

## Treatment of peri-anal fistula in Crohn's disease

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### Abstract

Anal fistulas are a common manifestation of Crohn's disease (CD). The first manifestation of the disease is often in the peri-anal region, which can occur years before a diagnosis, particularly in CD affecting the colon and rectum. The treatment of peri-anal fistulas is difficult and always multidisciplinary. The European guidelines recommend combined surgical and medical treatment with biologic drugs to achieve best results. Several different surgical techniques are currently employed. However, at the moment, none of these techniques appear superior to the others in terms of healing rate. Surgery is always indicated to treat symptomatic, simple, low intersphincteric fistulas refractory to medical therapy and those causing disabling symptoms. Utmost attention should be paid to correcting the balance between eradication of the fistula and the preservation

of fecal continence.

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**Key words:** Fistula; Crohn's disease; Perianal fistula; Surgery; Surgical treatment; Seton; Anal fistula treatment

**Core tip:** Treatment of anal fistulas in Crohn's disease is a challenging clinical problem. Although several studies have been published, a consensus on treatment strategy has not yet been achieved. Clinical experience suggests that treatment should be determined according to the type and clinical behavior of the fistula. Asymptomatic fistulas should not be treated, while symptomatic ones could benefit from combined medical and surgical treatment. Surgery can vary from simple drainage and setonage, to more complex and sophisticated procedures. The overall aim of the surgical procedures is fistula healing without compromising fecal continence.

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### INTRODUCTION

Crohn's disease (CD) causes inflammation of the lining of the digestive tract, which can lead to severe complications. Inflammation caused by CD can involve different areas of the digestive tract, including the perianal region and the colon (in about 30% of patients). The incidence of perianal fistulas in CD patients ranges from 11 to 38%, and the frequency has been shown to increase with disease duration, being more frequent in patients with colorectal involvement. The etiology of perianal

fistulas in CD remains unclear, but it is often indicative of a more aggressive disease<sup>[1-5]</sup>. The external openings of the sinus tracts are mostly localized in the perianal region, but can also be detected in the buttock, groin, vulva or scrotum. CD fistulas should always be regarded as complex, even though a simple and single sinus tract is the only finding in many instances. There are several classifications of fistula-in-ano according to current European guidelines<sup>[1]</sup>, although the Parks' classification<sup>[6]</sup> is currently used. Four groups of fistulae are recognized, according to their relation with the sphincter muscle: (1) extrasphincteric, extending from an internal opening in the bowel proximal to the anus; (2) intersphincteric, traveling along the intersphincteric plane to the perianal skin; (3) transsphincteric, encompassing a portion of the internal and external sphincter; and (4) suprasphincteric, encompassing the entire sphincter apparatus.

## CLINICAL MANIFESTATION

Symptoms can vary, including anal pain, purulent discharge and incontinence, and can be associated with high morbidity and an impaired quality of life. This issue assumes particular relevance in younger patients<sup>[1]</sup>. Perianal disease may develop before the appearance of gastrointestinal symptoms, even several years before the diagnosis of CD<sup>[1,3]</sup>. The natural history is characterized by a chronic relapsing course, and it may be complicated with perianal sepsis. The recent use of biologic treatments, coupled with a surgical approach, has significantly changed the natural history of perianal disease.

## DIAGNOSIS AND ASSESSMENT

A rectosigmoidoscopy is always mandatory when assessing perianal disease in patients with CD, as the presence of rectosigmoid involvement of the lesions is predictive of a more aggressive course<sup>[1]</sup>. The gold standard for assessing a fistula-in-ano is the exploration of the anal canal and distal rectum under anesthesia (EUA)<sup>[1,3,7]</sup>. The aim of this procedure is to find the internal orifice and to classify the fistula according to its relationship with the sphincteric apparatus. EUA can be also accompanied by drainage of abscesses and fistula treatment, thus allowing the use of immunomodulators. As also stated by the current European guidelines<sup>[1]</sup>, EUA is considered the gold standard only in the hands of an experienced surgeon.

