Perianal Crohn’s disease: challenges and solutions

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Abstract: Perianal Crohn’s disease affects a significant number of patients with Crohn’s disease and is associated with poor quality of life. The nature of the disease, compounded by presentation of various disease severities, has made the treatment of perianal Crohn’s disease difficult. The field continues to evolve with the use of both historical and contemporary solutions to address the challenges associated with it. The goal of this article is to review current literature regarding medical and surgical treatment, as well as the future directions of therapy.

Keywords: Crohn’s disease, fistula, surgery, perirectal

Introduction
Perianal disease is commonly diagnosed in individuals with Crohn’s disease (CD). It is a marker of more severe disease and is associated with multiple surgical interventions and frequent relapses.1,2 The incidence of perianal Crohn’s disease (pCD) ranges from 17% to 43% of CD cases.1,3,4 pCD is associated with more distal CD.3 In 5% of individuals, however, CD will only manifest as perianal disease without associated luminal disease.1,5 Individuals will most commonly develop perianal disease prior to the diagnosis.1

pCD is particularly difficult to manage, due to the complexity of its presentation. The incidence of pCD is similar in men and women. Women, however, have greater complications associated with the adjacent vaginal wall and risks associated with childbirth.6 Patient-reported symptoms associated with it include pain with associated perianal swelling and fevers, drainage of pus, stool, or blood from the vagina, scrotum, or perineum. Some may report fecal incontinence. The disease may physically manifest as a perianal fistula, anal fissure, anal canal stricture, rectovaginal fistula, or abscess.7 The etiology of the pCD is still unclear; theories suggest it arises from deep ulcers or anal gland abscesses. It is most likely a combination of genetic, microbiologic, and immunologic factors.8

Current clinical classifications for pCD were proposed by the American Gastroenterological Association.7 Fistulas are distinguished as simple and complex fistulas. Simple fistulas are low, below the dentate line, and include superficial, intersphincteric, or intrasphincteric fistulas, with a single external opening without other complications. Complex fistulas are high, arising above the dentate line, and may have multiple external openings. They may be associated with perianal abscesses, rectal stricture, proctitis, or connections with the bladder or vagina. This classification has been elaborated to include a clinical activity score using the Perianal Disease Activity Index, described...
tissue. MRI is also capable of identifying clinically silent abscesses and inflammation. Schwartz et al compared pelvic MRI and EUS with a reported accuracy of 91% and 87%, respectively, compared to an EUA at 91%. Currently, the higher diagnostic quality of EUS and pelvic MRI precludes the use of computed tomography and fistulography.

**Treatment**

**Medical**

Medical therapy is a critical adjunct in the treatment of pCD, and should be started once the diagnosis of active pCD is made. The main goal of therapy is to achieve and maintain disease remission.

**Antibiotics**

Antibiotics are used to treat perianal sepsis and act as an effective bridge to immunosuppressive therapy. A positive clinical response within 6–8 weeks of initiation of treatment is observed in 70%–95% of patients. In mild-to-moderate symptoms, treatment with oral metronidazole has been used as the initial therapy, with improved symptoms in 50% of patients. Fistula healing rates from antibiotic therapy alone, however, are <50%, and the majority of cases will recur if antibiotics are withdrawn.

**Immunosuppression**

Immunosuppression is the definitive therapy for pCD. Azathioprine and 6-mercaptopurine (6-MP) are thiopurines that halt DNA replication, and are used for induction and maintenance of remission in fistulizing disease. A meta-analysis of five randomized controlled trials examined the efficacy of 6-MP and azathioprine, and demonstrated a 54% healing rate in patients versus 21% of controls. Cyclosporine and tacrolimus have been used, but less frequently. Cyclosporine, a T-cell suppressant, when given intravenously has an excellent, rapid effect in up to 83% of patients, but is not as effective when administered orally. In a randomized controlled trial, tacrolimus, an interleukin-2 (IL-2) inhibitor, resulted in improvement of CD symptoms in 43% of patients versus 8% in the placebo arm. Neither cyclosporine nor tacrolimus, however, were specifically studied in fistulizing pCD.

**TNF antagonists**

TNF antagonists are effective in achieving durable remission in pCD. First, infliximab is a chimeric monoclonal antibody to TNF-α, and was evaluated in the ACCENT 1 and 2 trials. ACCENT 1 demonstrated successful induction therapy with infliximab for fistulizing pCD: 68% of patients treated with infliximab had at least a 50% improvement in symptoms versus 26% with a placebo. The ACCENT 2 trial documented longer time to recurrence of fistulas with infliximab maintenance therapy. In addition, treatment with infliximab...
prevented additional surgeries and hospitalizations. Inter-
estsingly, rectovaginal fistula healing had a poor response to
infliximab therapy, compared to perianal fistula healing.

