Diagnosis and treatment of fistulising Crohn’s disease

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SUMMARY
A fistula is defined as a pathological connection between the intestine and an inner (bladder or other intestine) or outer (vagina or skin) epithelial surface. Fistulas are discovered in up to 25% of all Crohn’s disease patients during long term follow-up examinations. Most are perianal fistulas, and these may be classified as simple or complex. The initial investigation of perianal fistulas includes imaging (MRI of the pelvis and rectum), examination under anaesthesia (EUA) with digital imaging, endoscopy, probing and anal ultrasound. Non-perianal fistulas require contrast imaging and/or CT/MRI for complete anatomical definition. Any abscess should be drained, and the disease extent throughout the entire gastrointestinal tract should be evaluated.

Treatment goals for perianal fistulas include reduced fistula secretion or none, evaluated by clinical examination; the absence of abscesses; and patient satisfaction. MR imaging is required to demonstrate definitive fistula closure. Fistulotomy is considered for simple perianal fistulas. In complex perianal fistulas, antibiotics and azathioprine or 6-mercaptopurine, which are often combined with a loose seton, constitute the first-line medical therapy. In cases with persistent secretion, infliximab at 5 mg/kg is given at weeks 0, 2, and 6 and subsequently every 8 weeks. Adalimumab may improve fistula response in both infliximab-naive patients and following infliximab treatment failure. Local therapy with fibrin glue or fistula plugs is rarely effective. Definitive surgical closure of perianal fistulas using an advancement flap may be attempted, but this procedure is associated with a high risk of relapse. Colostomy and proctectomy are the ultimate surgical treatment options for fistulas. Intestinal resection is almost always needed for the closure of symptomatic non-perianal fistulas.

Abbreviations: EUA, examination under anaesthesia; MRI, magnetic resonance imaging; CT, computer tomography.

INTRODUCTION
Fistulas occur in 14-26% of patients with Crohn’s disease [1-3]. Perianal fistulas comprise half of all cases, whereas enterointestinal comprise 25%, recto/anovaginal comprise 10% and other fistulas (enterocutaneous and enterovesical) account for 10-15% of fistulas in these patients [3]. Two-thirds of patients experience just one fistula episode, while the remainder have two or more fistula episodes over 20 years of follow-up [3]. The presence of a fistula usually indicates a more aggressive course of Crohn’s disease, which may include a need for more frequent hospitalisations, surgery, and steroid treatment [4]. The diagnosis, assessment, and treatment of fistulising Crohn’s disease is a complex task that involves medical, surgical, and radiological team functions at a highly specialised level [5].

DEFINITIONS
A fistula is defined as a pathological connection between two epithelial surfaces. Examples of fistulas include a connection between a section of the gut and an outer (skin/vagina) or inner (organ or other intestinal) surface [6]. For practical reasons, perianal fistulas [7] are classified as simple or complex according to Park’s classification (Figure 1).

- Simple fistula: superficial (intersphincteric/transphincteric) and low (below the dentate line), without signs of abscess formation or anorectal stricture.
- Complex fistula: high intersphincteric/transphincteric/-extrasphincteric/suprasphincteric; multiple openings with abscesses; rectovaginal fistula; anorectal stricture with rectal inflammation.

The results of fistula treatment may be classified as follows [8]:
- Closure of the individual fistula, which will lead to the cessation of secretion by light bimanual compression.
- Improvement: reduction of an open or secreting fistula by greater than 50% compared with baseline levels on at least 2 consecutive examinations (at least 3 weeks after treatment).
- Remission: closure of all fistulas in relation to the baseline level on at least 2 consecutive examinations (at least 3 weeks after treatment).
- Definitive fistula closure: closure of the fistula, where probing is not possible and the fistula cannot be visualised by MR imaging.
For the evaluation of perianal disease, Irvine and coworkers have suggested the following medical treatment is rare, with a high risk of recurrence. For the patient, the primary goal is to reduce or eliminate fistula secretion and abscess risk. Moreover, avoidance of stoma and faecal incontinence are important. Symptom alleviation may be achieved with medical treatment, but definitive fistula healing often depends on follow-up time and continuing medication. An international consensus report has recommended the use of MRI and clinical examination to assess fistula closure in clinical trials [15].

