**Name of journal: World Journal of Gastroenterology**

**ESPS Manuscript NO: 9440**

**Columns: EDITORIAL**

**Treatment of peri-anal fistula in Crohn’s disease**

Sica GS *et al*. Treatment of peri-anal fistula in CD

**Giuseppe S Sica, Sara Di Carlo, Giorgia Tema, Fabrizio Montagnese, Giovanna Del Vecchio Blanco, Valeria Fiaschetti, Giulia Maggi, Livia Biancone**

**Giuseppe S Sica, Sara Di Carlo, Giorgia Tema, Giulia Maggi,** Department of Surgery, Tor Vergata University Hospital, Rome 00133, Italy

**Fabrizio Montagnese,** San Giuseppe Hospital, Albano Laziale, Rome 00041, Italy

**Giovanna Del Vecchio Blanco, Livia Biancone,** Department of Medicine, Tor Vergata University Hospital, Rome 00133, Italy

**Valeria Fiaschetti,** Department of Radiology, Tor Vergata University Hospital, Rome 00133, Italy

**Author contributions:** Sica GS, Di Carlo S, Tema G and Montagnese F contributed equally to this work; Sica GS and Biancone L designed research; Sica GS and Di Carlo S wrote the paper**;** Del Vecchio Blanco G and Fiaschetti V gave their contributions in their field of expertise**;** Tema G and Maggi G did data analysis bibliographic researches**;** Biancone L critically revised the manuscript.

**Correspondence to: Giuseppe S Sica, Professor,** Department of Surgery, Tor Vergata University Hospital, 81 Viale Oxford, Rome 00133, Italy. [sigisica@gmail.com](mailto:sigisica@gmail.com)

**Telephone**: +39-6-20903596 **Fax:** +39-6-20902927

**Received:** February 11, 2014 **Revised:** June 3, 2014

**Accepted:** July 11, 2014

**Published online:**

**Abstract**

Anal fistula is a common manifestation of Crohn’s disease (CD). Often, especially in CD affecting colon and rectum, the first manifestation of the disease is in the peri-anal region and it can occur even years before final diagnosis. The treatment of peri-anal fistula is difficult and always multidisciplinar. The European guidelines do 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 seems to be superior over 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. The greatest attention has to be paid to the correct balance between eradication of the fistula and the preservation of fecal continence.

© 2014 Baishideng Publishing Group Inc. All rights reserved.

**Key Words**: Fistula; Crohn’s disease; Perianal fistula; Surgery; Surgical treatment; Seton; Anal fistula treatment

**Core tip:** Treatment of anal fistula in Crohn’s disease is a challanging clinical problem. Although several studies have been published, a consensus on treatment’s strategy is not yet achieved.Clinical experience suggest that fistulas treatment should be determined according to type and clinical behavior. 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. Aim of the surgical procedures is fistula healing without compromising fecal continence.

Sica GS, Di Carlo S, Tema G, Montagnese F, Del Vecchio Blanco G, Fiaschetti V, Maggi G, Biancone L. Treatment of peri-anal fistula in Crohn’s disease. *World J Gastroenterol* 2014; In press

**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. Colon is involved in about 30% of patients. Almost one third of patients will develop perianal fistulae during the course of their disease. The incidence of perianal fistulae ranges from 11% to 38% of patients, and the frequency has been shown to increase with disease duration, being more frequent in patients with colorectal involvement. The etiology of perianal fistulae in CD remains unclear, but it often highlight a more aggressive disease[1-5]. The external opening of the sinus tracts is mostly localized in the perianal region but it can also be detected in the buttock, groin, vulva or scrotum. CD fistulas should be always regarded as complex, even though a simple and single sinus tract is the only finding in many instances. There are several classification of fistula in ano, although the Parks’ classification[6] is currently used, according to current European guidelines[1]. Four groups of fistulae are recognized, according to the relation with the sphincter muscle: (1) Extrasphincteric: extend from an internal opening in the bowel proximal to the anus; (2) Intersphincteric: travel along the intersphincteric plane to the perianal skin; (3) Transphincteric: encompass a portion of the internal and external sphincter; and (4) Suprasphincteric: encompass the entire sphincter apparatus.

