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TOPIC HIGHLIGHT

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Multidisciplinary and evidence-based management of fistulizing perianal Crohn's disease

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Abstract

Perianal symptoms are common in patients with Crohn's disease and cause considerable morbidity. The etiology of these symptoms include skin tags, ulcers, fissures, abscesses, fistulas or stenoses. Fistula is the most common perianal manifestation. Multiple treatment options exist although very few are evidence-based. The phases of treatment include: drainage of infection, assessment of Crohn's disease status and fistula tracts, medical therapy, and selective operative management. The impact of biological therapy on perianal Crohn's disease is uncertain given that outcomes are conflicting. Operative treatment to eradicate the fistula tract can be attempted once infection has resolved and Crohn's disease activity is controlled. The operative approach should be tailored according to the anatomy of the fistula tract. Definitive treatment is challenging with medical and operative treatment rarely leading to true healing with frequent complications and recurrence. Treatment success must be weighed against the risk of complications, specially anal sphincter injury. A full understanding of the etiology and all potential therapeutic options is critical for success. Multidisciplinary management of fistulizing perianal Crohn's disease is crucial to improve outcomes.

Key words: Perianal Crohn's disease; Fistula; Abscess; Management; Review

Core tip: This manuscript is a comprehensive review that focuses on the multidisciplinary management of fistulizing perianal Crohn's disease. The treatment options discussed in this review are based on a current literature review as well as our experience with the disease. Diagnostic and treatment algorithms are also provided.

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INTRODUCTION

Although Gabriel[1] first described patients with granulomatous perianal disease 17 years before the formal description of the disease by Burrill Crohn's[2] in 1932, Bissell[3] was the first to describe the associated perianal manifestations of Crohn's disease (CD). Furthermore, Morson *et al*[4] documented the appearance of perianal non-caseating granulomas and fistulas many years before the onset of intestinal CD.

The reported prevalence of anorectal involvement in patients with CD has varied but the most current population-based series have found involvement in 14 to 38 percent of patients[5-7], with isolated perianal disease seen in only five percent[8]. The prevalence of perianal mani-

festations increases as the disease progresses distally, with up to 92 percent of patients with CD involving the colon and rectum developing fistulas[9]. In most cases, bowel involvement precedes perianal disease[9], but up to 40 percent of patients can experience perianal symptoms before intestinal manifestations[10]. There does not seem to be a predilection for age but a younger age of onset increases the odds of developing perianal disease over time[11-12].

The most common presentation of perianal CD is abscess and fistula. However, patients with CD are frequently affected by other perianal pathologies including hemorrhoids, fissures, skin tags, ulcers, and strictures. Perianal CD has been associated with a disabling natural history[13], with common extraintestinal manifestations[14] and greater steroid resistance[15]. Perianal disease is often recurrent, with 35 to 59 percent of patients relapsing within two years[16]. More than 80 percent of patients require operative treatment, and up to 20 percent may require proctectomy[5,7]. Patients with perianal CD have also shown an increased risk for anal malignancies[17,18], with active and long duration of disease being identified risk factors[19-21].

The treatment of perianal CD continues to be a challenge, especially with the plethora of literature addressing both medical and operative treatment strategies. The purpose of this review is to summarize the efficacy of currently described methods for the management of fistulizing perianal CD and its complications.

ABSCESS

Abscesses usually occur with active perianal CD with an incidence of up to 62 percent during the course of the disease[22]. Ischiorectal abscesses account for 40 percent of all perianal abscesses[23]. Fistula tract location can influence abscess development and transsphincteric fistulas pose the greatest risk[23].

Abscesses are uncommon with superficial fistula tracts. Makowiec *et al*[24] evaluated 61 patients with perianal CD and found that 73 percent of all abscesses were related to an ischiorectal fistula and 50 percent with a transsphincteric fistula. Recurrences occurred in 53 percent with a median time to recurrence of 14 mo. No patients with superficial fistula tracts had a second abscess, whereas about two thirds of patients with transsphincteric and ischiorectal fistulas recurred after 36 mo.

A detailed anorectal exam should be performed before any type of treatment is initiated. This frequently requires evaluation under anesthesia (EUA) with evaluation of the rectum to rule-out active disease. Perianal infection can occur in any anatomic plane (superficial, intersphincteric, ischiorectal, or supralevator), and requires immediate drainage and treatment of systemic symptoms with broad-spectrum antibiotics[6,25]. Many authors recommend drain placement or partial sphincter division to facilitate drainage, but these have not been associated with better outcomes[26,27]. In the setting of persistent perianal sepsis, imaging modalities such as magnetic resonance imaging (MRI) and computed tomography (CT) are used to guide the drainage of deep or complex abscesses[28,29].