### Methods

Literature searches were completed on April 1, 2010. Searches were performed using the PubMed database (http://www.ncbi.nlm.nih.gov/pubmed) with Medical Subject Headings (MeSH) terms that included "intestinal fistula" and "Crohn disease" and with the following limits: species (human), languages (English) and type of article (clinical trials). Reference lists in identified papers were reviewed for original articles relevant to the topic.

### Diagnosis of Perianal Fistulas

Of the currently used methods for the mapping of fistula anatomy, examination under anaesthesia (EUA), MRI of the pelvis and rectal, and endoanal ultrasound show similar accuracies [9-12]. By combining two of these modalities, diagnostic accuracy approaches 100%, although the definition of a gold standard is controversial [12].

### Treatment Goals

For the patient, the primary goal is to reduce or eliminate fistula secretion and abscess risk. Moreover, avoidance of stoma and faecal incontinence are important. Symptom alleviation may be achieved with medical treatment, but definitive fistula healing following medical treatment is rare, with a high risk of recurrence. For the evaluation of perianal disease, Irvine and coworkers have suggested the Perianal Disease Activity Index (PDAI) [13], which has been validated and used as a secondary endpoint in the assessment of perianal fistula healing [8]. The PDAI is a useful and clinically relevant system, although not specifically developed for assessing fistula closure. Definitive fistula closure, which is defined as the absence of a tract upon probing or imaging, has been investigated in only a few studies. Indirect measures, such as cessation or reduction of secretion, are most often used. Present and coworkers used a Fistula Drainage Assessment to assess fistula closure after treatment with infliximab [8]. This diagnostic system has gained general acceptance for clinical assessment [14,15].

### Antibiotics for Perianal Fistulas

One randomised, placebo-controlled study of fistulising Crohn’s disease patients [16] compared placebo (n=8), metronidazole at 500 mg x 2 (n=7) and ciprofloxacin at 500 mg x 2 (n=10) treatment for 10 weeks. There was no significant difference regarding the primary endpoint, remission (closure of all fistulas), which was achieved in 12.5% (placebo), 0% (metronidazole), and 30% (ciprofloxacin) of patients. In addition, there were no significant differences regarding the secondary endpoint, improvement (at least 50% closed fistula), which was achieved in 12.5% (placebo), 14.3% (metronidazole) and 40% (ciprofloxacin) of patients. Data from uncontrolled studies [17-19] have shown reduced symptoms after treatment, but rarely complete fistula closure. Furthermore, these studies have been accompanied by a high risk of relapse after discontinuation [20]. Healing rates during antibiotic treatment may be enhanced by combination therapy with azathioprine [21].

#### Clinical Recommendations
- Ciprofloxacin or metronidazole may result in symptom improvement.
- Due to high relapse rates after discontinuation, the above treatment should be combined with azathioprine or 6-mercaptopurine.
AZATHIOPRINE/6-MERCAPTOPURINE FOR PERIANAL FISTULAS

No controlled clinical study has evaluated azathioprine/6-mercaptopurine as primary therapy but is rarely sufficient alone.

BIOLOGICAL AGENTS FOR PERIANAL FISTULAS

Infliximab 5 mg/kg is typically administered as an induction therapy at weeks 0, 2, and 6 and then as maintenance therapy every 8 weeks. A randomised, controlled trial of 94 patients with at least one secreting fistula compared infliximab at a dose of either 5 or 10 mg/kg with placebo. Ninety percent had perianal fistulas, and almost half had only one fistula [8]. Among the actively treated patients, 62% improved and 56% obtained fistula closure within a median of 2 weeks of the onset of their response. Maintenance therapy for up to 12 months has proven better than placebo in preventing relapse, but up to half of infliximab-treated patients experience a recurrence within the first year of treatment [23,24]. In patients receiving concurrent treatment with anti-TNF-α for other intestinal involvement, a significantly lower response rate should be expected [25]. Adalimumab has been evaluated in a clinical controlled trial (either 160 mg or 80 mg and then 40 mg subcutaneously every other week versus 40 mg weekly versus placebo) in 117 patients with actively secreting fistulas (60% perianal and 60% with only one fistula). Fistula closure was achieved in 36% of the patients in the adalimumab group compared with 16% in the placebo group after 16 weeks of treatment [26]. In the open label extension of the study, response was maintained up to 60 weeks in all patients who had a primary response after 26 weeks. It is unclear whether these long-term effects were drug-dependent.

