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Review Article: Medical, surgical and radiological management of perianal Crohn’s fistulas

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Abstract

Background
Crohn’s anal fistulas are common and cause considerable morbidity. Their management is often difficult; medical and surgical treatments rarely lead to true healing with frequent recurrence and complications.

Aim
In this review, we examine medical treatments previously and currently used, surgical techniques and the important role of optimal imaging.

Methods
We conducted a literature search in the Pub Med database using Crohn’s, Anal Fistula, Surgery, Imaging and Medical Treatment as search terms.

Results
Antibiotics and immunosuppressants have a role but slow initial response, side effects and relatively low remission rates of up to around a third with frequent recurrence limit their value. Long term infliximab produces clinical remission in 36-58% of patients with combined medical and surgical management achieving optimal outcomes. Traditional and newer surgical procedures often have a high rate of recurrence with a significant risk of temporary or, in up to 10% of cases, permanent stomas, incontinence and unhealed or slowly healing wounds in 30%.

Conclusions
Management of Crohn’s anal fistulae remains challenging. Established principles are to drain infection, use setons as required, aggressively manage active proctitis, give antibiotics, immunosuppressants, and employ anti TNFα therapy
and they demand significant co-operation between gastroenterologists and surgeons.

Key words: perianal fistula, Crohn’s disease, MRI, infliximab, surgery
**The scale of the problem**

Perianal Crohn’s disease is particularly distressing, it is difficult to treat and unfortunately occurs in around a third of all patients with Crohn’s disease\(^1\), one study supplying a cumulative risk of anal fistula of 26% at 20 years\(^2\). In a small proportion of patients with Crohn’s disease, anal fistula is their initial manifestation. One third of patients have recurring anal fistulas and two thirds of them have multiple fistulas\(^3\). An early series of patients from a tertiary referral centre found low fistulas (superficial, low intersphincteric or low trans-sphincteric) represented 46 of 73 (63%), whereas 25 (35%) were high intersphincteric, high trans-sphincteric or suprasphincteric fistulas and the remaining 2 were extrasphincteric\(^4\).

**Fistula classification**

Low intersphincteric fistulas, low transphincteric fistulas and those with a single track with no extensions or complicating abscesses are classified as ‘simple’. Complex fistulas have extensions, high tracks (whether intersphincteric, transphincteric or suprasphincteric) involve the vagina or have an associated stricture or proctitis\(^5\). The differentiation between simple and complex has prognostic relevance. Complexity, historically at least, worsens the prognosis, reduces the chance of healing and threatens continence\(^3\). As yet no medical trials have randomized specifically based on complexity of fistula. Perhaps contrary to expectation, a more recent prospective cohort of patients with
perianal Crohn’s disease treated with anti-TNFα antibodies showed no relation between fistula complexity and the likelihood of healing with biologic agents \(^6\).

The Montreal classification has recognised that perianal disease requires a separate subclassification because it is distinct from and is not usually associated with internal fistulating/penetrating disease \(^7\). This classification guides management and may have an aetiological basis.

**Predisposing factors**

Males, patients with distal disease, those who have a younger age of onset of Crohn’s disease, non Caucasians and Sephardic (as opposed to Ashkenazi) Jews are all at higher risk of developing perianal Crohn’s disease \(^8\text{-}^{11}\).

**Differential diagnoses**

As previously discussed, a small group of patients with Crohn’s disease present with an anal fistula \(^3\). In this situation the presentation of luminal and perianal disease is often contemporaneous but sometimes the anal fistula presents weeks, months or years before the evolution of luminal disease and in a few cases the finding of non-caseating granulomas in specimens from anal fistula surgery is the only evidence of Crohn’s disease in a patient otherwise free from symptoms throughout their life.
Isolated perianal Crohn’s disease and Crohn’s disease in evolution may then prompt an incorrect diagnosis of cryptoglandular fistula in some cases. Other causes of fistulae include as cancer, radiation, trauma and hidradenitis suppurativa.