**CLINICAL MANIFESTATIONS AND DIAGNOSIS**

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

**DIAGNOSIS AND ASSESSMENT OF PERIANAL DISEASE**

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[1].

The gold standard for assessing a fistula in ano is the exploration of the anal canal and distal rectum under anesthesia (EUA)[1,3,7]. 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[1], EUA is considered the gold standard only in the hands of an experienced surgeon.

Additional diagnostic modalities useful to assess perianal disease in CD include magnetic resonance imaging (MRI) or transanal endoscopic ultrasound (EUS). Sensitivity and specificity of both techniques is lower that EUA and an experienced radiologist or gastroenterologist, respectively, are required in order to achieve a reliable assessment of the perianal lesions[1,8,9]. Pelvic MRI is accurate and non-invasive, although patients’ compliance or obesity may not allow its use in subgroup of patients[10-12]. Moreover, differently from transanal EUS, pelvic MRI does not allow the visualization of the rectal mucosa. This represents a major limit in the assessment of perianal disease in CD, as rectal involvement is associated with worst outcome of perianal disease. Nevertheless, according to some authors, MRI can provide an MRI-based score to assess the activity of CD, based on the extent and severity of intestinal inflammation, post-operative recurrence and perineal disease[13]. EUS, has shown an accuracy comparable to pelvic MRI for assessing perianal CD but, as said, it also allows the assessment and histological examination of the rectal mucosa[8-10,12]. Tansanal EUS can’t be performed in the presence of rectal stenosis.

The few studies comparing the sensitivity, specificity, negative and positive predictive values of these 3 diagnostic modalities, support that the gold standard is represented by EUA performed by an experienced dedicated surgeon, allowing not only a proper assessment but also a local treatment of the disease. The combined use of all these 3 procedures has been reported to represent the best modality to assess perianal disease in CD[1,10,12]. 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 are also used in order to assess the response to biologic therapies, including anti-tumor necrosis factor (TNF) monoclonal antibodies.

The usefulness of computed tomography (CT) with intravenous contrast is limited to the visualization of abscesses in the ischiorectal fossa. Differently, fistulography is not recommended for assessing perianal disease[1].

**TREATMENT**

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 showed to significantly improve the course of perianal disease in CD.

Treatment should be determined according to type and severity of the fistula. However treatment is related to symptoms: asymptomatic perianal fistulas should not be treated. Also, as for treatment of luminal CD, a multidisciplinary approach including dedicated gastroenterologist, surgeon and radiologist is advisable.

For symptomatic fistulas, antibiotic treatments is suggested before treatment with immunomodulators and/or anti-TNFs[5,14,15].

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, show efficacy in terms of temporary relief of symptoms and in treating local complications. Antibiotic-therapy hasn’t been proven efficacious in terms of fistula closure[1,5,14,15]; moreover trials on the use of metronidazole and ciprofloxacin for perianal CD, do include different study design, with different antibiotic dosage, combination and duration of treatment, thus not allowing a proper evaluation of the optimal treatment strategies.

Azathioprine (AZA) (2-2.5 mg/kg by mouth) or 6-mercaptopurine (6-MP)(1-1.5 mg/kg per oral) are immunomodulators indicated for perianal fistulae in CD patients failing treatment with antibiotics with or without previous surgical treatment[1,16,17]. The presence of 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[1].