Additional diagnostic modalities useful for assessing perianal disease in CD include magnetic resonance imaging (MRI) or transanal endoscopic ultrasound (EUS). The sensitivity and specificity of both techniques are lower than EUA and an experienced radiologist or gastroenterologist, respectively, are required in order to achieve a reliable assessment of the perianal lesions<sup>[1,8,9]</sup>. Pelvic MRI is accurate and non-invasive, although patients' compliance or obesity may not allow its use in a subgroup of patients<sup>[10-12]</sup>. Moreover, in contrast to transanal EUS, pelvic MRI does not allow the visualization of the rectal

mucosa. This represents a major limitation in the assessment of perianal disease in CD, as rectal involvement is associated with a worse outcome of perianal disease. Nevertheless, MRI-based scores can be derived to assess the activity of CD, based on the extent and severity of intestinal inflammation, post-operative recurrence and perianal disease<sup>[13]</sup>. The accuracy of EUS is comparable to pelvic MRI for assessing perianal CD, and additionally also allows the assessment and histological examination of the rectal mucosa<sup>[8-10,12]</sup>. However, transanal EUS cannot be performed in the presence of rectal stenosis.

The few studies comparing the sensitivity, specificity, and negative and positive predictive values of these three diagnostic modalities support EUA performed by an experienced dedicated surgeon as the gold standard, which allows not only a proper assessment, but also a local treatment of the disease. The combined use of the three procedures is thought to represent the best modality to assess perianal disease in CD<sup>[1,10,12]</sup>. Nevertheless, the high cost of this approach limits its use in clinical practice. Therefore, even in referral centers, EUA by an experienced surgeon is often the chosen method, particularly in symptomatic patients requiring surgical drainage or treatment. For asymptomatic patients, local availability of either pelvic MRI or EUS should determine the choice for assessing perianal disease in CD. MRI and EUS can also be used in order to assess the response to biologic therapies, including anti-tumor necrosis factor (TNF) monoclonal antibodies.

The usefulness of computed tomography with intravenous contrast is limited to the visualization of abscesses in the ischiorectal fossa. Additionally, fistulography is not recommended for assessing perianal disease<sup>[1]</sup>.

## MANAGEMENT

Management of perianal CD is a relevant clinical issue, as this condition is characterized by a recurrent course and relapses after temporary fistula closure. The aim of treatment is to reduce symptoms, prevent or treat complications, induce fistula closure and improve the quality of life. The recent use of anti-TNFs has been shown to significantly improve the course of perianal disease in CD. Treatment should be determined according to the type and severity of the fistula. However, treatment is related to symptoms, and asymptomatic perianal fistulas should not be treated. Furthermore, for treatment of luminal CD, a multidisciplinary approach including a dedicated gastroenterologist, surgeon and radiologist is advisable. For symptomatic fistulas, antibiotic treatment is recommended before treatment with immunomodulators and/or anti-TNFs<sup>[5,14,15]</sup>.

Although multicenter, randomized placebo-controlled studies including large series of patients are currently lacking, current evidences suggest that the use of metronidazole (750-1500 mg/d), ciprofloxacin (1 g/d) or both, shows efficacy in terms of temporary relief of symptoms and in treating local complications. Antibiotic-therapy has

not been shown to be efficacious in terms of fistula closure<sup>[1,5,14,15]</sup>. However, a proper evaluation of the optimal treatment strategies has been constrained as trials on the use of metronidazole and ciprofloxacin for perianal CD utilize different study designs, with different antibiotic dosages, combinations and durations of treatment.