**Hidradenitis Suppurativa**

Hidradenitis suppurativa (HS) is associated with perianal Crohn’s disease, can coexist with it and causes diagnostic difficulty in some patients. The clinical and histological features of the two diseases can be similar and it is possible to confuse HS with Crohn’s perianal sepsis or with the cutaneous manifestations of Crohn’s. Early series highlighted the diagnostic difficulty \(^{12,13}\); the presence of granulomas in the submucosal layer of cutaneous biopsies led to a diagnosis of Crohn’s disease but the appearance of abscesses in the axillae suggested HS and subsequent intestinal inflammation confirmed the dual diagnoses. Epithelioid granulomas were subsequently shown also to exist in patients with HS alone \(^{14}\). Further series reinforced the association between HS and perianal Crohn’s disease and the potential for missing one or other diagnosis as well as describing the outcome for these patients in whom (in one series) 22 of 24 had a stoma and 17 had undergone proctectomy \(^{15,16}\). Further evidence of a link between the diseases comes from two case reports in which concurrent luminal Crohn’s and HS responded to treatment with infliximab with improvement in all sites of HS \(^{17,18}\).
Clinical and radiological features may be valuable in distinguishing the two diseases. The presence of abscesses at other sites including the groin and axillae are clearly suggestive of HS, as are multiple sinus tracts and fistulae, especially when they lack a clear focus on the anorectum. Severe disease at onset rather than a gradual natural history is also suggestive of HS. Case reports in the literature suggest that MRI may be valuable; skin thickening and subcutaneous induration away form the perianal area, subcutaneous abscesses remote form the rectum or anus, enlarged inguinal lymph nodes and no communication with pelvic organs are consistent with HS rather than Crohn’s anal fistulae ¹⁹.

**Implication of anal fistulas on Crohn’s disease course**

Patients with Crohn’s disease with perianal involvement are more likely to have a severe disease course. Beaugerie and colleagues in 2006 reported that perianal lesions at diagnosis were associated with a more disabling course in addition to factors such as age below 40 years at onset or need for steroids for the first flare of disease ²⁰. Lakatos and colleagues in 2009 reported that perianal disease (in addition to other factors such as small bowel disease, smoking, prior steroid or early azathioprine/biological therapy) is a predictor of disease behaviour change (from inflammatory to stricturing or penetrating) over time in patients with Crohn’s disease ²¹.
In 2003, before many patients were treated with biologic agents, a group of 78 Crohn’s patients with anal fistulas treated at St Mark’s Hospital were assessed and at long term follow up 76% of fistulas had healed, 16% were persistent and 7% had a seton in situ. Median time to healing was 44 months with a median of 3 (simple) or 6 (complex) treatments per patient.  

**Assessment of perianal Crohn’s disease**  

There are three ways to assess a patient with perianal Crohn’s disease besides history and physical examination:

1) endoscopy, for evaluating proximal luminal disease and in particular the state of the rectum;

2) local imaging with MRI or anal endosonography;

3) examination under anaesthesia with surgical drainage of any abscesses and seton placement as required.

These assessment methods are generally complementary and are often undertaken in combination. Endoscopy will assist in diagnosis and map the extent and severity of the known case. Additional small bowel imaging may be used to fully map the disease.
Pelvic MRI has been shown to be the most accurate method for classification of primary track and extensions, although anal ultrasound, particularly when enhanced by hydrogen peroxide, can occasionally be useful for detecting the internal opening where uncertainty exists. Anal ultrasound (in combination with anorectal physiology tests) can also assess sphincter integrity and function to inform an optimal surgical strategy. However, ultrasound will not reliably identify ischioanal fossa or supralevator sepsis due to rapidly declining resolution with distance from the probe. Furthermore, there is considerable variation in operator expertise and insertion of the ultrasound probe may be very uncomfortable in the setting of active sepsis, or impossible with stenosis.

On the other hand, MRI can be performed without a radiologist needing to be present at the time the test is done. Sequential images are easier to compare, particularly when monitoring treatment. Interpretation is more intuitive and the strategic view is better, which can be helpful intra-operatively. However, the test is expensive and the internal opening is less well seen (its position is usually inferred), and some patients feel claustrophobic in the confined space of the MRI scanner.

As well as being diagnostic, examination under anaesthetic (EUA) by an experienced surgeon allows infection to be drained and either definitive surgery (lay open or other curative procedures) or placement of a temporary loose seton for drainage while medical management is optimised. However, injudicious
probing may cause iatrogenic tracks, increasing the complexity of the fistula and therefore the risk of recurrence or subsequent incontinence.