The efficacy of AZA and 6-MP requires at least 3-6 mo treatment. In patients failing treatment with AZA or 6-MP, biologics therapy using the anti-TNF-alpha monoclonal antibodies Remicade or Adalimumab is recommended[1,18]. Remicade (5 mg/kg *iv*) at 0, 2, 6 wk, followed by maintenance treatment every 8 wk or Adalimumab (160, 80, 40 mg *sc*) at 0, 2, 4 wk, followed by maintenance treatment every 2 wk currently represents the more effective treatments for inducing fistulae healing in CD. The maintenance treatment showed to induce fistula closure in up to 36% of patients at 56 wk[1,18-21]. Interestingly, MRI showed that anti-TNFs treatment, although able to induce the healing of the external orifice, may not be able to close the fistulous tract[22]. This observation accounts for the relapse of local discharge or for the development of a perianal abscess along the fistulous tract.

**SURGICAL TREATMENT**

Preliminary observations from few studies suggest that local injection of Remicade in the fistulous tract, may be useful in inducing fistula healing[23,24]. However, due to the preliminary observations deriving from monocentric uncontrolled studies, the reported encouraging findings needs to be confirmed by randomized controlled trials. Fistulous tracts have been injected with biologic glue. A novel cyanoacrylic glue has been injected using image-guided percutaneous techniques, mostly to treat post-surgical fistula treatment, but results need to be confirmed[25]. In a randomized controlled trial, injection of the fistulous tract with fibrin glue has shown a 38% success rate[26]. The failure rate associated with fibrin glue injection is attributed to the difficulty in ensure that the glue remains in the fistula tract and closes the internal opening[27]. Discrepant findings have been reported in a meta-analysis[28].

As for local injections, these observations need to be confirmed by multicenter studies including a higher number of patients.

Additional preliminary observations suggest, in a preclinical work, that autologous fibroblasts added to the collagen glue, may improve the outcome of perianal disease when compared with patients treated with the glue only[27]. The addition of autologous fibroblasts to the collagen glue has been suggested to reduce the slippage of the glue from the fistulous tract[28].

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

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 finally proctectomy.

For patients with intersphincteric or low transphincteric fistulas, fistulotomy is advised and may lead to healing in a significant number. It is not a feasible option when the fistula incorporates a significant amount of the internal and external anal sphincter as for high transphincteric fistulas. A good patients’ selection is mandatory and delay surgery whilst optimizing the treatment of active proctitis is the key of success to avoid poor healing and higher recurrence risk[30].

Advancement flaps can be used as a sphincter preserving technique for some higher fistulas in CD. The transanal mucosal advancement flap involve 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 sort of 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%[31].

It is authors’ believe 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, it prevents from a even more complex scenario and it is mostly well tolerated. A loose seton may be passed and subsequently associated treatment with anti-TNF therapy offered: in this case the healing rate is approximately 47% to 79%[30]. A loose seton can be converted, in selected cases, in a cutting seton. Cutting setons results in low recurrence rates but can cause incontinence in up to two-thirds of patients[32].

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 and mostly all the reported results, comes from series of fistulas not associated to CD or mix-cases 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 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[33,34]. In one study the LIFT procedure was associated to the placement of a biosynthetic graft and in the study were also included 4 CD patients. The procedure was successful in all 4 CD patients[35]. Further studies are necessary before the LIFT procedure in any form can be recommended in the treatment of CD perianal fistulas.

The Surgisis® (Cook Surgical, Bloomington, IN) anal fistula plug (AFP) is a bioabsorbable xenograft made of lyophilized porcine intestinal submucosa. The material has a resistance to infections, provides no foreign body or giant cell reactions, and becomes repopulated with patient’s cells and tissues over a period of 3 mo. The success rates reported for the AFP are variable and range from 13% and 86%[36]. A theoretical advantage of the AFP is that the operative technique involves suturing the plug to the internal anal sphincter at the site of the internal opening, to keep the material in place to allow time for ingrowth.

A promising technique could be that of using stem cells to stimulate fistula closure. Garcia-Olmo performed a randomized clinical trial comparing adipose-derived stem cells and fibrin glue. The stem cells were injected into the rectal mucosa. The fistula closed in 71% in the stem cell group compared with 16% in the fibrin glue group[37].