When a fistula is encountered, a non-cutting seton should be placed to facilitate drainage and prevent recurrent infection, with improvement seen in 79 to 100 percent of patients[30-35]. Long-term drainage with non-cutting setons without definitive therapy has been reported to result in fistula recurrence in 20 to 80 percent of cases[33,36,37]. The combination of non-cutting setons and anti-tumor necrosis factor (TNF) therapy has been associated with fistula healing rates of up to 67 percent and will be discussed below[38,39]. Fecal diversion to increase fistula healing and control perianal sepsis continues to be controversial with no level A data supporting its role but in the setting of persistent perianal sepsis, a temporary diverting stoma can be effective. Patients should be aware that these stomas are rarely reversed[40].

Cryptoglandular abscess/fistulas can and do occur in patients with CD and should be recognized as so because treatment differs. These abscess/fistulas tend to be superficial and are not associated with active anorectal CD; therefore, anti-TNF therapy is not indicated. Abscess drainage should follow the same principles as mentioned above. Placement of a non-cutting seton is encouraged and any attempt of local surgical treatment should take into consideration the patients underlying continence and CD status. Supplemental imaging studies, such as endoanal ultrasound (EAUS), are very helpful even when cryptoglandular etiology is suspected.

FISTULA

A population-based study[7] with up to 20 years of follow-up showed that one out every two patients with CD develop perianal fistulas. The etiology of perianal fistula formation in CD is not completely clear but genetic, microbiological, and immunological factors play a role. Most authors believe that fistulas originate either from the penetration of a rectal ulcer or from cryptitis spreading to the intersphincteric space. Intersphincteric and transsphincteric fistulas are the most common fistula tracts of cryptoglandular origin that occur in patients with CD. Suprasphincteric fistulas result from cryptoglandular disease or rectal ulceration, and extra sphincteric fistulas are frequently seen in patients with severe proctitis or iatrogenic injury.

At St. Marks Hospital, Tozer[41] studied biopsy samples from Crohn's and idiopathic anal fistulas. Although immunological analysis showed no significant differences in interleukin (IL)-2, IL-4, IL-6, IL-10, TNF, and interferon levels, CD patients had significantly higher interleukin 17 levels and significantly lower CD65 levels. The authors showed data suggesting aberrant expression of homing molecules on dendritic cells in Crohn's anal fistulas suggesting a non-directed immune response, which may contribute to the pathophysiology.

Pelvic MRI is the preferred imaging study to assess fistulizing perianal disease. It has an accuracy of 90 percent for evaluating fistula tracts and of 97 percent for characterizing complex abscesses[42,43]. Furthermore, operative management may be altered in ten to 20 percent of patients by the addition of MRI to EUA, and this increases to up to 40 percent in patients with CD[44,45].

Once the anorectal disease is delineated, evaluation for proximal CD with endoscopy should also be considered. Although some studies have found an association between proximal fistulizing disease and perianal fistulas[46], other investigators have not observed this finding[47,48]. In patients with fistulizing perianal CD it is our practice to combine a pelvic MRI with EUA and rigid proctoscopy to evaluate for rectal inflammation.

Medical treatment

Once perianal infection is controlled, the fistula tract is characterized, and CD status is assessed; combined definitive medical and surgical therapy should be initiated (Figure 1). When active proctitis is encountered, this must be aggressively treated. Medical therapy includes antibiotics (metronidozole and ciprofloxacin), immunosuppressives (6-mercaptopurine, azathioprine, cyclosporine, and tacrolimus), and immunomodulators (infliximab, adalimumab, and certolizumab pegol). Although steroids are frequently used to manage concomitant luminal disease, there is no demonstrable role for corticosteroids in perianal CD. Medical treatment of perianal CD demands significant cooperation between gastroenterologists and surgeons as patient management is challenging and requires frequent feedback between medical professionals to optimize therapeutic strategies.

Antibiotic therapy

Antibiotics are commonly initiated when perianal infection is diagnosed and are frequently continued until immunosuppressive therapy is initiated[49], with 70 to 95 percent of patients having a positive response within six weeks[50,51]. It is our practice to continue antibiotic therapy for two weeks with perianal infection, and for three to four weeks with active proctitis. Metronidazole is the most common antibiotic prescribed for perianal CD and has been associated with fistula healing rates ranging from zero to 56 percent[50,52,53]. Seventy-five percent of patients relapse after suspending treatment and side effects which include nausea and peripheral neuropathy commonly limit its long-term use.

Ciprofloxacin has been studied in small, uncontrolled series of patients with perianal CD[54,55]. Improvement has been shown in approximately half of patients without detailed data on fistula healing. Ciprofloxacin was compared to metronidazole and placebo in a small randomized study including 25 patients[53]. After receiving treatment for ten weeks, clinical remission and response were 30 percent and 40 percent with ciprofloxacin, 12.5 percent and 12.5 percent with placebo, and 0 percent and 14 percent with metronidazole; none of these differences being significant.