Second, adalimumab is a fully humanized monoclonal
antibody against TNF-α. In the CHOICE trial, 673 patients
achieved complete fistula healing after 8 weeks of adalim-
umab therapy. In a post hoc analysis of the CHARM trial,
complete fistula closure was seen at 1 year in 39% of patients
treated with adalimumab, versus 13% in the placebo arm.
These results were shown to be durable at 2 years. A retro-
spective cohort study comparing infliximab and adalimumab
in achieving and maintaining closure of perianal fistulas in
ambulatory CD patients demonstrated complete response in
77.0% of patients at 36 months of follow-up, with no difference
between infliximab and adalimumab.

Third, certolizumab pegol has improved solubility and
decreased immunogenicity compared with the other TNF
antagonists. Durable remission for at least 4 years and heal-
ing of perianal fistula in 36% of patients was reported. All
three major TNF antagonist antibodies are effective in pCD,
but head-to-head comparisons have not yet been performed.

In summary, the medical approach to the treatment of
pCD is evolving. Recently, Choi et al identified a significantly
greater proportion of healing in septic perianal disease with
the addition of anti-TNF interventions in a retrospective
review of 114 patients. Their treatment algorithm appears to
be quite successful. In the past, therapy has been increased
in a stepwise fashion to achieve remission, adding increas-
ingly potent immunosuppressant medications. The value of
early combination therapy to prevent disease progression may
find a role in fistulizing pCD (REACT trial), or the addition
of anti-TNF agents earlier in therapy.

**Surgical**

Surgical interventions for pCD vary, depending on disease
extent and severity and can be facilitated by concurrent use
of medical therapy (Figure 1). Although an attempt is made
to be conservative with surgical interventions, the overarching
goal is to manage perianal sepsis, drain any abscesses,
and place setons in delineated fistulas. Treatments can be
highly variable among practitioners, requiring a multidisci-
plinary approach. Here, we have reviewed specific Crohn’s
literature regarding surgical interventions (Table 1). Perianal
abscesses, which commonly precede or accompany perianal
fistulas, should be incised and drained when first identi-
fied. Surgical drainage, as opposed to spontaneous drain-
age, minimizes the risk of further septic complications. It
is important to note that the surgical removal of skin tags
associated with pCD is not recommended, due to the risk
of poor wound healing, infection, and fistula formation.
If fistulas are identified at the time of intervention, noncutting seton placement is recommended, which will maintain patency of the fistula tracts and limit recurrent abscess formation.42 Seton placement allows drainage without closure and increases effectiveness of medical therapy, while preserving external sphincter function.42,43 Fistulotomies at the time of perianal sepsis are contraindicated, as there is an increased risk of incontinence.44 The rate of incontinence after seton placement is 12%.45 One should also consider the addition of an anti-TNF antibody, which has been shown to improve response rate, recurrence rate, and time to recurrence.12 The duration of seton placement is not clear; studies, however, have reported that effective treatment is observed after longer durations of infliximab, and setons may be removed.40,46 Our institution waits at least 6 weeks before any further surgical intervention is discussed.

After resolution of perianal sepsis and remission of active distal disease, a fistulotomy is the preferred procedure, for simple, superficial fistulas. The tract is identified, the overlying tissue is divided, the base of the tract is curetted, and the wound is left open to close by secondary intention. In addition, marsupialization may improve the rate of wound healing.47 Successful healing is reported in ~80% of patients with a 20% risk of recurrence over a follow-up between 2 and 20 years.42,48–50 Fistulotomy is strongly discouraged in complex fistulas, due to high risk of fecal incontinence, decreased healing, and need for proctectomy.50,51 Minor continence issues following fistulotomy occur in 25% of patients.52

Other interventions include the use of fibrin glue, which consists of two parallel syringes of fibrinogen and thrombin that facilitate healing, hemostasis, and angiogenesis. These syringes are injected together via a catheter to fill a fistula tract, resulting in clot formation, sealing the fistula. Current literature is discordant with the success of this intervention.53,54 One dedicated randomized controlled trial55 found 38% of patients experienced remission with fibrin glue, which was twice than that for individuals with no intervention; this, however, was in 16 weeks of follow-up. These results echo smaller series previously performed that demonstrated healing in 31% of patients with pCD after fibrin glue over 26 months.54

