Fistulizing Crohn’s Disease: The Aggressive Approach

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Case Presentation: Summary Points

• Ileal and colonic disease, including rectum
• Recurrent flares and steroid tapers, eventual azathioprine
• Presentation with moderately severe flare (luminal disease) and perianal fistulas
• CT shows perianal fistulas and fluid collections
• Antibiotics, TPN, exam under anesthesia, setons placement, IV corticosteroids, and infliximab done in rapid succession
• Recurrence after stopping infliximab for pregnancy
• Attenuated response on resuming infliximab
Fistula: a common complication of Crohn’s disease

- Reflects a transmural inflammatory process
- May arise at any time in course of disease
  - 46% of fistulas noted before or at diagnosis
- Cumulative incidence estimated to range from 20 to 40%
- Surgery is common: 83% of fistula episodes

Fistula by type

- Perianal: 54%
- Enteroenteric: 24%
- Rectovaginal: 9%
- Other: 13%

Gastroenterologist’s Role in the Management of Fistulizing CD

- Control overall disease activity
- Determine course/complexity of fistula
- Induce/maintain closure of fistula
- Limit scope of surgical intervention
- Improve quality of life
- Reduce hospitalizations
Perianal Fistulae: Parks’ Classification System

A Superficial fistula
B Intersphincteric fistula
C Transsphincteric fistula
D Suprasphincteric fistula
E Extrasphincteric fistula

Surgical therapy

- Incision and drainage
- Seton
- Fistulectomy
- Diverting procedure
- Rectal advancement flap or sleeve
- Proctectomy / total proctocolectomy
Metronidazole

• Four open trials
  – Small studies: n = 8 to 34 for each
  – Complete healing reported in about 50% of patients receiving metronidazole, alone or in combination
  – <30% of metronidazole-treated patients successfully discontinued antibiotic treatment

• Controlled trial
  – N = 52
  – Complete closure reported in 40% with metronidazole alone

Ciprofloxacin

• Two uncontrolled trials
  – 8 patients with active perineal CD
    • Ciprofloxacin 1000 mg to 1500 mg per day
    • 3 to 12 months
    • Improved physician and global patients assessments
  – 5 patients with active perineal CD
    • Ciprofloxacin for 4 days to 5 weeks
    • 4/5 had resolution of perineal pain

Azathioprine / 6-Mercaptopurine

*Complete healing or decreased discharge


0 20 40 60 80 100
% Patient Response*

Placebo

AZA/6-MP

21%

6/29

54%†

22/41

†Odds Ratio 4.44 (CI, 1.50 to 13.20) favoring fistula healing
Cyclosporine

- 10 open trials
  - 64 patients received IV cyclosporine (usually 4 mg/kg/d)
  - Initial response rate: 83%
  - Onset rapid (often ≤1 week)
  - High rate of relapse on switch to oral

Tacrolimus

- Randomized double-blind trial
  - 48 patients
  - 10 weeks
- Oral tacrolimus 0.2 mg/kg per d

\[ p=0.004 \quad 43\% \]

\( \% \) Fistula Improvement

* >50% reduction from baseline in the number of draining fistulae for at least 4 weeks

Infliximab: Inducing Response in Fistulizing CD

Infliximab

$5\,\text{mg/kg}$

Infliximab

$10\,\text{mg/kg}$

Placebo

Treatment Group

% Patients With Complete Closure of All Fistulae

$4/31$ 13%

$17/31$ 55%

$12/32$ 38%

$p=0.04$

$p=0.001$

$N = 94$

All patients received infliximab at Weeks 0, 2, 6

Infliximab: Duration of Fistula Closure After Induction Therapy*

*Infusion at Weeks 0, 2, 6
†With interquartile range


Median Duration of Fistula Closure† (week)

- 5 mg/kg (n=21): 12 weeks
- 10 mg/kg (n=18): 14.1 weeks
- Total (n=39): 12.3 weeks
ACCENT II: Time to loss of response
Responders (n=195, 69%)

Responders represented 69% of randomized patients

* p<0.001 compared to placebo maintenance

ACCENT II: Complete fistula response
Responders (n=195, 69%)

ACCENT II: Fistula response after week 14

Patients Randomized as Non-responders

ACCENT II: Response after Crossover
All Randomized Patients

Fistula closure by location

Abdominal: 79.5%
Perianal: 97.2%
Rectovaginal: 64.0%

All randomized patients
ACCENT II: Hospitalizations and surgeries

Number per 100 patients up to week 54

- **All randomized patients**
- **Patients randomized as responders**
- **All randomized patients**
  - Placebo: p=0.041
  - Infliximab: p=0.069
  - Infliximab: p=0.003
  - Infliximab: p=0.007