Immunomodulators

The definitive medical treatment of perianal CD includes immunomodulation. A meta-analysis of five randomized controlled trials evaluated the efficacy of 6-mercaptopurine and azathioprine[56]. Fistula healing occurred in 54 percent of patients *vs* 21 percent of controls (OR 3.09; 95%CI, 2.45 to 3.91). Intravenous cyclosporine has also shown to have a good response in up to 83 percent of patients[57,58], but the effect is short-lasting when it is discontinued or transitioned to oral formulations[59]. Tacrolimus has also been effective in the treatment of perianal CD, as shown in one randomized controlled trial. Clinical improvement was seen in 43 percent of patients *vs* 8 percent receiving placebo ($P = 0.004$)[60].

Anti-TNF therapy

Anti-TNF therapy, which includes monoclonal antibodies that are given intravenously [Infliximab (chimeric – murine/human)] or subcutaneously [Adalimumab and Certolizumab pegol (human)], has shown good results in the multidisciplinary management of perianal CD. Most patients who receive anti-TNF therapy receive concomitant immunomodulators. This combination has been poorly studied, specifically in perianal CD, but may be associated with less perianal complications and increased fistula healing[61]. What must be taken into consideration is that most studies evaluating anti-TNF therapy in the setting of perianal CD are of small numbers that involve heterogeneous patient groups with short follow-up. These studies also use varying definitions of fistula healing, disease improvement and "response".

Infliximab alone: Present *et al*[62] reported that three infusions of infliximab resulted in closure of perianal fistulas in 46 percent of patients over 3 mo follow-up. A large study from Hungary including 148 patients with CD reported a perianal fistula closure rate of 49 percent at a mean of 3 mo follow-up[63]. A multicenter Italian study evaluating the impact of infliximab alone in 188 patients with perianal CD reported an initial response in 76 percent of patients with a 44 percent fistula closure rate[64]. Ng *et al*[65] prospectively evaluated the response to infliximab therapy with MRI in 34 patients with perianal Crohn's fistulas. At six months, 58 percent of patients showed fistula closure, with 37 percent showing good clinical response.

Infliximab plus surgery: Regueiro *et al*[66] demonstrated an improved clinical response and less fistula recurrence when patients had EUA and seton placement before starting infliximab compared to patients who received infliximab alone. Topstad *et al*[38] also achieved improved outcomes with combined seton drainage, infliximab infusion, and immunosuppressives in 29 patients. At a mean follow-up of nine months, 67 percent of patients showed a complete response. Hyder *et al*[67] evaluated

long-term healing rates with this approach in 22 patients. At a median follow-up of 21 mo, the authors only observed an 18% fistula closure rate. Van der Hagen *et al*[68] developed a multistep multidisciplinary approach that involved EUA with seton placement, fecal diversion when fistulas and abscesses recurred, infliximab therapy in case of persistent proctitis, and definitive fistula surgery. At a mean follow-up of 23 mo, fistula healing occurred in 90 percent of patients who received infliximab (9/10) compared to 71 percent in those who did not (5/7).

At the University of Minnesota, Gaertner *et al*[39] evaluated the outcomes of 226 patients who underwent operative treatment for perianal Crohn's fistulas, with 79 of these patients also receiving preoperative infliximab. Fistula healing rates were similar regardless of infliximab therapy (59% *vs* 60%). However, patients who underwent surgery plus infliximab healed faster than those who did not receive infliximab (6.5 mo *vs* 12.1 mo; $P < 0.0001$), and seton placement plus infliximab infusion resulted in significantly improved fistula healing rates compared to seton placement alone ($P = 0.001$). Regardless of infliximab therapy, lay-open fistulotomy was the operation with the best healing rates. Active proctitis did not significantly impact healing after fistula surgery.

Adalimumab alone: Adalimumab has shown similar efficacy to infliximab in randomized controlled trials. In the CHARM (Crohn's trial of the fully Human Antibody Adalimumab for Remission Maintenance) study, 113 patients with perianal Crohn's fistulas received induction adalimumab; with subsequent maintenance adalimumab or placebo[69]. Evaluation at 26 wk showed complete fistula closure in 30 percent of patients treated with adalimumab, with improved outcomes at 56 wk compared to placebo (33% *vs* 13%). The durability of these results have been confirmed at two years follow-up[70]. In the CLASSIC-1 (Clinical Assessment of Adalimumab Safety and Efficacy Studied as an Induction Therapy in Crohn's disease) trial, adalimumab was compared to placebo with the aim to evaluate short-term outcomes[71]. Thirty-two of 299 patients had perianal fistulas and no significant differences were observed in fistula healing.

Adalimumab has also been used in patients who have failed to respond to other anti-TNF agents, specially infliximab. In the GAIN (Gauging Adalimumab efficacy in Infliximab Nonresponders) trial, CD patients who were intolerant or who had lost response to infliximab received adalimumab or placebo[72]. Forty-five of 325 patients had perianal fistulas and no significant differences in fistula healing were found between placebo and adalimumab. Based on these results, most physicians consider that a second biological agent has minimal efficacy in patients who have already failed anti-TNF therapy.