The Surgisis (COOK biotech, West Lafayette, IN, USA) fistula plug is a lyophilized porcine intestinal submucosa. It is inert, eliciting no foreign body or inflammatory reaction, and acts as a collagen scaffold, that is populated by a patient’s endogenous cells over the course of 3 months.56 A recent systematic review of the fistula plug in normal patients demonstrated a closure rate of 58.4% after a median follow-up of 9 months.57

### Table 1 Summary of the literature on perianal Crohn’s disease interventions

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Study design</th>
<th>Rate of healing</th>
<th>Follow-up time</th>
<th>Other complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fistulotomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hobbiss and Schofield²⁸</td>
<td>22</td>
<td>Retrospective</td>
<td>80%</td>
<td>1–10 years</td>
<td>Minor anal stenosis</td>
</tr>
<tr>
<td>Halme and Sainio²⁶</td>
<td>35</td>
<td>Retrospective</td>
<td>60%</td>
<td>Undocumented</td>
<td>Fecal incontinence</td>
</tr>
<tr>
<td>Scott and Northover²⁷</td>
<td>27</td>
<td>Retrospective</td>
<td>81%</td>
<td>2 years</td>
<td>None reported</td>
</tr>
<tr>
<td><strong>Fibrin glue</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lindsey et al²¹</td>
<td>2</td>
<td>Randomized (fibrin vs seton,</td>
<td>100% (1 needed a</td>
<td>12 weeks</td>
<td>None reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td>fistulotomy or flap)</td>
<td>second intervention)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loungnarath et al²⁴</td>
<td>13</td>
<td>Retrospective</td>
<td>31%</td>
<td>26 months</td>
<td>None reported</td>
</tr>
<tr>
<td>Grimaud et al²⁵</td>
<td>36</td>
<td>Randomized (glue vs observation)</td>
<td></td>
<td>16 weeks</td>
<td>Four abscess</td>
</tr>
<tr>
<td><strong>Fibrin plugs</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Champagne et al²⁶</td>
<td>46</td>
<td>Prospective</td>
<td>83%</td>
<td>6 months–2 years</td>
<td>None reported</td>
</tr>
<tr>
<td>Senejoux et al²⁷</td>
<td>106</td>
<td>Randomized (plug vs seton removal)</td>
<td></td>
<td>12 weeks</td>
<td>None reported</td>
</tr>
<tr>
<td><strong>LIFT</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Rojanasakul et al²⁸</td>
<td>17</td>
<td>Prospective observational</td>
<td>94.4%</td>
<td>6 months</td>
<td>None reported</td>
</tr>
<tr>
<td>Zirak-Schmidt and Perdawood⁵⁹</td>
<td>612</td>
<td>Systematic review</td>
<td>70.6%</td>
<td>4 weeks–26 months</td>
<td>None reported</td>
</tr>
<tr>
<td>Gingold et al²⁰</td>
<td>15</td>
<td>Prospective observational</td>
<td>67%</td>
<td>12 months</td>
<td>None reported</td>
</tr>
<tr>
<td>Parthasarathi et al²⁰²¹</td>
<td>167</td>
<td>Prospective observational</td>
<td>94/1%</td>
<td>12.8 months</td>
<td>None reported</td>
</tr>
<tr>
<td><strong>Endomucosal advancement flap</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Kobayashi and Sugihara²²</td>
<td>2</td>
<td>Case report</td>
<td>100%</td>
<td>1 year</td>
<td>Fecal incontinence</td>
</tr>
<tr>
<td>van Koperen et al²³²¹</td>
<td>60</td>
<td>Randomized (plug vs flap)</td>
<td>29% (plug) vs 48% (flap)</td>
<td>11 months</td>
<td>None reported</td>
</tr>
<tr>
<td>Marchesa et al²⁳²¹</td>
<td>13</td>
<td>Retrospective</td>
<td>62%</td>
<td>1 year</td>
<td>None reported</td>
</tr>
<tr>
<td><strong>Abbreviation:</strong> LIFT, intersphincteric fistula tract.</td>
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If fistulas are identified at the time of intervention, noncutting seton placement is recommended, which will maintain patency of the fistula tracts and limit recurrent abscess formation.52 Seton placement allows drainage without closure and increases effectiveness of medical therapy, while preserving external sphincter function.42,43 Fistulotomies at the time of perianal sepsis are contraindicated, as there is an increased risk of incontinence.44 The rate of incontinence after seton placement is 12%.45 One should also consider the addition of an anti-TNF antibody, which has been shown to improve response rate, recurrence rate, and time to recurrence.12 The duration of seton placement is not clear; studies, however, have reported that effective treatment is observed after longer durations of infliximab, and setons may be removed.40,46 Our institution waits at least 6 weeks before any further surgical intervention is discussed.
The ligation of the intersphincteric fistula tract (LIFT) is designed to close complex fistulas with sphincter preservation. An incision is made in the intersphincteric groove at both the internal and external sphincters. The external tract is then curetted out, and the external opening is widened at the skin. Eventually, the skin is closed. LIFT is a safe procedure that provides a mean healing rate of 70.6% with no reports of impairment of the sphincter function, based on a systemic review with follow-up between 4 weeks and 26 months (average 10.3 months). In prospective studies, healing was seen in 67% of patients at 12-month follow-up. A prospective observational study concluded the LIFT procedure has a high success rate (94.1% in 167 patients) in complex fistulae-in-ano. Recurrence is associated with diabetes, perianal abscesses, tract abscesses, and multiple tracts. A second LIFT procedure may be a feasible intervention if needed.