- **Patients randomized as responders**

### Prospective Pregnancy Outcomes Reports (Maternal Cases)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CD/UC/Regional Enteritis</th>
<th>RA</th>
<th>AS</th>
<th>Other</th>
<th>Unknown</th>
<th>Total</th>
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<tbody>
<tr>
<td>Live Birth with no defect or other adverse event</td>
<td>18</td>
<td>2</td>
<td>1</td>
<td>1*</td>
<td>1</td>
<td>23</td>
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<tr>
<td>Spontaneous Abortion</td>
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<td>Elective Termination</td>
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<tr>
<td>Fetal deaths</td>
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<td>0</td>
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<tr>
<td>Live births with defect</td>
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<td>0</td>
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<td>0</td>
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<tr>
<td>Live births with other adverse event</td>
<td>3**</td>
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<td>0</td>
<td>0</td>
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<td>3</td>
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<tr>
<td>Unknown outcome at time of data-lock</td>
<td>49</td>
<td>2</td>
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<td>0</td>
<td>15</td>
<td>66</td>
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<td><strong>Total</strong></td>
<td>74</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>16</td>
<td>97</td>
</tr>
</tbody>
</table>

* Includes the one and only report of JRA as an indication

**3 adverse events: 2 cases of premature rupture of membranes, 1 case of hyperemesis and gestational hypertension
# Retrospective Pregnancy Outcome Reports (Maternal Cases)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CD</th>
<th>RA</th>
<th>PSA</th>
<th>Other</th>
<th>Unknown</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Live birth with no defect or other adverse event</td>
<td>11</td>
<td>4*</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>18</td>
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<tr>
<td>Spontaneous abortion</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
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<tr>
<td>Elective termination</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Fetal deaths</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Live births with defect**</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Live births with other adverse event***</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
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<tr>
<td>Unknown</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

| Total                                            | 20 | 7   | 2   | 0     | 4       | 33    |

* A mother gave birth to infant diagnosed with malignancy (neuroblastoma) at 2 months of age
**defects: 1 male infant born with atrial septal defect that required surgical correction; 1 female infant with 6 fingers
***adverse events: 1 male neonate required surgical repair of opening in the bowel; 1 neonate born with a hemoglobin of 6; 1 infant diagnosed with carcinoma at 2-month of age (neuroblastoma [same infant as discussed under “Live Births with no defect or other adverse event”])
Maintenance of Complete Healing of Draining Fistulas at Weeks 26 and 56 with Adalimumab: All Randomized Patients

- Placebo
- 40 mg eow
- 40 mg weekly
- Both adalimumab groups*

Week 26:
- Placebo 6/47
- 40 mg eow 13/30
- 40 mg weekly 11/40
- Both adalimumab groups 21/70

Week 56:
- Placebo 6/47
- 40 mg eow 13/30
- 40 mg weekly 12/40
- Both adalimumab groups 23/70

*Based on pre-specified analysis plan, data from both adalimumab dosing arms were combined to obtain a more robust sample size

### Effect of EUA and seton on response to infliximab

<table>
<thead>
<tr>
<th></th>
<th>No EUA</th>
<th>EUA/Seton</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial response</td>
<td>82.6%</td>
<td>100%</td>
<td>0.014</td>
</tr>
<tr>
<td>Recurrence</td>
<td>79%</td>
<td>44%</td>
<td>0.001</td>
</tr>
<tr>
<td>Time to recurrence</td>
<td>3.6 mo</td>
<td>13.5 mo</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Combination therapy for perianal fistulas with ciprofloxacin and infliximab

Therapeutic Options for Perianal Fistulæ in CD

<table>
<thead>
<tr>
<th>No Efficacy</th>
<th>Possible Efficacy</th>
<th>Proven Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Aminosalicylates</td>
<td>• Antibiotics</td>
<td>• Infliximab</td>
</tr>
<tr>
<td>• Corticosteroids</td>
<td>• Immunomodulators</td>
<td>• Tacrolimus</td>
</tr>
<tr>
<td></td>
<td>– Azathioprine/6-mercapto</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Cyclosporine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Methotrexate (MTX)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Adalimumab</td>
<td></td>
</tr>
</tbody>
</table>

Algorithm for the Management of Perianal CD

DIAGNOSTIC EVALUATION

Fistula Type?

Not superficial

Noncutting Seton Abx
AZA/6-MP +/- Infliximab

Maintenance Therapy With AZA/6-MP or Infliximab

Failure

Definitive Surgery

Failure

Superficial

Fistulotomy + Short Course of Abx

Failure

Observe

Failure

Tacrolimus