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Management of Perianal Fistulas in Crohn's Disease

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Keywords

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Abstract

Background: Perianal fistulizing Crohn's disease is associated with severe symptoms such as pain, fecal incontinence, and a significant reduction in quality of life. ***Results:*** In refractory cases, many patients face the decision of having a stoma and/or requiring proctectomy. In former years, the standard of care was a complete fistulectomy, bringing with it a high rate of continence disorders. Additionally, many patients received indefinite treatment, namely the placement of a seton to maintain surgical drainage. ***Conclusion:*** More recently, newer biologics, cell-based therapies as well as novel surgical techniques have been introduced, raising new hopes that outcomes can be improved upon.

Introduction

Perianal fistulation is common in patients with Crohn's disease (CD), the estimated life-time risk of perianal fistula being between 14 and 38% in population-based estimates [1]. Perianal fistulizing CD (PFCD) is associated with severe symptoms such as pain, fecal incontinence, and a significant reduction in quality of life. In refractory cases, many patients face the decision of having a stoma and/or requiring proctectomy [2]. In former years, the standard of care was a complete fistulectomy, bringing with it a high rate of continence disorders. Additionally, many patients received indefinite treatment, namely the placement of a seton to maintain surgical drainage [3].

Perianal fistulas in CD can be simple or complex, and treatment algorithms vary according to the severity of the perianal involvement and this classification [4].

More recently, newer biologics, cell-based therapies as well as novel surgical techniques have been introduced, raising new hopes that outcomes can be improved upon.

Classification and Predictive Factors

Fistulas can be discriminated into simple and complex fistulas (according to the AGA-classification). A simple fistula is a low fistula with only a single external opening and is not associated with abscess formation, rectovaginal fistula, or an anorectal stricture.

In a single-center study involving 232 patients with perianal CD longstanding remission for complex fistulas was seen in only 37% of the patients after a 10-year follow-up compared to almost 67% for simple fistulas [5]. A recent systematic review concluded that a combination of medical and surgical treatment approaches is superior to either single treatment alone. The importance of a multidisciplinary patient care is highlighted by superior rates of complete remission (52%) in the combination versus single-therapy (43%) group [6]. An important and worrisome aspect of PFCD is the occurrence of malignant transformation of perianal fistulas. Although this event is rare, it nevertheless is of crucial importance for the affected patients [7, 8].

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Before thinking about therapy, we should keep in mind that fistulas rarely heal spontaneously, and surgical therapy is often necessary [9]. The data need to be interpreted carefully as the definitions of response varied, and it is difficult to ascertain what the true fistula closure rate is [6, 10].

Antibiotics and Other Medical Agents

Conventional agents reported to be of clinical benefit in uncontrolled trials include antibiotics and the thiopurines. They often lead to symptomatic improvement with a decrease in fistula drainage. Many of the authors, however, will use these antibiotics in combination with other therapies. There is little evidence on the use of antibiotics alone in the treatment of PFCD, with meta-analyses on the use of ciprofloxacin suggesting a marginal effect in remission [11]. In combination with adalimumab, it may offer additional benefit in healing [12]. Recent guidelines suggest that antibiotics in perianal sepsis might be of benefit only in immunosuppressed patients.

Aminosalicylates

There is no evidence for the efficacy of 5-ASA agents for the treatment of PFCD, neither for orally nor rectally applied formulations. Therefore, these agents cannot be recommended for this indication. However, there might be a role especially for rectally applied 5-ASA formulations to address clinical symptoms of active rectal inflammation [10].

Anti-TNF Therapy

The roles of anti-TNF-α therapy and azathioprine are well established in this setting, so their positions as drugs of choice are merited [11–15].

Infliximab

Infliximab (IFX) revealed to achieve impressively high complete (55 vs. 13% placebo) and partial (i.e., reduction of ≥50% of the draining fistula; 68 vs. 26% placebo) fistula closure rates [15].

The ACCENT II trial published prospective data from 304 patients with PFCD. It reported a complete healing in 36% of the IFX group and 19% of the placebo group ($p = 0.0009$) [16]. Due to the high proportion of recurrent fistulas in the follow-up study, one must assume that it is not a cure of the fistula but a lack of symptoms as long as the patients receive medication.

Adalimumab

Regarding adalimumab, there are no trials investigating fistula closure as primary endpoint.

In a subgroup analysis, the CHARM randomized trial reported a significant decrease in the number of draining fistulas per day compared with placebo in a cohort of 117 patients [17].