Adalimumab plus surgery: As the experience with anti-TNF therapy expands, many authors have reported on a combined approach with adalimumab and local anorectal procedures. Tozer *et al*[73] reviewed the outcomes of 41 consecutive patients with fistulizing perianal CD treated with infliximab ($n = 32$) or adalimumab ($n = 9$), and followed radiologically with MRI. Fifty-eight percent of all patients (66% infliximab and 43% adalimumab) demonstrated remission or response at three years. Fistula healing, as demonstrated by MRI, lagged behind clinical healing by a median of 12 mo. All patients who achieved radiological healing maintained fistula closure while on anti-TNF therapy but only 43 percent maintained fistula closure after cessation of anti-TNF agents. El-Gazzaz *et al*[74] reviewed the Cleveland Clinic experience with combined anti-TNF therapy and anorectal surgery in 218 patients. Mean follow-up was 3.2 years. Two hundred and eighteen patients underwent operative treatment, 101 with anti-TNF therapy (74 infliximab and 27 adalimumab). Patient groups were comparable in demographic data and CD history but operative treatment was significantly heterogeneous. Patients who received combined anti-TNF therapy and surgery had significant overall improvement compared to patients who underwent surgery alone (36% *vs* 71%, $P = 0.001$).

Local anti-TNF therapy: Local injections of anti-TNF agents have also been attempted in fistulizing perianal CD, specifically in patients with contraindications to systemic treatment and resistance to infliximab. Poggioli *et al*[75] performed three to 12 local injections of infliximab (15-20 mg) adjacent to both internal and external openings and fistulous tract in 15 patients. Fistula closure occurred in ten patients at a mean follow-up of 18 mo. Asteria *et al*[76] achieved clinical response in six of eleven patients treated with local infliximab. Four of the eleven remained healed at a median of ten months of follow-up.

Tonelli *et al*[77] reviewed the outcomes of 12 patients with fistulizing perianal CD who underwent local injection of Adalimumab. Each patient received a median of seven (range, 4-16) injections. At a mean follow-up of 17.5 mo, 75 percent of patients (9 of 12) no longer had fistula drainage, and three patients (25%) showed clinical improvement. No adverse side effects were noted.

Certolizumab pegol: Certolizumab pegol is a humanized monoclonal antibody directed against TNF alpha. The antibody is fused with polyethylene glycol, which does not cross the placenta, so it should be safe in pregnancy. In 2008, the Food and Drug Administration approved Certolizumab pegol for the treatment of CD. Schreiber *et al*[78] evaluated its impact in patients with fistulizing CD. Patients with fistulizing CD from a randomized controlled study (PRECiSE 2, $n = 108$) comparing certolizumab pegol *vs* placebo were further randomized (if a good initial response was noted) to certolizumab pegol ($n = 28$) or placebo ($n = 30$) every four weeks until 24 wk. The majority of patients (55/58) had perianal fistulas. At week 26, fistula closure occurred in 36 percent of patients in the certolizumab pegol group compared to 17 percent of patients receiving placebo ($P = 0.038$).