The continue search for innovative techniques, have led to the use of video assisted anal fistula treatment (VAAFT). Initial experiences on the use of VAAFT reported by Meinero and Mori have shown that the technique has promising results in patients with complex anal fistulas[38]. This technique allows a direct visualization of all the sinus tracts with the hope to reduce the recurrences. Schwandner has combined the VAAFT with advancement flaps. This study showed a high identification rate of occult side tracts with encouraging short terms healing rates[39]. A small percentage of the VAAFT series were CD patients and the technique needs further evaluations with increased sample sizes and long term follow up.

In our unit, in a preliminary study we are assessing the feasibility of outpatients exploration of anal canal and distal rectum. Preliminary findings suggest that outpatients explorations is feasible in the vast majority of patients and that it was possible to perform a complete treatment in over 80% of patients[40]. We strongly believe that the key of success was the multidisciplinary approach: all the patients were in regular follow-up at our IBD referral Centre and patients well known to all the members of the team. Patients with perianal CD are all seen in a joint clinic by the referral gastroenterologist and surgeon; a specialist nurse trained as theatre nurse is also always present. Finally, a diverting stoma may become necessary in case of recurrent fistula, refractory to medical treatment or in case severe urogenital complications, fecal incontinence or severe proctitis. It is however our experience that very rarely a stoma will be reverse and in many instances a proctectomy will follow.

**CONCLUSION**

Perianal disease is a troublesome condition for both patient and surgeon. The management is a delicate balance between eradication of the fistula and preservation of fecal continence. It requires a multidisciplinary collaboration between dedicated gastroenterologist, surgeon and radiologist.

Healing is more likely to occur with the aid of biologic treatments. Surgery has to be conservative and patient’s collaboration and understanding of the scope of surgery is crucial for optimal management.

In the treatment of perianal disease in CD patients, perfectly applies the old latin motto “*primum: non nocere”* (first of all, do not arm).

**REFERENCES**

1 **Van Assche G**, Dignass A, Reinisch W, van der Woude CJ, Sturm A, De Vos M, Guslandi M, Oldenburg B, Dotan I, Marteau P, Ardizzone A, Baumgart DC, D'Haens G, Gionchetti P, Portela F, Vucelic B, Söderholm J, Escher J, Koletzko S, Kolho KL, Lukas M, Mottet C, Tilg H, Vermeire S, Carbonnel F, Cole A, Novacek G, Reinshagen M, Tsianos E, Herrlinger K, Oldenburg B, Bouhnik Y, Kiesslich R, Stange E, Travis S, Lindsay J. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Special situations. *J Crohns Colitis* 2010; **4**: 63-101 [PMID: 21122490 DOI: 10.1016/j.crohns.2009.09.009]

2 **Tang LY**, Rawsthorne P, Bernstein CN. Are perineal and luminal fistulas associated in Crohn's disease? A population-based study. *Clin Gastroenterol Hepatol* 2006; **4**: 1130-1134 [PMID: 16905369 DOI: 10.1016/j.cgh.2006.06.021]

3 **Schwartz DA**, Loftus EV, Tremaine WJ, Panaccione R, Harmsen WS, Zinsmeister AR, Sandborn WJ. The natural history of fistulizing Crohn's disease in Olmsted County, Minnesota. *Gastroenterology* 2002; **122**: 875-880 [PMID: 11910338 DOI: 10.1053/gast.2002.32362]

4 **Ingle SB**, Loftus EV. The natural history of perianal Crohn's disease. *Dig Liver Dis* 2007; **39**: 963-969 [PMID: 17720635 DOI: 10.1016/j.dld.2007.07.154]

5 **Bernstein LH**, Frank MS, Brandt LJ, Boley SJ. Healing of perineal Crohn's disease with metronidazole. *Gastroenterology* 1980; **79**: 357-365 [PMID: 7399243]

6 **Parks AG**, Gordon PH, Hardcastle JD. A classification of fistula-in-ano. *Br J Surg* 1976; **63**: 1-12 [PMID: 1267867 DOI: 10.1002/bjs.1800630102]

