Management of Fistulizing Crohn’s Disease
Definition

- Crohn’s Disease is an idiopathic, chronic, transmural inflammatory process of the bowel that can affect any part of the GI tract from the mouth to the anus.
- Most cases involve the small bowel, particularly the terminal ileum.
History

- 1806: First reported case of Crohn’s by Combe and Sanders to the Royal College of Physicians in London, England
- 1823: John Abercrombie of Edinburgh clearly outlined a difference in ileal and colonic diseases
- 1913: Surgical evidence of the disease reported in the paper ‘Chronic Intestinal Enteritis’ written by Dr. Kennedy Dalziel at the Western Infirmary in Glasgow
History

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History

- Described in 1932 by Crohn, Ginsburg, and Oppenheimer of Mount Sinai Hospital in New York
- Their paper ‘Regional Ileitis’ recorded cases of "non specific granulomas of the intestine"
- Based on fourteen surgical cases mostly operated on by surgeon, Dr. A. A. Berg
6 of 14 patients had fistulizing disease affecting various colon segments

“As the necrotizing process of mucosa of the ileum progresses through its several coats, the serosa become involved. Any hollow viscus, usually the colon, now becomes adherent to the point of threatened perforation. A slowly progressive perforation is thus walled off, but results in a fistulous tract being formed between the 2 viscera.”

Crohn BB, Ginzburg L, Oppenheimer GD. Regional ileitis: a pathologic and clinical entity. JAMA 1932;99:1323-9
Pathogenesis
Pathogenesis

- Exaggerated T cell response to luminal antigens
  - Normal quiescence lacking due to immunologic defect
  - Certain pathogens may evoke a destructive immune response in susceptible individuals
Statistics

- Lifetime risk of fistula development in patients with Crohn’s disease 20-40%
- Development of fistula may precede or coincide with the diagnosis of CD
- Rate of recurrence 34-82%\(^1\)

Common fistulas

- Perianal
- Enterocutaneous
- Peristomal
- Enteroenteric
- Rectovaginal
- Enterovesical
Goals of treatment

- Defining the anatomy of the fistula
- Draining any associated infectious material
- Attempting to eradicate the fistulous tract through medical or surgical therapies
- Preventing recurrence of fistulas
Medical therapy

- Anti-inflammatory medications
- Antibiotics
- Immunomodulators
- Anti-tumor necrosis factor-α therapies
Anti-inflammatory medications

- Sulfasalazine and mesalamine derivatives
  - Efficacious in induction of remission
  - No demonstrated efficacy in healing of fistulas

- Corticosteroids
  - Efficacious in induction of remission
  - No demonstrated efficacy in healing of fistulas
  - Deleterious outcomes in patients with fistulizing CD\textsuperscript{1}
  - However, abdominal abscess is not a contraindication to steroid therapy\textsuperscript{2}

Anti-inflammatory medications

- Corticosteroids and postop complications
  - Bruewer et al. reviewed 397 patients with CD who underwent bowel resection
    - Three groups: No steroids, low-dose steroids, and high-dose steroids
    - No difference among the groups in terms of post-operative complications
  - High-dose steroid administration is not an absolute contraindication to bowel anastomosis

Antibiotics

- **Metronidazole**
  - Most frequently used antibiotic in fistulizing CD
  - Multiple small, uncontrolled trials demonstrate efficacy in treatment of perianal disease
    - Bernstein et al\(^1\) noted clinical response in 20 of 21 patients with complete healing in 56% at 8 weeks
  - High recurrence rate (78%) necessitates maintenance therapy\(^2\)
  - In conjunction with immunomodulator may represent most cost-effective initial therapy\(^3\)

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Antibiotics

- Ciprofloxacin
  - Efficacy demonstrated only in small, uncontrolled trials
  - High recurrence rate
  - Combination therapy with metronidazole may be of benefit

Turunen U, Farkkila M, Valtonen V. Long-term outcome of ciprofloxacin treatment in severe perianal or fistulous Crohn’s disease.
Gastroenterology 1993;104:A793
Immunomodulators

- Purine analogs (6-MP, AZA)
  - Among the few agents with demonstrated efficacy in fistulizing CD
    - Effective in management of perirectal, enterocutaneous, enteroenteric, rectovaginal, and vulvar fistulas
    - Overall response rate 65%; complete healing in 39%
    - Delayed onset of action (approx 3 months)
    - High recurrence rate upon cessation of therapy