Operative treatment

If the attempt to heal a fistula has significant impact on

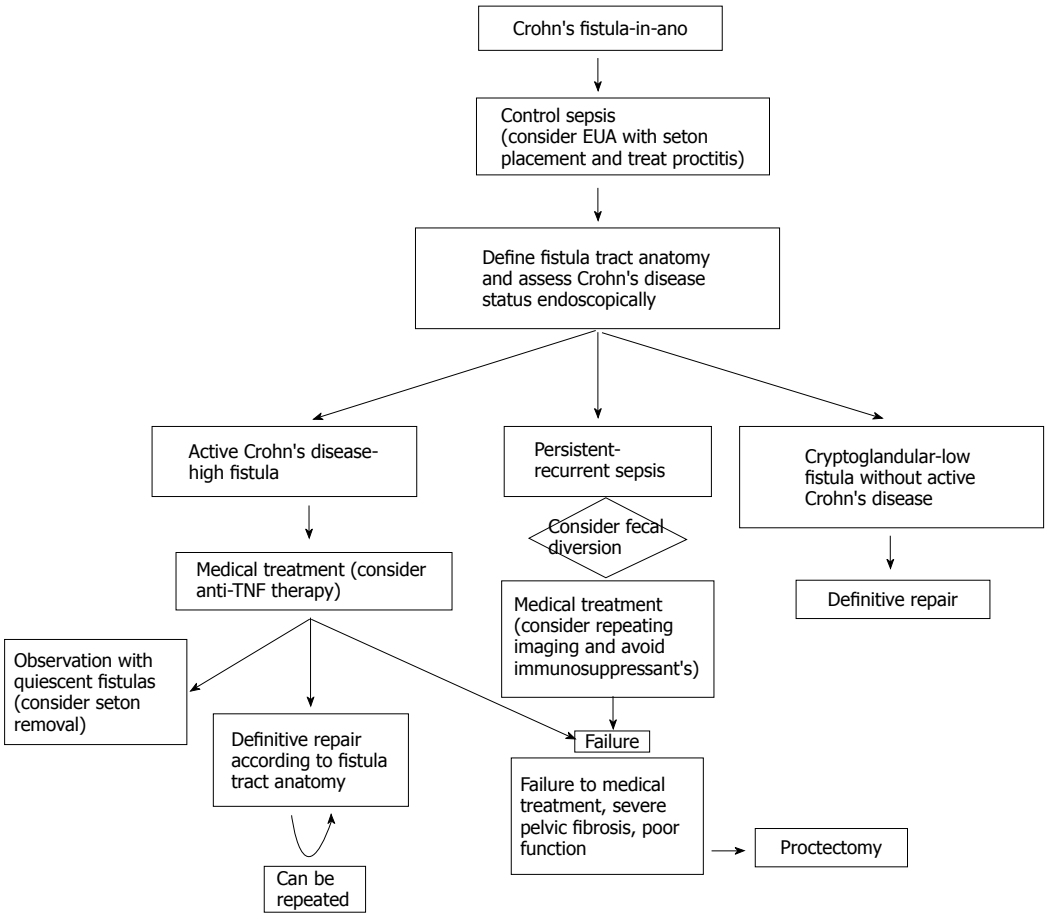

Figure 1 Diagnostic and treatment algorithm for fistulizing perianal Crohn's disease.

a patient's quality of life, operative treatment should be undertaken. Currently, the majority of operations for fistulizing perianal CD are performed in conjunction with medical therapy (immunomodulators or anti-TNF agents), and because this approach has been covered above, this section will focus on operative indications and efficacy of the most popular surgical techniques.

Most low, simple fistulas can be treated by fistulotomy. Healing rates from 80 to 100 percent have been reported with this technique[27,31,79,80]. Despite careful patient selection, an occasional fistulotomy wound may result in a chronic ulcer. In this situation, medical treatment is preferred as further operations have been associated with recurrent infection, fistula, and sphincter damage.

If partial sphincter division would compromise fecal continence, one can choose between minimally invasive techniques and anorectal repairs. Minimally invasive techniques include fibrin glue injection and collagen plug insertion. These techniques have no significant effect on fecal continence, are well tolerated by the patient, can be repeated, and are associated with fistula healing rates between 38 and 71 percent[81-84]. Fistula recurrence is common and occurs in approximately 50 to 70 percent of patients[81-84]. Video-assisted anal fistula treatment (VAAFT) and local injection of adipose-derived stem cells are recently described minimally invasive techniques that have been employed in patients with fistulizing perianal CD[85,86]. VAAFT involves performing fistuloscopy to identify the etiologic crypt and rule-out secondary tracts and then excise the internal opening. After this, the fistula tract is fulgurated. Stem cell therapy is a novel and promising approach for the treatment of chronic inflammatory conditions, and its use in fistulizing perianal CD has increased in Europe. Fistula healing rates between 30 and 82 percent have been reported with these techniques but the long-term safety and outcomes have not been adequately studied in the Crohn's population. Overall, studies assessing the efficacy of minimally invasive techniques for Crohn's perianal fistulas tend to be of small patient numbers, non-comparative and heterogeneous patient groups, retrospective nature, and with short duration of follow-up.

The most commonly employed anorectal operation for transsphincteric Crohn's fistulas is a rectal advancement flap. This procedure has been associated with incontinence rates between five and nine percent but has not been associated with an increased risk for proctectomy[87]. Contraindications include significant proctitis, a cavitating ulcer or anal stenosis. Crohn's fistula healing rates reported in the literature average 64 percent[87]. A recently described technique, ligation of intersphinc-