7 **Haggett PJ**, Moore NR, Shearman JD, Travis SP, Jewell DP, Mortensen NJ. Pelvic and perineal complications of Crohn's disease: assessment using magnetic resonance imaging. *Gut* 1995; **36**: 407-410 [PMID: 7698701 DOI: 10.1136/gut.36.3.407]

8 **Sloots CE**, Felt-Bersma RJ, Poen AC, Cuesta MA, Meuwissen SG. Assessment and classification of fistula-in-ano in patients with Crohn's disease by hydrogen peroxide enhanced transanal ultrasound. *Int J Colorectal Dis* 2001; **16**: 292-297 [PMID: 11686526 DOI: 10.1007/s003840100308]

9 **Buchanan GN**, Halligan S, Bartram CI, Williams AB, Tarroni D, Cohen CR. Clinical examination, endosonography, and MR imaging in preoperative assessment of fistula in ano: comparison with outcome-based reference standard. *Radiology* 2004; **233**: 674-681 [PMID: 15498901 DOI: 10.1148/radiol.2333031724]

10 **Al-Khawari HA**, Gupta R, Sinan TS, Prakash B, Al-Amer A, Al-Bolushi S. Role of magnetic resonance imaging in the assessment of perianal fistulas. *Med Princ Pract* 2005; **14**: 46-52 [PMID: 15608481 DOI: 10.1159/000081923]

11 **Koelbel G**, Schmiedl U, Majer MC, Weber P, Jenss H, Kueper K, Hess CF. Diagnosis of fistulae and sinus tracts in patients with Crohn disease: value of MR imaging. *AJR Am J Roentgenol* 1989; **152**: 999-1003 [PMID: 2705359 DOI: 10.2214/ajr.152.5.999]

12 **Orsoni P**, Barthet M, Portier F, Panuel M, Desjeux A, Grimaud JC. Prospective comparison of endosonography, magnetic resonance imaging and surgical findings in anorectal fistula and abscess complicating Crohn's disease. *Br J Surg* 1999; **86**: 360-364 [PMID: 10201779 DOI: 10.1046/j.1365-2168.1999.01020.x]

13 **Fiorino G**, Bonifacio C, Malesci A, Balzarini L, Danese S. MRI in Crohn's disease--current and future clinical applications. *Nat Rev Gastroenterol Hepatol* 2011; **9**: 23-31. [DOI: 10.1038/nrgastro.2011.2142]

14 **Thia KT**, Mahadevan U, Feagan BG, Wong C, Cockeram A, Bitton A, Bernstein CN, Sandborn WJ. Ciprofloxacin or metronidazole for the treatment of perianal fistulas in patients with Crohn's disease: a randomized, double-blind, placebo-controlled pilot study. *Inflamm Bowel Dis* 2009; **15**: 17-24 [PMID: 18668682 DOI: 10.1002/ibd.20608]

15 **Solomon MJ**, McLeod RS, O'Connor BI, Steinhart AH. Combination ciprofloxacin and metronidazole in severe perianal Crohn's disease. *Can J Gastroenterol* 1993; **7**: 571-573

16 **Pearson DC**, May GR, Fick GH, Sutherland LR. Azathioprine and 6-mercaptopurine in Crohn disease. A meta-analysis. *Ann Intern Med* 1995; **123**: 132-142 [PMID: 7778826 DOI: 10.7326/0003-4819-123-2-199507150-00009]

17 **Korelitz BI**, Adler DJ, Mendelsohn RA, Sacknoff AL. Long-term experience with 6-mercaptopurine in the treatment of Crohn's disease. *Am J Gastroenterol* 1993; **88**: 1198-1205 [PMID: 8338087]

18 **Sandborn WJ**, Fazio VW, Feagan BG, Hanauer SB. AGA technical review on perianal Crohn's disease. *Gastroenterology* 2003; **125**: 1508-1530 [PMID: 14598268 DOI: 10.1016/j.gastro.2003.08.025]

