

Management of perianal fistulas in Crohn's disease: An up-to-date review

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Abstract

Perianal disease is one of the most disabling manifestations of Crohn's disease. A multidisciplinary approach of gastroenterologist, colorectal surgeon and radiologist is necessary for its management. A correct diagnosis, based on endoscopy, magnetic resonance imaging, endoanal ultrasound and examination under anesthesia, is crucial for perianal fistula treatment. Available medical and surgical therapies are discussed

in this review, including new local treatment modalities that are under investigation.

Key words: Crohn's disease; Perianal fistula; Surgery; Drug therapy; Tumor necrosis factor alpha

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Core tip: Combined medical and surgical treatments are needed to treat perianal Crohn's disease, after a correct diagnosis.

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INTRODUCTION

Perianal fistulas are a very disabling manifestation and source of morbidity for Crohn's disease (CD) patients. Population-based studies showed that the cumulative incidence of perianal fistulas in CD range from 23% to 38%^[1,2]. Disease location, age at diagnosis, fistula type, presence or absence of abscesses and intestinal strictures may influence the natural history of perianal CD^[3]. The presence of colonic and rectal disease represents the greatest risk factor for the development of perianal fistulas^[1]. Main symptoms reported by patients are pain associated to perianal swelling and fever in case of abscess formation and drainage of pus, stool or blood from cutaneous fistula openings. In patients with longstanding chronic active perianal disease fecal incontinence may occur. The treatment of

perianal CD requires a combined surgical and medical approach^[4] and should attempt to the resolution and the prevention of septic complications, the reduction of fistula discharge with the improvement of patients' quality of life and, finally, the healing of fistulas.

AETIOLOGY AND PATHOGENESIS

The aetiology of perianal fistulas in CD is still unclear: according to one theory they result from deep penetrating ulcer of the rectum or anus; another hypothesis supports their origin from an anal gland abscess. CD pathogenesis is currently thought to derive from a disorder of intestinal barrier, triggering innate immunity activation on a genetic favorable background and an altered gut microbiota composition. Perpetuation of inflammation depends on an unbalanced stimulation of adaptive immune system, facilitated by inappropriate leukocyte recruitment. In this setting, specific pathways are recognized as specifically altered in perianal CD. Fistulae originate by an epithelial defect caused by inflammation whose repair is impaired because the migratory potential of colonic lamina propria fibroblasts is reduced in CD^[5]. This could lead to the migration of intestinal epithelial cells (IEC) as an alternate repair mechanism. IEC undergo a conversion into mesenchymal-like cells (myofibroblasts) by a process called epithelial-to-mesenchymal transition (EMT), mainly induced by TGF- β but also influenced by other cytokines like TNF- α and IL-13 and other mediators like Dickkopf-Homolog-1. Furthermore, the IEC present on the inner surface of the fistula tract undergo transformation into transitional cells (TC) that pave the fistula tract and express both mesenchymal and epithelial cell markers^[6,7]. Another key mechanism of fistula formation is the extracellular matrix (ECM) remodeling suggested by the up-regulation of some matrix metalloproteinases (MMP) like MMP-3 and MMP9 in CD fistulas^[7]. Bacteria have a recognized role in the occurrence and persistence of both idiopathic (criptoglandular) and CD perianal fistulas. It is known that polymorphisms in nucleotide oligomerization domain 2 (*NOD2*) gene are associated with fistula formation in CD^[8]. Distinct pathogen-associated molecular patterns (PAMPs) like muramyl-dipeptide, the *NOD2* ligand, seem to be critical for fistulas pathogenesis, by inducing EMT^[7].

PATHOLOGY

CD-associated fistulae appear as a fissure penetrating in the gut wall, surrounded by granulation tissue with acute (neutrophils) and chronic (lymphocytes) inflammation. Their lumen is filled up by nuclear debris, sometimes erythrocytes. Fistulas may show some degree of lining epithelium, consisting of flattened intestinal epithelium without goblet cells or

squamous epithelium, while non-epithelialised fistulae are covered by a thin layer of myofibroblasts, focally forming a new basement membrane. Differential mononuclear infiltrate is present in CD fistulae (a central infiltration by CD45R0⁺ T cells, followed by a small band of CD68⁺ macrophages and dense accumulation of CD20⁺ B cells), as opposed to non-CD fistulas where there is a dense infiltration by CD68⁺ macrophages with only few CD20⁺ B cells and CD45R0⁺ T lymphocytes^[9].