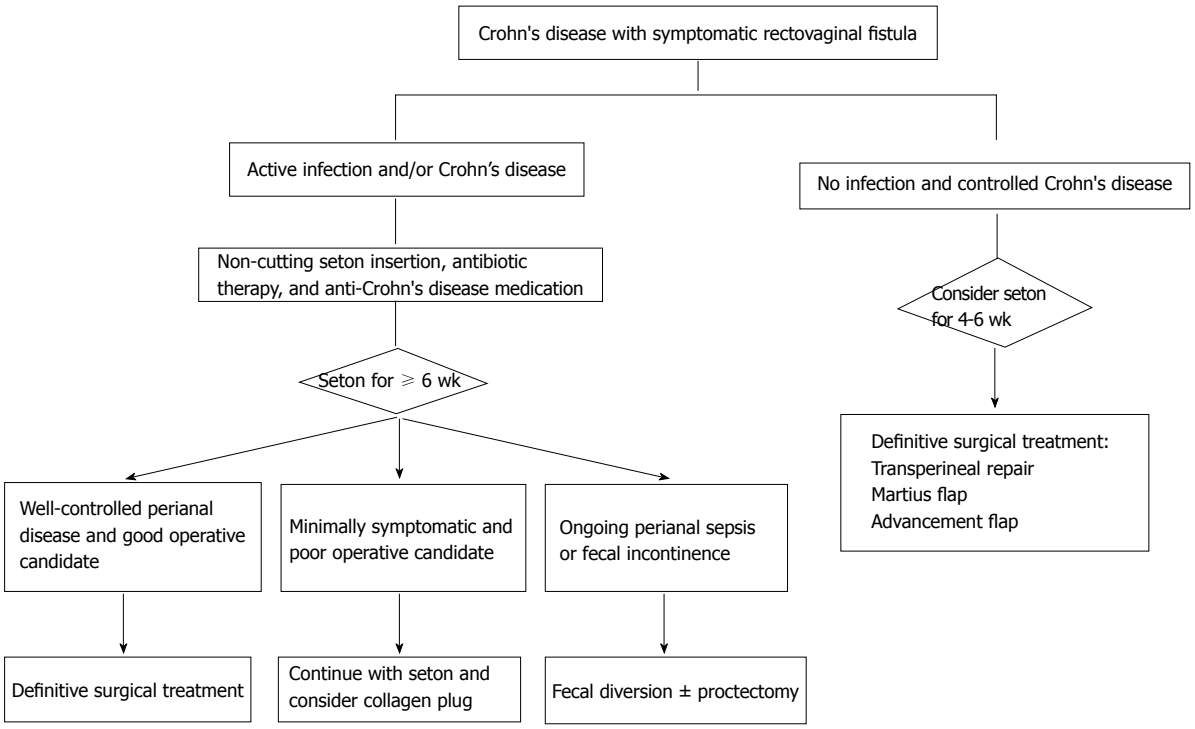

Figure 2 Treatment algorithm for patients with Crohn's disease and symptomatic recto-vaginal fistulae.

teric fistula tract (LIFT) which involves the identification and ligation/transection of the fistula tract in the intersphincteric plane, is being increasingly employed in patients with transsphincteric Crohn's fistulas[88]. This technique also has minimal to no repercussion on fecal continence but does involve a perianal wound. Although encouraging results have been reported in complex fistulas of cryptoglandular origin, experience in CD patients is limited[89,90].

In the setting of a large anal canal ulcer or severe stricture, an endorectal advancement flap can be performed in selective patients[91]. After the ulcer or stricture is excised, a full-thickness circumferential sleeve is mobilized and a formal rectoanal anastomosis is performed in combination with a diverting loop ileostomy.

SPECIFIC SITUATIONS

Rectovaginal fistulas

After obstetric trauma, CD is the second most common cause of rectovaginal fistula (RVF)[92], occurring in five to 23 percent of CD patients[93-95]. The majority of RVF's in the setting of CD are low and transsphincteric, and arise from rectal ulceration or infection of anterior anal glands[94,96].

The management of RVF in CD is challenging. Treatment depends on the degree of symptoms, CD activity, and the anatomy of the fistulous tract (Figure 2). Minimally symptomatic patients may not require any treatment[7,94,97,98]. However, carefully selected symptomatic patients should be treated with a step-wise multidisciplinary approach. Drainage of local infection, seton placement and medical therapy are the initial steps before any attempts at fistula closure[92,94].

Patient selection is very important. Women with extensive anorectal CD are not good candidates for definitive fistula operations without first eradicating local infection and controlling the activity of underlying CD. Contrast to what has been reported in non-CD patients, a previous failed repair does not dictate a worse outcome with a subsequent operation. Healing rates reported after secondary operations are similar to those seen after a first attempt repair (29%-54%)[99-101]. Fecal diversion to protect a repair is also controversial. Penninckx *et al*[99] evaluated the impact of fecal diversion and parenteral nutrition in 32 consecutive patients undergoing RVF repair and did not find any significant role for either of these interventions. However, when O'Leary *et al*[102] selectively used fecal diversion in a step-wise approach that included initial seton placement and delayed repair, fistula healing occurred in 80 percent of patients. A diverting stoma does not ensure fistula healing and should only be performed in complex and recurrent cases.

Most of current treatment algorithms include combined medical and operative treatment. Present *et al*[103] found that 6-mercaptopurine was more effective than placebo, when combined with surgery (31% *vs* 6%). Most RVF's recurred after discontinuation of 6-mercaptopurine. Similar results were observed with cyclosporine in two studies that included a total of six patients with RVF[104,105].

El-Gazzaz *et al*[106] evaluated long-term outcomes in 65 women with Crohn's RVF´s who underwent a variety of different procedures. At a median follow-up of