19 **Present DH**, Rutgeerts P, Targan S, Hanauer SB, Mayer L, van Hogezand RA, Podolsky DK, Sands BE, Braakman T, DeWoody KL, Schaible TF, van Deventer SJ. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999; **340**: 1398-1405 [PMID: 10228190 DOI: 10.1056/NEJM199905063401804]

20 **Sands BE**, Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, Kamm MA, Korzenik JR, Lashner BA, Onken JE, Rachmilewitz D, Rutgeerts P, Wild G, Wolf DC, Marsters PA, Travers SB, Blank MA, van Deventer SJ. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004; **350**: 876-885 [PMID: 14985485 DOI: 10.1056/NEJMoa030815]

21 **Colombel JF**, Schwartz DA, Sandborn WJ, Kamm MA, D'Haens G, Rutgeerts P, Enns R, Panaccione R, Schreiber S, Li J, Kent JD, Lomax KG, Pollack PF. Adalimumab for the treatment of fistulas in patients with Crohn's disease. *Gut* 2009; **58**: 940-948 [PMID: 19201775 DOI: 10.1136/gut.2008.159251]

22 **van Bodegraven AA**, Sloots CE, Felt-Bersma RJ, Meuwissen SG. Endosonographic evidence of persistence of Crohn's disease-associated fistulas after infliximab treatment, irrespective of clinical response. *Dis Colon Rectum* 2002; **45**: 39-45; discussion 45-46 [PMID: 11786762 DOI: 10.1007/s10350-004-6111-6]

23 **Poggioli G**, Laureti S, Pierangeli F, Bazzi P, Coscia M, Gentilini L, Gionchetti P, Rizzello F. Local injection of adalimumab for perianal Crohn's disease: better than infliximab? *Inflamm Bowel Dis* 2010; **16**: 1631 [PMID: 20848458 DOI: 10.1002/ibd.21210]

24 **Tonelli F**, Giudici F, Asteria CR. Effectiveness and safety of local adalimumab injection in patients with fistulizing perianal Crohn's disease: a pilot study. *Dis Colon Rectum* 2012; **55**: 870-875 [PMID: 22810472 DOI: 10.1097/DCR.0b013e31825af532]

25 **Mauri G**, Sconfienza LM, Fiore B, Brambilla G, Pedicini V, Poretti D, Lutman RF, Montorsi M, Sardanelli F. Post-surgical enteric fistula treatment with image-guided percutaneous injection of cyanoacrylic glue. *Clin Radiol* 2013; **68**: 59-63 [DOI: 10.1016/j.crad.2012.04.004]

26 **Grimaud JC**, Munoz-Bongrand N, Siproudhis L, Abramowitz L, Sénéjoux A, Vitton V, Gambiez L, Flourié B, Hébuterne X, Louis E, Coffin B, De Parades V, Savoye G, Soulé JC, Bouhnik Y, Colombel JF, Contou JF, François Y, Mary JY, Lémann M. Fibrin glue is effective healing perianal fistulas in patients with Crohn's disease. *Gastroenterology* 2010; **138**: 2275-2281, 2281.e1 [PMID: 20178792 DOI: 10.1053/j.gastro.2010.02.013]

27 **Cirocchi R**, Farinella E, La Mura F, Cattorini L, Rossetti B, Milani D, Ricci P, Covarelli P, Coccetta M, Noya G, Sciannameo F. Fibrin glue in the treatment of anal fistula: a systematic review. *Ann Surg Innov Res* 2009; **3**: 12 [PMID: 19912660 DOI: 10.1186/1750-1164-3-12]

28 **Cirocchi R**, Santoro A, Trastulli S, Farinella E, Di Rocco G, Vendettuali D, Giannotti D, Redler A, Coccetta M, Gullà N, Boselli C, Avenia N, Sciannameo F, Basoli A. Meta-analysis of fibrin glue versus surgery for treatment of fistula-in-ano. *Ann Ital Chir* 2010; **81**: 349-356 [PMID: 21294388]