Vedolizumab

Up to present, there is no specific clinical trial investigating a potential effect of vedolizumab on fistula closure in CD. However, a study with fistula healing at week 30 as primary endpoint appears to be currently recruiting patients (NCT02630966).

Local Treatments

The aim of this procedure is to reduce systemic side effects and focus treatment effects on the area of interest. In addition, these treatments are typically thought to be minimally invasive and offer quick recovery times.

Infliximab

Local injection of IFX is attractive as an option to limit its systemic immunosuppressant effect. There are a few small trials that have attempted this with improvement of symptoms [18, 19]. However, in patients who also have intestinal disease, systemic IFX would offer dual benefit and may be preferred. Surprisingly, to our knowledge, the therapy has not found its way into the daily clinical routine.

Cell-Based Therapy in PFCD

First small studies about 7 years ago using topically administered mesenchymal stem cells in fistulizing CD revealed promising results [20, 21]. A recent study in the Netherlands with 21 refractory fistulizing CD patients investigated the effect of locally administered bone marrow-derived mesenchymal stromal cells in three different dosages (groups 1–3) in a placebo-controlled, double-blind trial, with fistula healing [5]. In a phase III randomized controlled trial (RCT), 200 patients from 19 centers were randomized to receive 20 million stromal cells. While there were no significant differences in the healing rates at 24 and 52 weeks, the treatment groups had higher rates of healing than the controls, with 1-year healing rates of 57% as compared with 37% ($p = 0.13$) [22]. Despite the promising results, this is the only higher-evidence study that supports the treatment with mesenchymal stem cell therapy.

Principals and Surgical Techniques in the Treatment of Perianal Fistulas

In acute settings, most surgeons perform conservative and sphincter-preserving procedures, in the form of drainage of sepsis and use of a draining seton [11]. The use of cutting setons is obsolete and may lead to incontinence, especially in patients with inflammatory bowel disease. Patients with PFCD tend to have a chronic and recurrent disease course necessitating multiple interventions, and therefore efforts should be made to preserve continence where possible [23]. There is a wide range of procedures offered as definitive surgical options for patients with PFCD. Draining seton alone, fistulotomy with or without reconstruction, fistula plug, video-assisted

anal fistula treatment (VAAFT) and ligation of the intersphincteric fistula tract (LIFT) have been described in the literature, with varying outcomes [3, 11, 24].

Long-Term Seton for Complex Anal Fistulas

Long-term indwelling seton is an effective management modality for complex perianal fistulas in CD and seems to decrease the need for temporary or permanent stomas. The treatment allows the induction of anti-inflammatory agents [25]. Clinical symptoms decrease, but as in conservatively and medically treated fistulas there is no definitive healing [26].

Fistulectomy and Fistulotomy

Subanodermal, submucosal, subcutaneous, distal intersphincteric, and distal transsphincteric fistulas, which affect only a small part of the sphincter muscles, can be completely cut without compromising continence. The decision on how much sphincter can be cut is influenced by the following factors: gender, previous surgeries, age, fistula localization, and preoperative sphincter function. In general, complete healing of the lesion takes 6–12 weeks, depending on the size of the wound. The recurrence rate is low (below 10%) [27].

Flap Procedures

The advancement flap is probably the most used technique, with healing in approximately 50% of the patients. The reported data show heterogenous results and are summarized in Table 1.

Ligation of the Intersphincteric Fistula Tract

The aim of this procedure is to ligate the fistula through a perineal wound. So basically, the sphincter is not affected. There are several case series [35, 36] and one RCT in patients with and without CD. Primary healing rates ranged from 47 to 95%. Kamiński et al. [38] looked at the long-term outcome of patients with CD undergoing LIFT and reported reduced healing rates compared with those reported previously. Whilst there was a 67% healing rate at the 12-month follow-up, the overall fistula healing rate was 48% up to 58 months. Sirany et al. [37] summarized that the true efficacy of the procedure is unknown because of the number of technical variations and the divergent results reported in the literature (Table 2).

