>Patients (no.)</th>
<th>1 fistula episode</th>
<th>2 fistula episodes</th>
<th>&gt;2 fistula episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>39</td>
<td>13</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

Schwartz DA et al. Gastroenterology 2002;122:875

Number of Perianal Fistula Episodes (n=48)

<table>
<thead>
<tr>
<th>Patients (no.)</th>
<th>1 fistula episode</th>
<th>2 fistula episodes</th>
<th>&gt;2 fistula episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>8</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Schwartz DA et al. Gastroenterology 2002;122:875
Behavior at Crohn’s Disease Diagnosis (Montreal): Olmsted County, 1970 - 2004

- B1: 81.4% (n=249)
- B2: 4.6% (n=14)
- B3: 14% (n=43)

Cumulative Probability of Change in Crohn’s Disease Behavior Among B1 Disease at Diagnosis (n = 249)
Cumulative Probability of Change in Crohn’s Disease Behavior From Diagnosis: Olmsted County, 1970-2004 (n = 306)

Bowel resection associated with development of complication

25.4%

74.6%
CD – Clinical Patterns

Fistulization

- Enterocutaneous
  Drainage via scar
- Enterovesical
  Recurrent UTIs, pneumaturia
- Perianal
  Pain, drainage
- Rectovaginal
  Drainage: Feces and/or air
- Psoas abscess signs: Back, hip, and thigh pain; limp

Perianal Fistulae and Abscess
Frequency of Perianal Fistulas According to the Anatomic Location of Bowel Involvement

- Colon only (without rectal involvement): 41%
- Rectum only: 92%
- Small intestine only: 12%
- Combined ileocolic involvement: 15%


Simple vs. Complex Fistula

Antibiotics

- Metronidazole: Typical dose is 250 - 500mg po tid /qid, improvement seen after 6-8 weeks.
  - All studies are open label.
  - Largest study by Bernstein et al\(^1\)
    - 21 patients studied, healing seen in 83%
  - Other studies found healing rate of between 34 -50\(^%\) 2-5

5. Brandt LJ et al. Gastroenterology 1982;83:583
Antibiotics (Metronidazole)

- Fistulas re-occur once medicine is stopped
- Adverse events include metallic taste, glossitis, nausea and a distal peripheral sensory neuropathy

Antibiotics (Ciprofloxacin)

- Typical dose is 500 – 750 mg po bid, improvement seen after 6-8 weeks
- Only study was an open label study of 8 patients published in abstract form
  - 4 patients had persistent drainage and “several cases” required surgical excision.

1. Turunen et al. Gastro 1993;104:A793
Azathioprine / 6 - MP

- Five controlled trials were summarized in a meta-analysis
  - 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


Infliximab in Patients With Fistulizing CD


Infliximab in Active Crohn’s Disease

n = 94

Fistula Response

% Patients with Closure of ≥ 50% Draining Fistulas at ≥ 2 Consecutive Visits

- Placebo: 26%
- 5 mg/kg: 56%
- 10 mg/kg: 68%**

**P<0.02

Infliximab: Complete Fistula Closure

Complete response defined as all fistulae closed for 2 consecutive visits (at least 1 mo)


Infliximab Maintenance Therapy for Fistulizing CD: ACCENT II Trial
Median Time to Loss of Response Through Week 54

Patients with a Response at Randomization (%)

ACCENT II: Fistula Response, Week 54
Among Responders

Among Responders


ACCENT II: Time to Loss of Response
Among Responders

% Patients Who Maintained Response

Weeks

Infliximab Therapy: Approved* Indications in CD

- Reducing signs and symptoms, and inducing and maintaining clinical remission, in patients with moderately to severely active Crohn’s who have had an inadequate response to conventional therapy
- Reducing number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in patients with fistulizing Crohn’s disease

*FDA-approved indications as of July 2004

Adalimumab: CHARM Trial
Complete Healing of Draining Fistulas at Last 2 Visits, Total Randomized Patients

Healing = no draining fistulas for at least their last 2 post-baseline evaluations
Patients with fistulas: draining fistulas at both screening and baseline

<table>
<thead>
<tr>
<th></th>
<th>PBO</th>
<th>40 mg EOW</th>
<th>40 mg weekly</th>
<th>both ADA groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients Completely Healed (%)</td>
<td>6/47</td>
<td>11/30</td>
<td>12/40</td>
<td>23/70</td>
</tr>
</tbody>
</table>

p = 0.016
Adalimumab Maintenance of Healing of Draining Fistulas: Weeks 26 and 56; All Randomized Patients

![Graph showing patients healed with Adalimumab maintenance therapy at Weeks 26 and 56.](image)

- **PBO**
- **40 mg EOW**
- **40 mg weekly**
- **both ADA groups**

<table>
<thead>
<tr>
<th>Week 26</th>
<th>Week 26 and 56</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO</td>
<td>6/47</td>
</tr>
<tr>
<td>40 mg EOW</td>
<td>33/1030</td>
</tr>
<tr>
<td>40 mg weekly</td>
<td>28/1140</td>
</tr>
<tr>
<td>both ADA groups</td>
<td>30/2170</td>
</tr>
</tbody>
</table>

Healing = no draining fistulas

Patients with fistulas: draining fistulas at both screening and baseline

Schwartz DA et al. Am J Gastroenterol 2006 Abstract

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**Cyclosporine**

- 10 studies published using CYA to treat fistulas (a total of 64 patients) 1-10
  - Overall initial response rate is 83%, improvement seen by 2 weeks.
  - Response is not durable