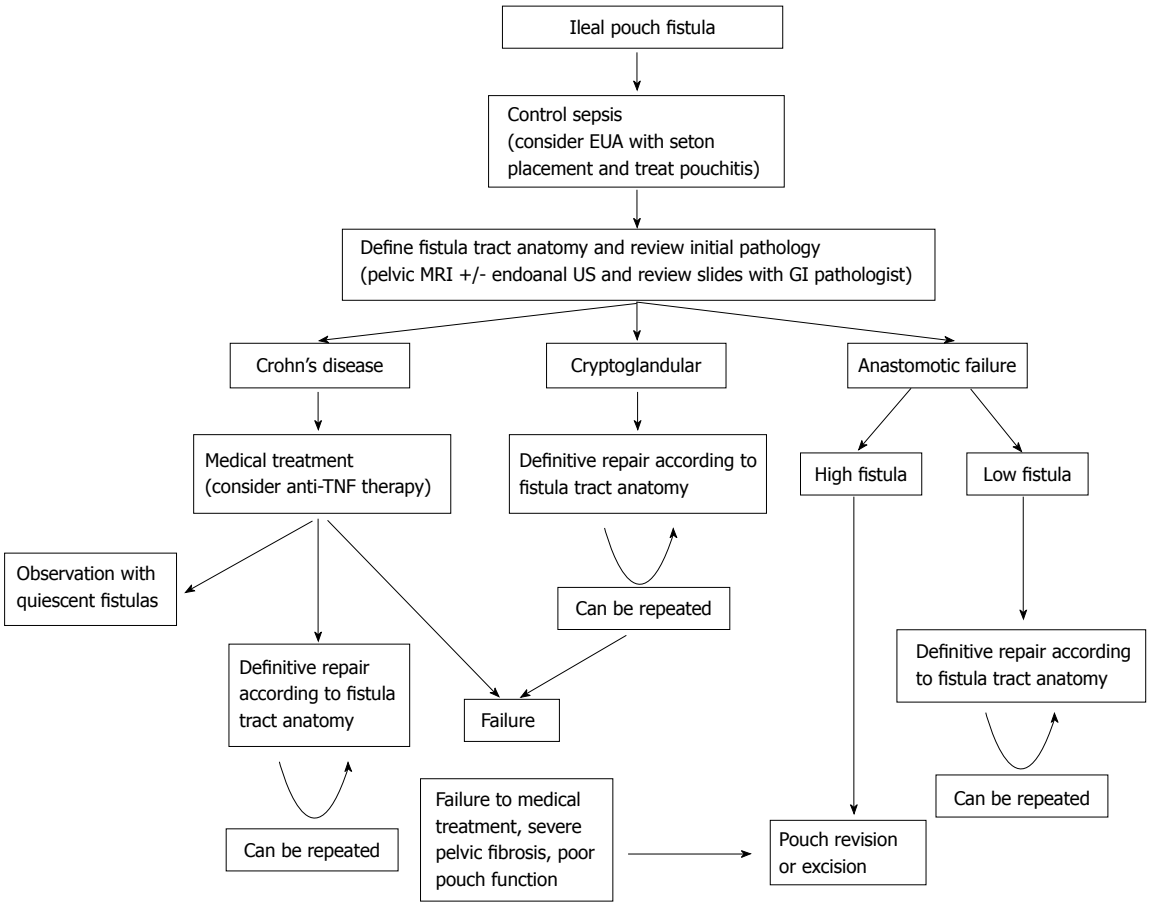

Figure 3 Diagnostic and treatment algorithm for patients with ileal pouch fistulas.

47 mo, 46 percent healed. Multivariate analysis showed that immunomodulators were associated with successful healing ($P = 0.009$); and smoking and steroids were associated with failure ($P = 0.04$).

The efficacy of infliximab in RVF and CD has been controversial[38,62,66-68,107-109]. In the ACCENT Ⅱ study[109], the initial response rate to infliximab was 64 percent. Rectovaginal fistula closure was maintained for longer with maintenance infliximab compared to placebo (46 wk *vs* 33 wk). Gaertner *et al*[110] reviewed the outcomes of 51 patients with Crohn's RVF's who underwent combined medical and operative treatment, 26 received preoperative infliximab. At a mean follow up of 38.6 mo, 27 fistulas (53%) healed. Transperineal repair was the operation with the highest healing rate regardless of infliximab therapy. Preoperative fecal diversion, active proctitis and infliximab therapy did not significantly impact fistula healing.

The definition of fistula healing tends to raise controversy when reviewing the RVF literature and seems to be influenced by the type of treatment, method of evaluation, and follow-up period. Rasul *et al*[111] assessed RVF healing by endoanal ultrasound in patients who clinically healed with infliximab therapy. Only five of 35 women demonstrated improvement but none showed fistula closure on ultrasound. Bell *et al*[112] found good correlation between clinical assessment and MRI in seven of ten patients treated with infliximab. Only two of these patients had RVF.

Ileal pouch fistulas

Patients who develop CD after restorative proctocolectomy with ileoanal anastomosis are at particularly high risk of developing pouch-anal fistulas. Although preoperative colorectal pathology, operative technique, and postoperative pelvic sepsis have also been identified as risk factors, CD is considered the most common[113-115]. Several operative techniques have been described to control pelvic and perianal sepsis and ultimately eliminate the fistula tract[116-120], but because of the low incidence of these fistulas, the optimal management continues to be controversial (Figure 3). Gaertner *et al*[121] reviewed the outcomes of 25 patients who presented with symptomatic ileal pouch fistulas over a 22-year period. Fistulas were classified as pouch-anal (48%), pouch-vaginal (28%), complex (16%), and pouch-perineal (8%). The most common etiology was CD. Overall fistula closure with a variety of local anorectal and abdominal procedures was 64 percent at a median follow-up of 29 mo. Postoperative pelvic sepsis, fecal diversion, and anti-TNF therapy did not significantly impact fistula healing. Three patients (12%) required pouch excision with end ileostomy.