CLASSIFICATION

An accurate classification of perianal fistulas in patients is crucial to allow the most appropriate therapeutic approach.

Anal fistulas can be due to CD but also to trauma, tuberculosis, hidradenitis suppurativa, immunosuppression including HIV infection, lymphogranuloma venereum, sacrococcygeal teratoma, rectal duplication and perianal actinomycosis, with similar clinical manifestations.

The first classification of perianal fistulas was proposed by Parks *et al.*^[10], who classified fistulas in 5 different types, using the external sphincter as the reference point and considering their surgical anatomy (*i.e.*, superficial, intersphincteric, transsphincteric, suprasphincteric, extrasphincteric). An empiric and easier classification most commonly used in clinical practice has then been proposed by the American Gastroenterological Association (AGA)^[11] and distinguishes between "simple" and "complex" fistula. Simple fistulas are low, including superficial, intersphincteric or intrasphincteric fistulas below the dentate line, with a single external opening, and are characterized by the absence of perianal complications. Complex fistulas are high, arriving above the dentate line (intersphincteric, transsphincteric, extrasphincteric, suprasphincteric), with many external openings, and may be associated with perianal abscesses, rectal stricture, proctitis or connection with bladder or vagina.

In order to assess the clinical activity of perianal disease in CD, the PDAI (Perianal Disease Activity Index) score, described by Irvine *et al.*^[12], has been proposed. It includes the evaluation of 5 elements: fistula discharge, pain and restriction of activities, restriction of sexual activity, type of perianal disease, degree of induration.

The fistula drainage assessment (FDA) has been proposed to quantify fistula healing^[13] and has been utilized to standardize the clinical assessment of perianal disease in clinical trials: the presence of purulent drainage after a gentle finger compression is considered as index of activity and, on the other hand, the absence of drainage is defined as remission. Clinical response is defined as a reduction of 50% or more in the number of draining tracts. Finally, if there is no pus drainage after compression, the fistula is

considered as closed.

The use of imaging techniques improves the characterization of fistula activity in CD patients: several studies have shown that the use of contrast-enhanced magnetic resonance imaging (MRI) improves the diagnostic accuracy of perianal fistulas compared to the only clinical evaluation^[14,15]. At this regard, an MRI-based activity score was developed to assess the anatomical evolution of CD fistulas after medical therapy, demonstrating that, despite of closure of draining external opening, inflammatory changes may persist into fistula tracts^[16]. Finally, it was shown that the computer-assisted anal ultrasound increases PDAI and FDA diagnostic accuracy up to 95% and 98%, respectively^[17].

DIAGNOSIS AND IMAGING

Examination under anesthesia (EUA) is considered the gold standard to diagnose and classify perianal fistulas in CD patients. An accurate diagnosis is also possible using imaging modalities such as pelvic MRI and/or endoanal ultrasound (EUS), and, in some cases, transcutaneous perineal ultrasound (TPUS). Any of these methods should be combined with the endoscopic examination to assess the presence or absence of active inflammation in the rectosigmoid colon, the presence of internal openings or an anorectal stenosis^[18].

EUA has demonstrated to have an accuracy of up to 90% to diagnose perianal disease^[19]: it should be always performed by a colorectal surgeon who may identify fistula tracts, with the possibility to drain abscesses and place setons. It has been shown that patients with perianal fistulizing CD treated with infliximab were more likely to maintain fistula closure if anti-TNF treatment was started after EUA and seton placement^[20].

EUS and MRI represent the principal non-invasive methods for diagnosis and monitoring of perianal CD.

EUS requires a high frequency endoluminal probe (5-16 MHz) that produces 2D or 3D ultrasound images to visualize all sphincteric structures^[21]. The use of hydrogen peroxide may enhance fistula tracts, improving their identification and image definition^[22-24]. It has been described^[25] that perianal CD fistulas reveal a characteristic aspect of hypoechoic fistula tract surrounded by a well-defined hyperechoic area with a thin hypoechoic edge, defined as "Crohn's Ultrasound Fistula Sign". There was a high degree of heterogeneity between studies reporting on EUS sensitivity and specificity for fistula detection: a recent meta-analysis reported values of 0.87 (95%CI: 0.70-0.95) and 0.43 (95%CI: 0.21-0.69), respectively^[26]. In spite of the high diagnostic accuracy, EUS presents several limits, such as the operator dependence with the necessity

of a specific learning curve, the limited visualization of the external sphincter, the penetration up to the ischioanal fossa and the impossibility to be performed in case of anal stenosis.