Azathioprine (AZA; 2.0-2.5 mg/kg, by mouth) or 6-mercaptopurine (6-MP; 1.0-1.5 mg/kg, by mouth) are immunomodulators indicated for perianal fistulas in CD patients failing treatment with antibiotics with or without previous surgical treatment<sup>[1,16,17]</sup>. The presence of a perianal abscess should be excluded by using EUA and/or EUS or pelvic MRI and it requires surgical drainage and often the placement of a draining seton<sup>[1]</sup>. The efficacy of AZA and 6-MP requires at least 3-6 mo of treatment. In patients failing treatment with AZA or 6-MP, biologics therapy using anti-TNFs such as Remicade or adalimumab is recommended, as they have been shown to induce fistula closure in up to 36% of patients at 56 wk<sup>[1,18-21]</sup>. Remicade (5 mg/kg, iv) at 0, 2, and 6 wk, followed by maintenance treatment every 8 wk, or adalimumab (160, 80, or 40 mg, sc) at 0, 2, and 4 wk, followed by maintenance treatment every 2 wk currently represent the more effective treatments for inducing fistula healing in CD. Interestingly, MRIs show that anti-TNF treatment, though able to induce the healing of the external orifice, may not be sufficient to close the fistulous tract<sup>[22]</sup>. This observation accounts for the relapse of local discharge and for the development of perianal abscesses along the fistulous tract. Preliminary observations suggest that local injection of Remicade in the fistulous tract may be useful in inducing fistula healing<sup>[23,24]</sup>. However, these are preliminary observations that need to be confirmed by randomized controlled trials.

Fistulous tracts have been treated by injection with biologic glues. Injection of a novel cyanoacrylic glue using image-guided percutaneous techniques has been used to treat post-surgical fistulas, but results need to be confirmed<sup>[25]</sup>. In a randomized controlled trial, injection of the fistulous tract with fibrin glue demonstrated a 38% success rate<sup>[26]</sup>. The failure rate associated with fibrin glue injection was attributed to the difficulty in ensuring that the glue remained in the fistula tract<sup>[27]</sup>. Discrepant findings concerning biologic glues have been reported in a meta-analysis<sup>[28]</sup>. As for local injections, these observations need to be confirmed by multicenter studies including a larger number of patients. Additional preliminary observations in a preclinical study suggest that autologous fibroblasts added to the collagen glue may improve the outcome of perianal disease when compared with patients treated with the glue only<sup>[27]</sup>. The addition of autologous fibroblasts to the collagen glue has been suggested to reduce the slippage of the glue from the fistulous tract<sup>[28]</sup>.

## SURGICAL TREATMENT

Surgical treatment of fistulas can vary from simple drain-

age to more complex and sophisticated procedures. The surgical approach depends upon the type of fistula and its anatomical extent. It is important to remember that in CD, only symptomatic perianal fistulas need surgery. Some fistulas can be surgically excised and a cure achieved, whereas other patients will benefit from symptom palliations. Palliation usually comes in the form of drainage and thereafter, a long-term, comfortable, loose, seton<sup>[29]</sup>.

Surgery should be considered in patients who have simple, low, intersphincteric fistulas or fistulas refractory to medical therapy and those who have severe or disabling symptoms. However, surgery should not be performed in patients with active proctitis. The goals of surgery are to eradicate the fistula while preserving fecal continence, or to reduce symptoms by making management easier for the patient, such as by transforming a complex fistula into one closer to the anus. Surgical options include long-term setons, cutting setons, fibrin glue, fistula plugs, fistulotomy, fistulectomy, advancement flaps, and proctectomy.

For patients with intersphincteric or low transsphincteric fistulas, fistulotomy is advised and may lead to healing in a significant number of patients. It is not a feasible option when the fistula incorporates a significant amount of the internal and external anal sphincter, as occurs with high transsphincteric fistulas. To avoid poor healing and higher recurrence risk, good patient selection is mandatory and surgery should be delayed whilst optimizing the treatment of active proctitis<sup>[30]</sup>.

Advancement flaps can be used as a sphincter-preserving technique for some higher fistulas in CD. The transanal mucosal advancement flap involves creating a flap of mucosa and a portion of the muscular wall of the rectum from around the internal opening of the fistula and into the lower rectum. The internal opening of the fistula is excised from the distal flap, and the flap is sutured to the distal dissection plane to cover the area of the formal internal opening and to create a neo-dentate line. The success rate of advancement flaps, based on a systematic review of more than 2000 procedures (a small subset having CD) is 64%, with incontinence rates of 9.4%<sup>[31]</sup>.