Fistula-associated cancer

In 1934, Rosser[122] first described carcinoma associated

with a chronic perianal fistula. Fistula-associated adenocarcinoma is a rare but increasingly reported malignancy[18,21,123-131] that is commonly found in CD patients with chronic anal fistulas[18,21]. This malignancy is frequently associated with chronic, complex fistulas and can be particularly difficult to diagnose. High clinical suspicion is crucial to avoid any delay in diagnosis and treatment. Chronic infection and inflammation (*i.e.*, CD and radiation) are the most frequently associated risk factors but even when the diagnosis is suspected clinically, confirmation requires EUA with biopsy. Misdiagnosis commonly occurs in elderly patients and patients with long-standing anorectal disease. Once the diagnosis of cancer has been established, EAUS and MRI are recommended for staging[132].

Mucinous adenocarcinoma is the most common malignancy reported in long-standing perianal fistulas. It is typically a slow growing, locally aggressive neoplasm that mainly spreads *via* the inguinal lymphatic's[133]. Outcomes are good when malignancy is diagnosed early[131,133-136]. Oncologic resection remains the standard treatment option. Abdominoperineal resection is the most frequently employed operation[131,137,138]. The role of neoadjuvant chemoradiotherapy in the treatment of this neoplasm has not been well studied, probably because of its rarity, but results are promising[21,131]. Neoadjuvant therapy may play a significant role to improve outcomes but remains investigational.

Gaertner *et al*[131] identified 14 patients with fistula-associated anal adenocarcinoma. The most common presentation was persistent perianal fistula (n = 9). Ten patients (71%) had CD. Abdominoperineal resection was performed in eleven patients, seven following neoadjuvant chemoradiotherapy. At a mean follow-up of 64 mo, ten patients were alive without evidence of disease and four patients died with metastatic disease. All seven patients who received neoadjuvant chemoradiotherapy had a complete pathologic response. In a systematic review by Iesalnieks *et al*[21], a total of 23 publications including 65 patients with fistula-associated adenocarcinoma and CD were reviewed. Abdominoperineal resection was performed in 56 patients with an overall 3-year survival rate of 54 percent.

We recommend that tissue from refractory, recurrent and chronic anal fistula tracts, regardless of their etiology, should be submitted for pathologic evaluation. All patients with long-standing perianal CD should undergo cancer surveillance. Although the impact of neoadjuvant chemoradiotherapy remains controversial, oncologic resection continues to be the standard treatment option for fistula-associated adenocarcinoma.

Proctectomy

Proctectomy is appropriate in patients in whom repeated medical and operative strategies fail. Historically, it is required in ten to 20 percent of patients with perianal CD[6], and is commonly associated with perineal wound breakdown, chronic open wounds and sinus formation in up to half of patients[139,140]. In our experience, intersphincteric proctectomy (when feasible) and the use of rectus abdominal and gracilis flaps can help with avoiding these complications.

A low Hartmann's procedure is an alternative approach that may result in a healed perineum in up to 60 percent of patients with perianal CD[141]. Despite this approach, Guillem *et al*[142] reported a 54 percent completion proctectomy rate in 28 patients who underwent rectal exclusion, plus an additional nine patients had persistent active disease at the rectal stump.

CONCLUSION

The appropriate treatment of fistulizing perianal CD must be individualized to each patient. The primary goals are to ameliorate symptoms and prevent complications. Overall, a less aggressive approach is preferred as many patients will require repetitive operations that can often result in outcomes that are worse than the disease itself.

Based on the current literature, multidisciplinary treatment includes: eradication of infection, assessment of CD status and fistula tract(s), medical therapy, and selective operative management. The first phase of treatment is to drain the perianal infection. This typically involves an EUA, seton drainage and a short course of antibiotics. The second phase consists of endoscopically evaluating the extent of CD and delimiting the anatomy of the fistula tract with EUA and either EAUS or MRI, or both. During this phase, medical therapy with immunomodulators and anti-TNF agents is typically initiated but if the fistula is thought to be of cryptoglandular etiology, CD medications are rarely required.

The third phase should ideally involve healing of the perianal pathology. Many patients who have minimal symptoms elect to continue with a non-cutting seton or removal and expect healing in some cases. On many occasions a non-cutting seton may actually act as a cutting seton, specially in low superficial fistula tracts. The extensive range of operations highlights the complexity of operative treatment. These include a variety of minimally invasive techniques and anorectal operations. Sphincter injury and fecal incontinence should be the main concern with any anorectal operation. The operative approach depends on the anatomy of the fistula tract, CD status, and the patients' functional status. Attempts to heal a fistula in the setting of active infection and proctitis are likely to fail. If the patient's symptoms persist or increase despite adequate medical and surgical treatment, a diverting stoma or proctectomy should be considered.

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