In 2001 Schwartz and colleagues reported 34 patients with perianal Crohn’s disease taking part in a prospective study comparing the accuracy of 3 methods, EUS, early generation MRI and EUA. There was good agreement between all three. EUS had 91% accuracy, MRI 87% accuracy and EUA 91% accuracy. A combination of any 2 methods yielded an accuracy of 100% 23. Two years earlier, Orsoni and colleagues had detected more abscesses and fistulas in 22 Crohn’s patients when using EUS compared to MRI 24. However the quality of MRI in this era was relatively poor.

A later blinded study at St Mark’s hospital comparing clinical examination, EUS and MRI was undertaken in 104 patients 25. Classification of fistula, presence of secondary tracts/abscesses and the site of internal openings were all most accurately assessed at MRI. For example, tract accuracy was 90% with MRI, 81% with ultrasound and 61% with clinical examination. The question of which modality is best for discriminating simple and complex fistulas was specifically addressed using established Evidence Based Practice principals by Sahni and colleagues in 2008 22. They found that MRI is the superior technique with sensitivity and specificity of 97% and 96% compared with 92% and 85% for anal ultrasound and 75% and 64% for clinical examination. MRI remains the bed rock of fistula imaging at St Mark’s, partly for this reason, partly because the surgeons
and gastroenterologists are able to interpret them themselves to some degree in theatre or in clinic, and partly because, as a more objective (less operator dependent) examination, MRI also facilitates serial assessment and comparison of images over different time points.

**Treatment of perianal Crohn’s disease**

The established principles are to drain infection, use setons as required, aggressively manage active proctitis, give antibiotics, immunosuppressants, and employ anti TNFα therapy and they demand significant co-operation between gastroenterologists and surgeons.

Few patients improve without any therapy (10% in the placebo arms of the early trials)\(^{26-28}\). Also, improving, either spontaneously or with treatment, is not the same as being cured. The majority of recent medical trials (particularly those assessing the anti-TNFα agents) use clinical assessments of healing i.e. Fistula Drainage Assessment, where response is defined as a reduction of 50% or more from baseline in the number of draining fistulas observed at 2 or more consecutive study visits \(\geq 4\) weeks apart\(^5,27,29\). A fistula is considered to be closed when it no longer drains despite gentle finger compression at examination. Remission is defined as the absence of any draining fistulas at two consecutive visits. However, studies utilising MRI findings as a more rigorous end-point of deep tissue healing, rather than simply closure of external openings,
demonstrate undrained sepsis in these patients who, in turn, are very likely to recur or develop more complex sepsis.

**Corticosteroids**

There is no demonstrable role for corticosteroids in perianal Crohn’s disease, although corticosteroids are sometimes used to treat concomitant luminal disease.

**Metronidazole and ciprofloxacin**

Both metronidazole and ciprofloxacin demonstrate slow and incomplete response, early recurrence and unwanted side effects. In an uncontrolled series, Bernstein and colleagues reported 21 patients with perianal Crohn’s disease treated with Metronidazole 20mg per kg daily. All had less discomfort and 10 of 18 (56%) had complete clinical healing. Improvement typically occurred after 6 to 8 weeks. Brandt and colleagues followed up 17 of these patients and added another 9. Three quarters relapsed on stopping metronidazole and side effects including peripheral neuropathy and nausea limited long term use. Jakobovtis and colleagues reported clinical healing in 33 to 50% of metronidazole-treated patients.
Ciprofloxacin has been used in a small open series. Turunen and colleagues in 1989 reported 8 patients with perianal fistulating Crohn’s disease resistant to metronidazole; all improved but half had persistent drainage. Solomon and colleagues reported 14 patients with perianal Crohn’s disease treated with both metronidazole and ciprofloxacin with approximately two thirds of patients responding. Metronidazole has been compared with ciprofloxacin or placebo in a small randomized double-blind placebo-controlled pilot study reported in 2008. Twenty five patients with perianal Crohn’s disease were randomised to ciprofloxacin 500mg twice a day or metronidazole 500mg twice a day or placebo twice a day and were treated for ten weeks. Clinical remission and response rates were 30% and 40% with Ciprofloxacin, 0% and 14% with Metronidazole and 12.5% and 12.5% with placebo, none of these differences being significant. There were no differences seen in the scores of PDAI, CDAI, IBDQ, and patient and physician global assessment at any time point during the study.