Pelvic MRI has become the gold standard imaging technique for perianal CD: it is accurate in achieving an optimal definition of the exact route of fistulas, the presence of abscesses, the relation with sphincteric structures and muscular layers, the difference between active granulation and fibrotic tissues^[27,28]. Recent studies reported that diffusion-weighted T2 imaging may be a helpful adjunct to standard T2-weighted images, especially in patients with risk factors for contrast agents^[29]. The combined sensitivity and specificity of MRI were 0.87 (95%CI: 0.63-0.96) and 0.69 (95%CI: 0.51-0.82), according to a recent meta-analysis^[26].

Several studies have compared MRI with EUA and EUS in the description of perianal CD: in 2001, Schwartz *et al.*^[19] reported a good agreement among EUS, MRI and EUA with accuracy respectively of 91%, 87% and 91%. The combination of any two exams increased the accuracy up to 100%. Another study showed a higher accuracy of MRI to assess classification of fistulas, the presence of secondary fistula tracts, abscesses and internal openings^[30]. Moreover, MRI resulted more sensitive than clinical examination (0.97, 95%CI: 0.92-1.01 and 0.75, 95%CI: 0.65-0.86, respectively), but comparable to EUS (0.92, 95%CI 0.65-0.86) for discrimination of complex from simple fistulas^[31].

TPUS seems to be a further simple and accurate diagnostic method for classifying perianal fistulas in CD and could be used for the preliminary assessment and follow-up of some cases of perianal CD, with the limit of a narrow view in identifying deep abscesses^[32,33].

Fistulography and CT are two obsolete techniques in the diagnostic evaluation of perianal fistulas in CD patients with several limitations: ionizing radiations and the limited resolution to distinguish between fibrotic and septic fistula tissue^[34].

MEDICAL TREATMENT

Antibiotics

Ciprofloxacin and metronidazole are used as first-line and adjuvant therapy for perianal CD. Literature data about their use are few, uncontrolled and characterized by studies with small simple sizes. In the first reports, patients treated with both metronidazole and ciprofloxacin showed good clinical response rates after 6-8 wk of treatment, but frequent recurrence of drainage, symptoms and fistula re-opening after discontinuation^[35,36]. In a pilot study, remission and response occurred more frequently in patients after 10 wk of treatment with ciprofloxacin compared with metronidazole, but

differences were not statistically significant^[37]. Other studies suggested a benefit using metronidazole ointment, that resulted effective to reduce pain and discharge with minimal adverse effects, even if without a significant reduction of PDAI score^[38]. Antibiotics have also been studied as bridge or adjuvant therapy to immunomodulators or biologics. Combination treatment with antibiotics and azathioprine was significantly superior to antibiotic therapy alone in achieving week-20 clinical response in a prospective open-label study (48% vs 15%, $P = 0.03$)^[39]. In a double-blind placebo-controlled study, 24 perianal CD patients were assigned to receive ciprofloxacin or placebo in addition to infliximab: week-18 response was 73% in the ciprofloxacin group vs 39% in the placebo group ($P = 0.12$)^[40]. A multicenter double-blind placebo-controlled study on 76 patients with perianal CD evaluated adalimumab in combination with ciprofloxacin: week-12 clinical response was observed in 71% of patients treated with adalimumab plus ciprofloxacin vs 47% of patients treated with adalimumab plus placebo ($P = 0.047$). Moreover, week-12 remission rates were significantly higher in the combination group compared with the placebo group (65% vs 33%, $P = 0.009$)^[41]. According to these evidences and to the most recent European guidelines for the treatment of perianal CD^[4], despite few published data, antibiotics should be added to medical and surgical treatment, in order to avoid local sepsis and to maintain clinical response.

Immunosuppressors

No randomized controlled trials have directly assessed the effect of thiopurines in patients with perianal CD. Data regarding the use of thiopurines in this setting come from a meta-analysis of 3 randomized-controlled trials, in which perianal fistula closure was assessed as secondary endpoint, showing that azathioprine and 6-mercaptopurine did not show significant efficacy as compared with placebo in improving or closing fistulas (risk ratio, = 2; 95%CI: 0.67-5.93)^[42]. However, this pooled analysis included only 18 patients, implying the need for further research to determine if azathioprine (and 6-mercaptopurine) could provide a benefit for perianal fistula healing in CD.