The endorectal mucosal advancement flap is a procedure that uses endogenous tissue to close the internal fistula opening. After complete excision of the fistula tract, the internal sphincter muscle is mobilized and approximated in the middle without tension. A flap is created consisting of mucosa, submucosa, and circular muscle, which is advanced and secured to cover the internal opening. Endorectal mucosal advancement flaps are the preferred approach for complicated anorectal fistulae without incontinence. Prior to advancement flap, most patients undergo a period of infection control with a draining seton, with or without a diverting stoma. Relative contraindications to advancement flap are anal stenosis and active proctitis due to high complication and failure rates. van Koperen et al reported that 52% of the population undergoing treatment with the mucosal advancement flap experienced healing after 11 months. A retrospective review of 127 patients with high anorectal fistulas had an overall recurrence rate of 26% with a mean follow-up of 13 months. Mucosal advancement flaps with or without the addition of fibrin glue have been shown to result in healing rates as high as 62% in complex fistulas.

Fistulas that do not respond to aggressive medical and surgical management may require fecal diversion with the creation of an ileostomy. Diversion may result in relief of local inflammation. In patients who underwent fecal diversion and drainage of local sepsis for their perianal disease, 81% went into early remission, although 68% of these relapsed at a median of 23 months after treatment. In this same group, a total of 25% of patients had long-term remission, but only 10% were able to restore intestinal continuity, which had been reported by others.

Patients with complex fistulas associated with abscesses, recurrent sepsis, colonic or perineal disease, refractory proctitis, and anal stenosis are candidates for proctectomy and permanent stoma. Some authors recommend doing this in a two-stage procedure to allow resolution of perianal sepsis. Furthermore, after resolution of sepsis, there may be large subcutaneous tissue defects, which may require advanced tissue transfers, such as gluteal flaps and gracilis flaps. Ileal pouch anal anastomosis has been attempted in these individuals; high rates of recurrence of pCD, however, have been reported. Therefore, we at our institution do not strongly recommend this procedure. Colo-anal pull-through is another surgical option; fistula recurrence, however, has been reported up to 25%, although the study did not define which of those occurred in Crohn’s patients. Thirteen percent developed anal strictures, and only 38% returned to normal continence. We do not perform this procedure at our institution.

**Other interventions**

Other interventions have been used to manage pCD. Local injections of anti-TNF alpha have been attempted. Two pilot studies were completed that demonstrated some improvement with injection of infliximab and adalimumab. Hyperbaric oxygen may also be utilized to facilitate healing. In addition, topical tacrolimus has been attempted, but with little success. Although multiple avenues in treatment have been attempted, it appears surgical intervention remains the most successful.

**Future directions**

Promising evidence suggests that the injection of stem cells may improve healing in fistulizing pCD. They are nonhematopoietic precursors of connective tissue cells with anti-inflammatory and tissue regenerative properties, extracted from subdermal adipose tissue. Peri- or intrafistula injection of autologous adipose-derived stem cells, as well as bone marrow-derived stem cells, is proven to be feasible and safe. Most recent trials have demonstrated closure rates over various lengths of follow-up from 37% to 85%, using a combination of autologous and allogenic mesenchymal and adipose-derived stem cells. Completion of Phase III trials is needed, but there is promising evidence that stem cells may aid in fistulizing pCD treatment.

**Conclusion**

Despite advancements in medical and surgical interventions for pCD, its treatment has remained challenging. Although current solutions for fistula management show varying...
degrees of success, additional research is needed to further the management of pCD. Current therapies, with the addition of a multidisciplinary team, will continue to improve the management of this difficult disease.

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References