Clinical recommendations

- Biological treatment with infliximab or adalimumab should be used in case of primary medical and surgical treatment failure.
- The onset of effects is usually rapid, but maintenance treatment is frequently required for a sustained response.

OTHER DRUGS FOR PERIANAL FISTULAS

Cyclosporine, tacrolimus, corticosteroids, 5-aminosalicylates, charcoal, granulocyte-macrophage colony-stimulating factor, parenteral nutrition, mycophenolate, methotrexate, thalidomide, hyperbaric oxygen, sargramostim, and Antegren (Tysabri®) have all been used in the treatment of Crohn’s disease; however, there have been no specific studies examining the use of these medications for the treatment of fistulising Crohn’s disease.

LOCAL TREATMENT OF PERIANAL FISTULAS

Fibrin glue: Only one randomised study has been published comparing conventional surgery with fibrin glue, and Crohn’s patients constituted only a minor part of the patient population [27]. With simple fistulas, healing was achieved in all surgically treated patients and in 50% of those treated with fibrin glue. With complex fistulas, healing was observed in 69% of patients treated with fibrin glue and in 13% treated with conventional surgery.

Fistula plugs (biological material obtained from porcine intestinal mucosa): Only a small number of uncontrolled studies with relatively short observation times and incomparable plug materials have been published. The reported healing rates varied between 29 and 86%.

Local infliximab installation and stem cell therapy (the application in the fistula tract of autologous stem cells derived from adipose tissue): There are new treatment principles under development. At present, the available evidence is too limited for these methods to be recommended [28-33].

Clinical recommendations

- Fibrin glue may be utilised for the treatment of complex fistulas.
- Fistula plugs may be attempted.

SURGICAL TREATMENT OF PERIANAL FISTULAS

The most common surgical procedure for perianal Crohn’s disease is abscess drainage. The treatment principles are not different.
from the treatment of common perianal abscesses [15]. Low subcutaneous fistulas can be treated primarily with fistulotomy or the ‘lay-open’ technique, with a healing rate of 75-85% [34,35]. However, in 29-47% of cases, the fistulas are transphincteric or complex [36]. Here, a loose seton can be inserted to facilitate drainage and prevent abscess formation, which will also avoid anal sphincter lesions during surgery [37-39]. Nevertheless, a seton is rarely curative. Thus, among 23 patients treated with setons, fistula closure was only seen in 3 patients 3 years after seton removal [40]. Regular follow-ups using invasive examinations under anaesthesia and anal ultrasound are crucial as guidance techniques for seton removal. Using this strategy, symptom relief was achieved in 75% of patients with a follow-up period of 35-101 weeks [41]. It is often preferable to leave the seton in place because it rarely causes significant discomfort, and the definitive surgical treatment of transphincteric and complex fistulas is rarely successful. If surgery is considered, an advancement flap of either rectal mucosa or skin or possibly a combination of both supplemented with fistulotomy can be tried. Regardless of which procedure is used, there is a high recurrence rate of up to 50%, depending on the observation time [42]. The relapse rate following advancement flap placement increases with the number of surgical procedures. A diverting colostomy should be considered in cases of reoperation [43].