The use of azathioprine in combination with antibiotics has already been reported^[39]. Other immunomodulators including cyclosporin, tacrolimus, methotrexate and thalidomide have been considered in the management of perianal CD. Most patients who respond to intravenous cyclosporine will maintain their response during subsequent oral therapy. However, the majority of them relapses when oral cyclosporine is discontinued^[43]. Therefore, the use of intravenous cyclosporine could be useful in the initial management of refractory CD fistulas, although

relapse as serum levels are lowered and infectious complications are limiting factors for long-term use as a single agent^[44]. A randomized, placebo-controlled trial was performed to investigate the role of oral tacrolimus in 48 patients with perianal CD: 43% of tacrolimus-treated patients had fistula improvement compared with 8% of placebo-treated patients ($P = 0.004$), but only 10% of tacrolimus-treated patients had fistula remission (maintenance of fistula closure for at least 4 wk) compared with 8% of placebo-treated patients ($P = 0.86$)^[45]. There are small case series and a little evidence about the use of methotrexate in monotherapy in fistulizing perianal CD: 56% of patients with perianal CD on methotrexate showed a complete or partial response to therapy, but further placebo-controlled studies are needed to confirm these findings^[46]. Also thalidomide seems to be an effective short- to medium-term treatment in patients with perianal CD refractory to standard therapies, but its long-term use is limited by toxicity^[47].

Anti tumor necrosis factor alpha agents

The introduction of anti-tumor necrosis factor alpha (TNF- α) agents has deeply improved the management of perianal CD. The mechanism of action of anti-TNF- α agents remains unknown. A down-regulation of pro-inflammatory cytokine, an activation of transmembrane TNF-mediated reverse signaling, an induction of apoptosis, a cytotoxicity cell- or complement-mediated, an activation of regulatory immune cells are the main molecular mechanisms of action proposed^[48].

Infliximab, adalimumab and certolizumab pegol have clearly demonstrated the benefit for the induction and the maintenance of remission in perianal CD^[49].

The first placebo-controlled trial with infliximab showed that 68% of patients who received 5 mg of infliximab per kilogram and 56% of those who received 10 mg per kilogram achieved the primary end point, that was a reduction of 50% or more from baseline in the number of draining fistulas, as compared with 26% of the patients in the placebo group ($P = 0.002$ and $P = 0.02$, respectively). In addition, 55% and 38% of patients assigned to receive respectively 5 mg and 10 mg of infliximab per kilogram had closure of all fistulas, as compared with 13% of the placebo group ($P = 0.001$ and $P = 0.04$, respectively). The median length of time during which fistulas remained closed was 3 mo^[13]. According to the ACCENT II trial, patients with fistulizing CD, who had a response to induction therapy with infliximab and continued it as maintenance treatment, had an increased likelihood of sustained response over a 54-wk period: cessation of drainage at week 54 was maintained in 36% of the patients in the infliximab group compared

with 19% of the placebo group ($P = 0.009$)^[50]. Results from the ACCENT II trial also reported that abscess development in patients with fistulizing CD was not dependent on cumulative infliximab exposure^[51] and that infliximab 5 mg/kg every 8 wk significantly reduced hospitalizations, surgeries, and procedures compared with placebo^[52]. Combination therapy with immunosuppressors, duration of seton drainage and long-term treatment with infliximab seem to be associated with better outcomes^[53]. In the SONIC trial, that assessed efficacy of infliximab and azathioprine in monotherapy compared with their combination in patients with CD, about 12% of included patients had perianal fistulas; however, a separate analysis was not performed to compare benefits among each treatment group^[54].

Adalimumab was more effective than placebo for inducing fistula healing: the CHARM extension study demonstrated that the mean number of draining fistulas was significantly decreased in adalimumab-treated patients compared with those treated with placebo during the double-blind treatment period (33% vs 13%, $P < 0.05$)^[55]. Among all patients with healed fistulas at week 56 (both adalimumab and placebo groups), 90% maintained healing following 1 year of open-label adalimumab therapy^[56]. In the CHOICE trial, adalimumab demonstrated to be effective in inducing complete fistula healing (39% of patients) with a good safety profile and improving quality of life and work productivity in patients with CD who previously failed infliximab therapy^[57]. Also, Echarri *et al.*^[58] evaluated the response to adalimumab in patients with perianal CD unresponsive to infliximab, showing 50% of complete response after 4 wk of adalimumab therapy with 87.5% of these patients remaining in remission after 48 wk of maintenance treatment.