29 **Himpson RC**, Cohen CR, Sibbons P, Phillips RK. An experimentally successful new sphincter-conserving treatment for anal fistula. *Dis Colon Rectum* 2009; **52**: 602-608 [PMID: 19404061 DOI: 10.1007/DCR.0b013e31819ece3e]

30 **Garg P**, Song J, Bhatia A, Kalia H, Menon GR. The efficacy of anal fistula plug in fistula-in-ano: a systematic review. *Colorectal Dis* 2010; **12**: 965-970 [PMID: 19438881 DOI: 10.1111/j.1463-1318.2009.01933.x]

31 **Lewis RT**, Maron DJ. Anorectal crohn's disease. *Surg Clin North Am* 2010; **90**: 83-97 [PMID: 20109634 DOI: 10.1016/j.suc.2009.09.004]

32 **Soltani A**, Kaiser AM. Endorectal advancement flap for cryptoglandular or Crohn's fistula-in-ano. *Dis Colon Rectum* 2010; **53**: 486-495 [PMID: 20305451 DOI: 10.1007/DCR.0b013e3181ce8b01]

33 **Shanwani A**, Nor AM, Amri N. Ligation of the intersphincteric fistula tract (LIFT): a sphincter-saving technique for fistula-in-ano. *Dis Colon Rectum* 2010; **53**: 39-42 [PMID: 20010348 DOI: 10.1007/DCR.0b013e3181c160c4]

34 **Bleier JI**, Moloo H, Goldberg SM. Ligation of the intersphincteric fistula tract: an effective new technique for complex fistulas. *Dis Colon Rectum* 2010; **53**: 43-46 [PMID: 20010349 DOI: 10.1007/DCR.0b013e3181bb869f]

35 **Ellis CN**. Outcomes with the use of bioprosthetic grafts to reinforce the ligation of the intersphincteric fistula tract (BioLIFT procedure) for the management of complex anal fistulas. *Dis Colon Rectum* 2010; **53**: 1361-1364 [PMID: 20847616 DOI: 10.1007/DCR.0b013e3181ec4470]

36 **van Koperen PJ**, Bemelman WA, Gerhards MF, Janssen LW, van Tets WF, van Dalsen AD, Slors JF. The anal fistula plug treatment compared with the mucosal advancement flap for cryptoglandular high transsphincteric perianal fistula: a double-blinded multicenter randomized trial. *Dis Colon Rectum* 2011; **54**: 387-393 [PMID: 21383557 DOI: 10.1007/DCR.0b013e318206043e]

37 **Garcia-Olmo D**, Garcia-Arranz M, Herreros D. Expanded adipose-derived stem cells for the treatment of complex perianal fistula including Crohn's disease. *Expert Opin Biol Ther* 2008; **8**: 1417-1423 [PMID: 18694359 DOI: 10.1517/14712598.8.9.1417]

38 **Meinero P**, Mori L. Video-assisted anal fistula treatment (VAAFT): a novel sphincter-saving procedure for treating complex anal fistulas. *Tech Coloproctol* 2011; **15**: 417-422 [PMID: 22002535 DOI: 10.1007/s10151-011-0769-2]

39 **Schwandner O**. Video-assisted anal fistula treatment (VAAFT) combined with advancement flap repair in Crohn's disease. *Tech Coloproctol* 2013; **17**: 221-225 [PMID: 23179892 DOI: 10.1007/s10151-012-0921-7]

40 **Scaramuzzo R**, Iaculli E, Fiorani C, Biancone L, Tema G, Di Carlo S, Gaspari A, Sica G. Outpatient anal exploration and fistula treatment in patient with symptomatic perianal chron’s disease. *JCC* 2012; **7 Suppl 1**: S179

**P- Reviewers:** Mauri G

**S- Editor:** Nan J **L- Editor: E- Editor:**