A diverting stoma can result in symptomatic remission in 83% of patients with severe perianal Crohn’s disease [44]. The chance of having a stoma closed at a later time depends on several clinical variables. If the indication is either for perianal fistula, rectovaginal fistula, or complicated rectal inflammation, the chance of remission is only 40% [45] or lower. In severe perianal Crohn’s, the risk of a permanent stoma is 49% at 7 years after disease onset. Multivariate analysis has shown that concomitant colonic Crohn’s and anal stenosis are predictors of permanent stoma [46]. Proctocolectomy is a definitive treatment option, although it has a high complication rate. This procedure is associated with perineal wound complications in 35% of patients, intra-abdominal sepsis in 17%, and stoma complications in 15% of cases [47]. The application of myocutaneous flaps may reduce the frequency of perineal wound complications [48].

Clinical recommendations
- Abscesses should be drained.
- Simple low symptomatic fistulas can be treated with fistulotomy.
- The primary treatment of complex fistulas is the insertion of a loose seton.
- Definitive closure of complex fistulas includes an advancement flap combined with fistulotomy. Occasionally, this may require a diverting stoma.
- A diverting stoma itself can lead to remission of perianal Crohn’s disease.

TREATMENT OF NON-PERIANAL FISTULAS

Enterocutaneous fistulas. A distinction should be made between postoperative and primary enterocutaneous fistulas. Postoperative fistulas represent the vast majority of cases [49,50]. Fistulas occurring during the first postoperative week may be due to anastomotic leak or an unrecognised accidental bowel lesion. The majority (60-75%) of these fistulas will close after conservative treatment with an ostomy bag and nutritional therapy [49-51]. If the fistula does not close during conservative treatment, the fistula and the bowel section involved should be resected. The timing of surgery is crucial, and surgical intervention should not be planned earlier than after 3 months postoperatively [49,52]. Fistulas occurring later in the postoperative period typically originate from the anastomosis area [53-55] and usually require resection of the fistula and the affected bowel segment at a later stage. Primary enterocutaneous fistulas originate from actively inflamed intestine. In cases of substantial comorbidity or risk of short bowel syndrome after surgery, medical treatment may be attempted; however, permanent closure usually requires surgical intervention [56]. Peristomal enterocutaneous fistulas may be conservatively treated with appropriate bandaging. Otherwise, treatment is surgical, with revision or relocation of the stoma, and is most commonly accompanied by resection of the affected bowel.

Enteroanovaginal fistulas. Rectovaginal and anovaginal fistulas are the most frequent [57] and are found in 5-10% of female Crohn’s patients [58]. The more analy a fistula is located, the better the prognosis is for healing. Conversely, active small-intestinal Crohn’s disease and proctitis reduce the likelihood of successful surgical treatment [59-61]. Transrectal or transvaginal advancement flaps are the most frequently used treatments for recto/vaginal fistulas, with no significant differences in fistula closure rates [54% and 69%, respectively] [62]. Combined surgical and medical treatment with infliximab appears to have no influence on healing rate [63]. Enteroenteric and other enterogynaeco logical fistulas can usually be treated with resection of the affected bowel and surgical closure of the fistula [15].

Enteroenteric fistulas. An internal fistula has been observed in approximately one-third of patients who undergo surgery for Crohn’s disease. Out of these cases, only 54% were diagnosed preoperatively [64]. These fistulas are often asymptomatic [54], and the presence of a fistulas alone is not an indication for surgery [6%] [54,64]. Symptomatic fistulas are treated by surgical resection of the affected bowel segments.

Enterovesical fistula. Fistulas to the bladder are rare (2%) [65] and typically present with recurrent urinary tract infections and pneumaturia [65,66]. Imaging may not visualise fistulas properly [64,67], but CT scans and cystography seem most useful. In most cases, treatment consists of resection of the affected bowel segment, closure of the bladder defect, and postoperative bladder drainage for 7 days [65,66].

Clinical recommendations
- Early postoperative enterocutaneous fistulas: conservative treatment. In cases of treatment failure, resection of the involved bowel and fistula no earlier than 3 months postoperatively.
- Late postoperative enterocutaneous fistulas: Resection of the fistula and the affected bowel segment.
- Rectovaginal and anovaginal fistulas: Transrectal or transvaginal advancement flap.
- Enteroenteric fistulas: Resection of the affected bowel segment in case of symptoms.
- Enterovesical fistula: Resection of the affected bowel segment and closure of the bladder defect.

REFERENCES