There are very few data about the role of certolizumab in perianal CD. A subgroup analysis of the PRECISE trial found a significant increase in the number of fistula closure in the treatment group compared to placebo: at week 26, 36% of patients in the certolizumab pegol group had 100% fistula closure compared with 17% of patients receiving placebo ($P = 0.038$), but no statistical difference was found in the primary endpoint (closure of at least 50% of fistulas)^[59].

Guidelines are evolving on the topic of first line medical treatment of perianal complex CD. The published 2010 European guideline^[4] proposes thiopurines with antibiotics, in combination with surgical therapy, as the first line therapy, and anti-TNF- α agents as second line drugs. According to the IG-IBD (Italian Group for the study of Inflammatory Bowel Disease) clinical practice guidelines, anti-TNF- α agents should be used as the first choice of medical therapy for complex perianal CD^[60]. This concept is also advocated by the most recent consensus

paper^[34], that also considers anti-TNF- α agents as the current gold standard for the medical treatment of perianal complex CD. Maintenance therapy after successful biological agents induction is mandatory. Infliximab or adalimumab or thiopurines, after drainage of sepsis, should be used as maintenance therapy^[60].

SURGICAL TREATMENT

Surgical management of perianal CD is complex and many surgical options are available

Fistulectomy and fistulotomy are the preferred options in case of simple superficial fistulas and occasionally in low intersphincteric fistulas, because of the risk of incontinence: in these selected perianal disease the healing rate is up to 80%-100%^[11].

Complex or high fistulas typically require a different approach. The most common acute presentation of perianal CD is an abscess that requires drainage in order to avoid sepsis. After surgical abscess drainage, the next step in order to prevent further abscess formation and stable sepsis drainage, while preserving the external sphincter function, is the placement of non-cutting setons^[61,62]. A combined surgical and medical approach has been demonstrated to be extremely effective for the treatment of complex perianal CD^[63,64]. The use of non-cutting seton placement combined with infliximab have shown better results in several studies, as compared to infliximab alone. Obviously, it is important to perform surgery for perianal disease including abscess drainage and seton placement before anti-TNF- α therapy, to avoid septic complications and to optimize the therapeutic results. In the open label Regueiro's study CD patients treated with infliximab and non-cutting seton placement had a better outcome than patients treated with infliximab alone in terms of response rate (100% vs 82.9%, $P = 0.014$), recurrence rate (44% vs 79%, $P = 0.001$), time to recurrence (13.5 mo vs 3.6 mo, $P = 0.0001$)^[20]. Similar results were obtained in two other case series with a complete response in 67% of patients^[65], and a complete perineal healing in 47% of cases with a follow-up of 20 mo^[66]. However, the best clinical management in complex perianal CD has yet to be defined since the timing of seton removal is not clearly established. In the first studies^[20,50,66] it was reported that setons were removed at the time of the second infliximab infusion or 2-4 wk after the second infusion. Most recent evidences show that seton removal after the complete induction of infliximab^[63] or at least after 5 rounds of infliximab infusion^[67] ensures a longer duration of the effect and a lower recurrence rate.

Moreover, reparative surgery, which includes "mucosal advancement flap", during infliximab therapy, may improve long-term healing rates. Notably, it can be successfully performed only in case of

lack of active proctitis. The concept of endorectal advancement flaps is to preserve the sphincter by closing off the primary opening by means of a mobilized flap. A systematic review of the literature to assess the role of this technique reported that weighted success and incontinence rates were 64% and 9.4% for CD fistulas^[68].

Fibrin glue is a mix of fibrinogen and thrombin that allows healing, hemostasis and angiogenesis: in order to assess the effectiveness of injecting heterologous fibrin glue as a mean of treating CD fistulas that are refractory to medical treatment, many case series were published but the results are discordant^[69-72].