Video-Assisted Anal Fistula Treatment

Key steps included excision of the external (perianal) opening of the fistula tract, insertion of the fistuloscope, visualization of the fistula tract and/or side tracts using the fistuloscope, and correct localization of the internal fistula opening under direct vision with irrigation. If potential side tracts were identified, fistula tissue was destroyed by using electrocautery or brushing. Schwander [40] demonstrated the first results of the VAAFT technique in PFCD. The aim of this prospective study was to analyze the feasibility and short-term efficacy of the VAAFT technique combined with transrectal advancement flap repair for the closure of complex fistulas in CD. Additional side tracts not detected preoperatively could be identified in 64% (7/11) of the patients. The follow-up was too short to provide definite healing rates. However, after a mean follow-up of 9 months, the success rate was 82% (9/11). In addition to the high costs of this procedure, the long-term results should be awaited. As in other studies, significantly worse cure rates can be expected over the long term.

Table 1. Results with the flap procedures

First author [ref.]	Year	*n*	Healing, %	Recurrence, %
Joo [28]	1998	26	65	35
Makowiec [29]	1995	20	75	25
Athanasiadis [30]	1995	29	52	48
Sonoda [31]	2002	44	50	50
Mizrahi [32]	2002	28	57	43
van Koperen [34]	2009	9	45	55

Table 2. Results with LIFT

First author [ref.]	Year	*n*	Healing, %	Recurrence, %
Abcarian [35]	2014	1	–	–
Ellis [39]	2010	4	–	–
Gingold [36]	2014	15	60	40
Kaminski [38]	2017	23	48	52

Table 3. Results with fistula plugs

First author [ref.]	Year	*n*	Healing, %	Recurrence, %
Champagne [41]	2006	20	80	20
Ky [42]	2008	14	28	72
Schwandner [43]	2009	9	77	23
Ellis [39]	2010	12	66	34
Herold [44]	2016	4	25	75
Cintron [45]	2013	8	50	50

Table 4. Results with fistulectomy with primary sphincter reconstruction

First author [ref.]	Year	*n*	Healing, %	Recurrence, %
Herold [46]	2009	10	86	14
Seyfried [3]	2018	24	>85	?

Fistula Plugs

There are two types of plugs that are commonly used in perianal fistulas. The bioabsorbable plug (Surgisis; Cook Surgical, Bloomington, IN, USA) is a xenograft made of lyophilized porcine intestinal submucosa. Its advantages include resistance to infections, absence of foreign-body reaction, and allowance for the repopulation of cells and tissues from the patient in a period of approximately 90 days [41]. The other available device is the synthetic plug (GORE Bio-A; W.L. Gore and Associates, Flagstaff, AZ, USA), which is composed by polyglycolic acid and trimethylene carbonate, two absorbable synthetic materials placed into the fistula tracks and fixated to the internal openings [27]. A recent meta-analysis reviewed the literature for the use of fistula plugs versus flap procedures in cryptoglandular fistulas. The authors revealed that the flap procedures had superiority over the plug in terms of healing and recurrence rates after pooling of RCTs with long-term follow-up. There were no significant differences in fistula complications between the procedures. In all studies, the healing rate and recurrence are between 20–80%. The GORE plug has since been taken off the market.

The literature on PFCD is summarized in Table 3.

Fistulectomy with Primary Sphincter Reconstruction

In recent years, a direct repair (primary reconstruction) in distal fistulas was investigated and shows excellent results. There is no prospective trial including this technique in PFCD. However, retrospective studies could demonstrate promising results [3, 33, 46] (Table 4).

Conclusion

Fistulas remain one of the major unmet needs in the treatment of CD patients. To date, only a limited number of effective therapies have been established. Most of the evidence on the following treatment options is derived from subgroup analyses or insufficiently defined secondary outcome measures. As a consequence, any interpretation of the effectiveness of agents (above all comparative statements) have to be made with great caution. Long-term follow-up demonstrates that recurrence rates after the repair of complex fistulas for CD are high and continuously increase over time [47]. The dogma of surgery being but the last resort for anal CD needs to be revised. A strategy combining optimal medical therapy and sphincter-sparing surgery may successfully treat anal manifestations of CD and avoid progress without causing relevant functional impairment.

As mentioned above, it is not the singular surgical or medicinal measure that is effective in the therapy of PFCD. The best approach is a multimodal therapy concept in cooperation with an experienced gastroenterologist and experienced coloproctological surgeon. Through a combination of promising approaches in both disciplines, significant improvements in the therapy of PFCD can be achieved. Furthermore, a precise definition of fistula healing as opposed to asymptomatic fistula should be defined for the interpretation of future and existing literature.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

Author Contributions

S. Seyfried and A. Herold acquired and analyzed the data.

Both authors interpreted the data, revised the article for important intellectual content, and gave final approval of the version to be published.

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