Modern Management of Perianal Fistulas in Crohn’s Disease (PFCD): Future Directions

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• I have no financial relationship to disclose.
Learning objectives

- Explain the physiology, etiology, and anatomical classification of Perianal fistulas
- Discuss the clinical manifestations, prognosis, and diagnosis of perianal fistulas
- Discuss pharmacological and surgical treatment options for perianal fistulas in Crohn’s disease (PFCD)
What is a Perianal Fistula

• An epithelialized track that can form and connects the abscess in the anus or rectum with the perirectal skin
• Anal fistulas are sometimes also referred to as "fistula-in-ano"
Epidemiology

- The incidence of an anal fistula developing from an anal abscess ranges from 26 to 38 percent
- The mean age for presentation of anal abscess and fistula disease is 40 years
- The presence of perianal fistulas can be the initial manifestation of CD in 10% of the patients
- PFCD tends to be more prevalent in colonic disease and rectal involvement than in those with isolated ileal disease
- Adult males are twice as likely to develop an abscess and/or fistula compared with women
Etiology

- An infected anal crypt gland
- Crohn disease
- Lymphogranuloma venereum: chronic infection in the lymphatic system caused by Chlamydia trachomatis
- Radiation proctitis: Pelvic radiation
- Actinomycosis: in immunocompromised patients
- Obstetric injury: prolonged labor
- Rectal foreign bodies
Pathogenesis
Classification

Relationship to the anal sphincter muscles:

• Intersphincteric
• Transsphincteric
• Suprasphincteric
• Extrasphincteric
• Superficial
Classification

- Levator ani muscle
- Puborectalis muscle
- Internal anal sphincter
- External anal sphincter
- Extrasphincteric fistula (Parks type 4)
- Transphincteric fistula (Parks type 2)
- Superficial fistula
- Intersphincteric fistula (Parks type 1)
- Suprasphincteric fistula (Parks type 3)
Perianal complications in Crohn’s disease

- “Nonhealing" anorectal abscess following drainage
- Chronic purulent drainage and a pustule-like lesion
- Intermittent rectal pain and pruritis
- Bleeding
Prognosis

- Anorectal abscesses
- Anal stenosis
- Hemorrhoids
- Risk of Adenocarcinoma
Management principles

• Why is it challenging?

• Active rectal inflammation
• Persistence of inflammation
• Mechanical abnormalities in the perineum
Management principles

• Combined medical-surgical management constitutes the best approach to achieve fistula healing
• 33 percent remained asymptomatic despite continued presence of the fistula
• 38 percent had spontaneous healing during 10 years of follow-up

• Symptomatic relief
  • Decrease fecal soilage by reducing diarrhea
  • Sitz baths
  • No excessive wiping or astringent use
Management principles

• Antibiotics
• Uncontrolled case series
• Only if symptomatic measures were not successful in 5 days
  • Metonidazole
  • Ciprofloxacin
  • Combination
• Topical nitroglycerin or calcium channel blockers
Severe/ Complex fistulizing disease

• Thiopurines (Conventional therapy)
  • **Azathioprine**
    • *Monotherapy*: 2 to 2.5 mg/kg/day; begin within 2 to 4 weeks after surgery and continue for 12 to 24 months
    • *Combination therapy (in combination with metronidazole)*: 100 mg daily (<60 kg) or 150 mg daily (≥60 kg) for up to 52 weeks
    • Oral: 1.5 to 2.5 mg/kg/day in combination with an anti-TNF agent (e.g., adalimumab, infliximab)
  • **6-Mercaptopurine**
    • 1.5 mg/kg/day (in combination with metronidazole) for ~18 months after surgery
    • Oral: 0.75 to 1.5 mg/kg/day in combination with an anti-TNF agent
Severe/ Complex fistulizing disease

• Anti-TNF agents

  • **Infliximab (IFX)**
    • IV: 5 mg/kg at 0, 2, and 6 weeks, followed by 5 mg/kg every 8 weeks thereafter; dose may be increased to 10 mg/kg in patients who respond but then lose their response.
    • If no response by week 14, consider discontinuing therapy

  • **Adalimumab (ADA)**
    • SQ: Initial: 80 mg (given on day 1), then 40 mg 2 weeks later (day 15)
    • Maintenance: 40 mg every week or 40 mg every other week beginning day 29
Severe/ Complex fistulizing disease

• Alpha-4-beta-7 integrin monoclonal antibody

• **Vidolizumab (VDZ)**
  • selectively modulating leucocyte trafficking to the bowel
  • IV: 300 mg at 0, 2, and 6 weeks and then every 8 weeks thereafter
  • Discontinue therapy in patients who show no evidence of therapeutic benefit by week 14.
  • (GEMINI) 2 trial, (OBSERV-IBD), (ENTERPRISE) trial

• **Certolizumab pegol (CZP)**
  • SubQ: Initial: 400 mg, repeat dose 2 and 4 weeks after initial dose
  • Maintenance: 400 mg every 4 weeks
• **Ustekinumab (UST)**
  - blocks the p40 subunit shared by both interleukins (IL-12 and IL-23)
  - Inhibition of the inflammatory cascade through multiple pathways and consequently reduces systemic inflammation
  - Induction: IV: (weight-based) 260-520 mg
  - Maintenance: SubQ: 90 mg every 8 weeks; begin maintenance dosing 8 weeks after the IV induction dose
  - (UNITI) trial, (IM-UNITI) trial, (CERTIFI)
Severe/ Complex fistulizing disease

<table>
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<tr>
<th>Agent</th>
<th>Author (YOP)</th>
<th>Type of study</th>
<th>Fistula closure as primary endpoint</th>
<th>Number of patients</th>
<th>Fistula closure (%)</th>
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<td>Present et al (1999)</td>
<td>Randomized controlled trial</td>
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<td>Schreiber et al (2011)</td>
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<td>UST</td>
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<td>37</td>
<td>24.7%</td>
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</table>

Main studies with efficacy data from biological agents in PFCD

[Image 0x0 to 960x540]
Keeping in mind

- Optimized dosing of Anti-TNF therapy
- Combination of anti-TNF therapy and surgery
- Local injections of anti-TNF agents?
- Future strategies: cell-based therapy for PFCD
- The role of endoscopy in the management of PFCD: Endoscopic fistulotomy, Endoscopic drainage, clipping and suturing..etc
- Fibrin glue injections