It is our belief and experience that in complex fistulas, the first line of treatment is often a loose non-cutting seton. This option is a safe one; it helps the drainage of the sinus, prevents development of a more complex scenario, and it is mostly well-tolerated. A loose seton may be passed and subsequently, associated treatment with anti-TNF therapy is offered; in this case the healing rate is 47%-79%<sup>[30]</sup>. A loose seton can be converted, in select cases, in a cutting seton. Cutting setons result in low recurrence rates, but can cause incontinence in up to two-thirds of patients<sup>[32]</sup>.

Apart from the original technique of fistulectomy and fistulotomy, several different approaches have been described to treat perianal fistulas. However, it is important to remember that all these techniques have been designed to treat complex fistulas in otherwise healthy individuals.

Moreover, most of the reported results are from series of fistulas not associated with CD or mixed-case series.

The ligation of the intersphincteric fistula tract (LIFT) procedure is a modern technique based on secure closure of the internal opening and removal of infected tissue through the intersphincteric approach. Essential steps of the procedure include incision at the intersphincteric groove, identification and ligation of the intersphincteric tract close to the internal opening, and removal of the intersphincteric tract. LIFT has been associated with fistula closure rates between 57% and 94%, but higher quality of evidence with longer follow-up is still needed<sup>[33,34]</sup>. In one study involving four CD patients, the LIFT procedure was successfully combined with the placement of a biosynthetic graft<sup>[35]</sup>. However, further studies are necessary before the LIFT procedure in any form can be recommended in the treatment of CD perianal fistulas.

The Surgisis® anal fistula plug (Cook Surgical, Bloomington, IN, USA) is a bioabsorbable xenograft made of lyophilized porcine intestinal submucosa. The material is resistant to infection, provides no foreign body or giant cell reactions, and becomes repopulated with patient's cells and tissues over a period of three months. The success rates reported for this plug are variable and range from 13% to 86%<sup>[36]</sup>. A theoretical advantage to using this plug is that the operative technique involves suturing the plug to the internal anal sphincter at the site of the internal opening, which keeps the material in place and allows time for ingrowth.

A promising technique involves the use of stem cells to stimulate fistula closure. Garcia-Olmo *et al.*<sup>[37]</sup> performed a randomized clinical trial comparing adipose-derived stem cells injected into the rectal mucosa and fibrin glue. The fistula closed in 71% of patients in the stem cell group compared with 16% in the fibrin glue group.

The continued search for innovative techniques, have led to the use of video-assisted anal fistula treatment (VAAFT). An initial report by Meinero and Mori showed promising results with the VAAFT technique in patients with complex anal fistulas<sup>[38]</sup>. This technique allows a direct visualization of all the sinus tracts with the aim to reduce recurrence. Schwandner combined VAAFT with advancement flaps and showed a high identification rate of occult side tracts with encouraging short-term healing rates<sup>[39]</sup>. However, only a small percentage of the VAAFT series included CD patients, thus the technique needs further evaluations with increased sample sizes and long-term follow-ups.

In our unit, we are currently assessing the feasibility of outpatient exploration of the anal canal and distal rectum. Preliminary findings suggest that outpatient explorations is feasible in the vast majority of patients and that it is possible to perform a complete treatment in over 80% of patients<sup>[40]</sup>. We strongly believe that the key to success is a multidisciplinary approach; the patients were well-known to all the members of the team, and were in regular follow-ups at our Inflammatory Bowel Disease Refer-

ral Center. Patients with perianal CD are all seen in a joint clinic by the referring gastroenterologist and surgeon, and a specialist nurse trained as a theater nurse is also always present. Finally, a diverting stoma may become necessary in cases of recurrent fistulas refractory to medical treatment or in cases with severe urogenital complications, fecal incontinence or severe proctitis. It is our experience, however, that a stoma will very rarely be reversed and in many instances, a proctectomy will follow.

## CONCLUSION

Perianal disease is a troublesome condition for both patient and surgeon. Management of this condition involves a delicate balance between the eradication of the fistula and preservation of fecal continence. It requires a multidisciplinary collaboration between a dedicated gastroenterologist, surgeon and radiologist. Surgery should be conservative and patient collaboration and understanding of the scope of surgery is crucial for optimal management.

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