Methotrexate

- Effective in induction of remission of CD
- Efficacy in fistulizing disease demonstrated only in small, uncontrolled trials²

Immunomodulators

- Cyclosporin A
  - High doses effectively and rapidly induce remission of CD
  - 88% response to continuous IV infusion with half closing completely
    - Mean time to respond 7.4 days
    - Relapse rate 82%

Immunomodulators

- **Tacrolimus**
  - 43% clinical response in actively draining fistulas (vs. 8% for placebo)\(^1\)
  - No efficacy in closure of chronic fistulas

- **Mycophenolate mofetil**
  - Case reports suggest efficacy in fistulizing CD, but placebo-controlled data lacking\(^2\)

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Anti-TNF-α therapies

- Tumor necrosis factor
  - 157-aa protein produced by T-cells, monocytes, and macrophages
  - Forms 51-kd trimeric cytokine which binds to surface receptors on target cells
  - Initiates transcription of genes involved in inflammatory response
  - Histologic consequence: granuloma formation
Granulomas

Definition:

- A benign tumor formed in the process of wound healing. Fibroblasts, fibrin and capillary endothelial cells replace the specific tissue cells at the location.
Granulomas
Granulomas
Granulomas
The culprit:

TNF alpha
51kd
The answer:

- Infliximab:
  - Chimeric anti-TNF IgG monoclonal antibody
Infliximab

- Monoclonal antibody
- Product of recombinant cell line
- Intravenously administered
- Half life of 8 to 10 days
- Method of elimination unknown
Infliximab

- Placebo-controlled multicenter evidence:

<table>
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<th></th>
<th>Placebo</th>
<th>5 mg/kg</th>
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<tr>
<td>Clinical response</td>
<td>26%</td>
<td>68%</td>
<td>56%</td>
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<tr>
<td>Complete closure</td>
<td>13%</td>
<td>55%</td>
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Infliximab

- **FDA-approved indications:**
  - Reduction in symptoms and induction of remission in patients with moderately to severe CD where there is inadequate response to conventional therapy
  - Reduction in the number of draining enterocutaneous fistulas in patients with fistulizing CD

- **Off-label indications:**
  - Avoidance of steroid initiation
  - Rapid induction followed by conventional maintenance
Other anti-TNF-α therapies

- Limits to use of infliximab:
  - Ineffective in 20%
  - Loss of response secondary to antibody formation
  - Adverse effects
    - Infusion reactions
    - Hypersensitivity
    - Drug-induced lupus
    - TB reactivation
Other anti-TNF-α therapies

- Thalidomide
  - Destabilizes TNF-α mRNA
  - Rapidly effective

- Pentoxiphylline
  - Inhibits phosphodiesterase IV, limiting TNF-α transcription
  - Disappointing clinical efficacy

- Etanercept
  - Recombinant soluble TNF receptor
  - Surprisingly ineffective

- CDP-571: More humanized anti-TNF-α antibody

- Adalimumab: Fully humanized anti-TNF-α antibody
Interventional radiology

Frank abscess complicating CD may be amenable to radiographically guided drainage

- Jawhari et al. found that surgery was avoided in approximately half of patients treated in this manner

Operative management

- Existence of fistula is not an indication for surgery in and of itself
  - Goal of initial therapy should be control of sepsis

- Surgical treatment should include resection of grossly involved bowel segment
  - “Target” is intrinsically normal and may be treated with simple closure and drainage
  - Bypass procedures are to be avoided
    - May result in persistent sepsis, bacterial overgrowth, carcinoma
Operative management

- Enterocutaneous fistulas
  - Primary enterocutaneous fistulas are rare
    - In a review of 1500 patients with fistulizing CD only four cases identified
  - Most common in postoperative setting, draining from a previous scar
  - Early postop fistulas are usually sequela of anastomotic breakdown
  - Late fistulas usually require surgery, but in high risk patients medical management may be attempted
  - Operative strategy:

Operative management
Operative management

- Perianal fistulas
  - Described as simple or complex
    - Inter- vs. transsphincteric
    - High vs. low track
    - Presence vs. absence of active rectal inflammation
  - Noncutting setons
  - Rectal mucosal advancement flaps
  - Anocutaneous advancement flaps
Conclusions

- Fistulizing Crohn’s disease is an aggressive variant of a troubling disease of multifactorial etiology
- The role of tumor necrosis factor α has proven critical in its pathogenesis
- Effective treatment of Crohn’s fistulas should combine aggressive medical therapy with judicious surgical intervention when warranted