1. Fukushima, Gastro Jpn 1989
2. Lichtiger, Mt Sinai J of Med 1990
3. Hanauer, Am J Gastro 1993
5. Markowitz, Gastro 1990
Efficacy of Cyclosporine for Refractory Fistula of Crohn’s disease

Conclusions

- Intravenous cyclosporine is effective in treating fistula
  response 24/28 = 86%
  closure 17/28 = 61%
  mean response time = 4–7 days
- Relapse occurs frequently on oral cyclosporine
  10/24 = 42%
- Toxicity potential is uncertain
- Requires long term maintenance with 6MP/AZA and/or combinations of medications with avoidance of steroids

Tacrolimus (FK-506)

- There have been 3 case studies and 1 controlled trial where fistula closure was included in the results.1-4
- Similar mechanism of action as Cyclosporine but is readily absorbed even from diseased small intestinal mucosa

 Tacrolimus for Crohn’s Disease Fistulas


Abscesses
Other Surgical Options for Fistulas

- Cutting Seton
- Diverting Ileostomy
  - Does not alter course of disease
  - Only a small percentage get restoration of the intestinal continuity
  - 6 / 29 (21%)\(^1\)
  - 2 / 21 (9.5%)\(^2\)

Proctocolectomy

- Despite intensive therapy around 10 -15% of patients with perianal Crohn’s disease will come to proctectomy.
- Rate of proctectomy at Mayo was 8.4% at 10 yrs and 17.5% at 20 years

1. Wolff, Diseases Colon Rectum 1985

How Can We Improve Outcomes for Patients with Crohn’s Perianal Fistulas?
Preoperative Imaging for Perianal Crohn’s: Rationale

- Examination under anesthesia (EUA) with drainage of abscesses and seton placement may improve response to medical therapy of fistulizing perianal disease
- Imaging prior to EUA may identify occult abscesses and high fistulas; may reduce missed abscesses or inadvertent sphincterotomies of high fistulas

Reguiero et al. Inflamm Bowel Dis 2003;9:98

Does Controlling Fistula Healing Make a Difference?

![Graph showing response to treatment and fistula recurrence comparing Infliximab only and EUA before Infliximab.](Image)

N = 32

Response to Treatment

- Infliximab only: 83%
- EUA before Infliximab: 99%
P = 0.014

Fistula Recurrence

- Infliximab only: 79%
- EUA before Infliximab: 44%
P = 0.001

21 pts with Perianal Crohn’s Disease

Rectal EUS / Colonoscopy
EUA with I&D and Seton Placement
AZA/6-MP, Cipro and Infliximab
Serial rectal EUS Exam
Setons were not removed unless EUS proved the Fistulas were inactive

Schwartz DA et al, Inflamm Bowel Dis 2005

Utilizing EUS to Improve Fistula Healing

<table>
<thead>
<tr>
<th>Percent</th>
<th>Initial</th>
<th>Long-term</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>14</td>
<td>24</td>
</tr>
<tr>
<td>100</td>
<td>86</td>
<td>76</td>
</tr>
</tbody>
</table>

N=21

Schwartz DA et al, Inflamm Bowel Dis 2005
### Results

- **Median time to cessation of drainage was 10.6 wks (4-32).**
- **Median time to EUS evidence of fistula inactivity was 21 weeks (12-37 weeks).**

*Nguyen D et al. ACG 2009.*

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#### Table 6. Medical Therapy and Abscess Recurrence

<table>
<thead>
<tr>
<th>Pharmacologic Therapy* at Abscess Resolution</th>
<th>Recurrence (n=52)</th>
<th>Hazard Ratio for Abscess Recurrence (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No therapy (n=13)</td>
<td>13</td>
<td>1.00 (reference)</td>
<td>Overall &lt; 0.01</td>
</tr>
<tr>
<td>Immunomodulator monotherapy (n=44)</td>
<td>10</td>
<td>0.42 (0.17 - 1.03)</td>
<td>0.059</td>
</tr>
<tr>
<td>Any anti-TNF therapy (n=38)</td>
<td>2</td>
<td>0.10 (0.02 - 0.36)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Therapy assessed as a time dependent covariate for association with abscess recurrence.*

*Nguyen D et al. ACG 2009.*
### Table 7. Medical Therapy and Abscess Recurrence on Anti-TNF Therapy

<table>
<thead>
<tr>
<th>Pharmacologic Therapy* at Abscess Resolution (n=38)</th>
<th>Recurrence</th>
<th>Hazard Ratio for Abscess Reoccurrence (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TNF monotherapy (n=18)</td>
<td>2</td>
<td>0.32 (0.07 - 1.48)</td>
<td>0.14</td>
</tr>
<tr>
<td>Combination therapy (n=20)</td>
<td>0</td>
<td>0.00</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*Therapy assessed as a time-dependent covariate for association with abscess recurrence.


### Conclusions

- Between 40% and 50% of Crohn’s disease patients will develop at least one fistula, most of which are perianal
- Two-thirds of patients will experience only one fistulizing episode
- Understanding the detailed anatomy of fistula(s) and/or abscess(es) relative to internal and external anal fistulas impacts management
**Conclusions**

- Perianal fistulas increase risk of fecal incontinence, especially if managed too aggressively by surgeon
- Multidisciplinary approach – close collaboration with surgeon
- For other than a simple single fistula, an exam under anesthesia (EUA) is indicated
  - Imaging procedure (MRI, EUS) may benefit surgeon prior to EUA

**Conclusions**

- Aggressive medical approach
  - Consider combination therapy
  - Antibiotics
  - Thiopurines
  - Anti-TNF agents
  - Calcineurin inhibitors (CyA, FK506) for salvage?
- Proctectomy is last resort