Higher rates of healing than those of the fibrin glue were obtained with the "fistula plug"^[73], consisting of inert porcine intestinal submucosa inserted in the internal fistula opening to fill the fistula tract^[74]. A recent systematic review summarizes the anal fistula plug literature for CD and non-CD perianal fistula in a homogenous patient population: fistula closure is achieved by using the anal fistula plug in approximately 54% of patients without CD, with similar proportion in CD patients^[75]. Plug protrusion after surgical insertion is the main cause of treatment failure.

"Ligation of the intersphincteric fistula tract" (LIFT) is a new surgical approach that consists of ligation of intersphincteric tract close to the internal opening and removal of intersphincteric tract, scraping out all granulation tissue in the rest of the fistulous tract and suturing of the defect at the external sphincter muscle^[76]. In a prospective study of fifteen consecutive cases of CD patients with transsphincteric fistulas, none of them developed fecal incontinence and LIFT site healing was seen in 67% of patients with a follow-up of 12-mo^[77].

Mesenchymal stem cells seem to have promising applications in perianal CD. They are non-haematopoietic precursors of connective tissue cells with anti-inflammatory and tissue regenerative properties, extracted from subdermal adipose tissue obtained through liposuction. They may be injected into the rectal mucosa around fistula opening and into fistula tract with fibrin glue^[78]. Garcia-Olmo *et al.*^[79] reported a phase II study in which adipose derived stem cells in fibrin glue vs fibrin glue alone were administered in 49 patients (14 affected by CD): fistula healing was observed in 16% of the patients who received only fibrin glue vs 71% of the patients who received stem cells plus fibrin glue ($P < 0.001$). An Italian study, employing autologous bone marrow-derived mesenchymal stromal cells confirmed that this novel approach represents a feasible, safe and beneficial therapy in refractory CD^[80]. A recent multicenter open-label, single-arm clinical trial was conducted at six Spanish

hospitals. Twenty-four CD patients with complex fistulas were treated intralesionally with 20-40 millions of expanded allogenic adipose-derived stem cells: 69% of patients showed a reduction in the number of draining fistulas at week 24, while 56% achieved complete closure of the treated fistula and 30% obtained complete closure of all existing fistula tracts^[81]. However, double-blind randomized placebo-controlled trials are necessary to draw any conclusions on this therapeutic modality.

Uncontrolled evidence suggest that local injection of anti-TNF- α into the fistula tract may be beneficial in patients not responding or intolerant to biological therapy. Two Italian groups described in pilot trials how local injections of both infliximab and adalimumab could improve fistula healing avoiding their systemic actions, but controlled and randomized trials are required to prove the value of this technique^[82-85].

In those patients with severe disease refractory to all medical and surgical therapy a diverting temporary stoma may be necessary. CD patient with complex fistulas associated with uncontrollable and debilitating abscesses, recurrent sepsis, colonic or perineal disease, refractory proctitis, anal stenosis are candidate, as last option, to perform proctectomy with a permanent stoma^[86].

The surgical management of perianal fistulas not related to CD often requires multiple procedures, causing a risk for continued symptoms and fecal incontinence^[87]. The first step of the treatment of simple perianal fistulas not CD related is a local treatment with fibrin glue in order to preserve the continence: the results about fistula plugs are promising but need further studies. Lower and intersphincteric fistulas can be treated by fistulotomy with a preservative sphincter surgery. Higher, complex and suprasphincteric fistulas can be treated initially with curettage and seton placement followed by surgery. Excision of the external fistula tract, closure of the internal opening, and a local advancement flap are alternative solutions^[88].

CONCLUSION

As evidenced by this review, combined medical and surgical treatments are needed to treat perianal CD, so the optimal management involves a multidisciplinary team including dedicated radiologists, colorectal surgeons and gastroenterologists experienced in the management of CD. After a precise diagnostic definition of the perianal disease using proctosigmoidoscopy, MRI, EUS and EUA, drainage of local sepsis represents the first line approach before other treatments. For simple perianal CD fistulotomy or non-cutting seton placement are the recommended options; antibiotics should be

added. The management of complex perianal CD provides an appropriate surgical therapy, usually with non-cutting seton placement, in combination with antibiotics and thiopurines^[4]. The concomitant rectal inflammation must always be treated. According to the recent experiences, the choice of anti-TNF- α agents as the first line treatment in complex perianal CD, associated to surgical therapy, seems to be the optimal strategy for the induction and maintenance of fistula closure^[34,60]. New topical treatment modalities, including the use of glues, plugs and stem cells injection, are under evaluation.

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