Overall, antibiotics remain a mainstay of treatment for perianal Crohn’s disease despite the lack of controlled trial evidence. If metronidazole is used, a dose of 750–1500 mg/day is suggested. Adverse events include metallic taste, glossitis, nausea and neuropathy. It should be discontinued if any signs of neuropathy occur, but generally therapy is continued for 3–4 months. If ciprofloxacin is used, a dose of 500–1000 mg/day is adequate and again is usually required for 3–4 months. Adverse events include headache, diarrhoea, nausea and rash.
**Immunomodulators**

There are no controlled trials using the immunomodulators azathioprine and 6MP with fistula outcome assessed as primary end points. Efficacy is suggested by a meta-analysis of controlled trials in which fistulas were assessed as secondary end points. This meta analysis reports a clinical fistula response of 54% in the azathioprine/6MP group compared with 21% in the placebo group \(^{35}\). There are two uncontrolled case series (one in children) that have been reported \(^{36,37}\). The larger series by Korelitz and Present in 1985 included 18 patients with perianal fistulas. Six patients demonstrated complete fistula closure and 4 patients demonstrated clinical improvement of their fistulas.

The combination of azathioprine and antibiotics has also been assessed \(^ {38}\). Fifty two patients with predominantly simple Crohn’s perianal fistulas were given metronidazole or ciprofloxacin for 8 weeks. Patients who received azathioprine as well had a better response at week 20 than those who had not suggesting combination treatment was better.

The slow initial response, side effects and relatively low remission and high recurrence rates with the drugs so far discussed have left the door open to newer treatments.

**Infliximab**
With the biological drugs, comes a change in treatment options for perianal fistulating Crohn’s disease. The potential not only to improve quality of life but also to heal the fistula tracks has been realised and the time to clinical improvement has changed from the order of several months to a few weeks.

The first placebo controlled trial using Infliximab was reported by Present and colleagues in 1999 \[^{27}\]. Ninety four patients were given three infusions of Infliximab at 0, 2 and 6 weeks. Sixty eight percent of patients had a clinical response and approximately 50% of patients closed all fistulas. The median time to achieve response was 2 weeks.

In the maintenance trial of infliximab in patients with perianal fistulating Crohn’s disease (A Crohn’s Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen in Patients with Fistulizing Crohn’s Disease, ACCENT II), 282 patients initially received 3 infusions of Infliximab at 0, 2 and 6 weeks and responders at week 14 were randomized to receive placebo or maintenance infliximab 8 weekly for 54 weeks \[^{39}\]. There was a significant difference in the primary outcome measure, which was time to loss of response. Among patients who had a response at the time of randomisation, those given infliximab maintenance therapy had a significantly longer time to loss of response (greater than 40 weeks) than those who received placebo maintenance (14 weeks) (p<0.001). Forty six percent of patients in the infliximab maintenance group had a fistula response at 54 weeks and 36% of patients had a complete response at 54
weeks. In the placebo maintenance group, 23% of patients still had a response at week 54 and 19% had a complete response.

The impact of Infliximab maintenance in the ACCENT II patients on hospital admissions and the need for surgery was examined by Lichtenstein in 2005. The treatment maintenance group had a reduction of >50% in hospital admissions compared with the placebo maintenance group and their length of stay was also significantly reduced (2.5 to 0.5 days). The treatment group also had an approximately 50% reduction in the mean number of all operations and procedures, rising to >80% for major procedures. Not only does infliximab impact on the number of hospitalisations and operations that a patient with perianal Crohn’s disease undergoes, but there is evidence that anti-TNF therapy improves health related quality of life in patients with Crohn’s perianal fistulas.

When infliximab is stopped, however, the risk of recurrence is high and it is higher in perianal than luminal disease. Domenech and colleagues followed patients with perianal Crohn’s disease for 1 year after they had stopped a one year course of infliximab (induction plus maintenance). They found 83% of luminal CD patients were free of relapse compared to only 34% of perianal CD patients.

More recently, a large open label case series from Hungary of 148 Crohn’s anal fistula patients reported a remission rate of 49% at 12 weeks follow up but longer
term follow up and confirmed healing on MRI were lacking\textsuperscript{43}. An Italian multicentre group reported an initial response to induction with infliximab in 76% of 188 patients with perianal Crohn’s disease and a 44% clinical remission rate\textsuperscript{44}. In a prospective study, 34 patients with perianal Crohn’s fistulas were followed up long term. At 6 months, 58% of the Infliximab treated patients were in clinical remission, 37% were in clinical response and 5% had had no response\textsuperscript{6}.

The question of whether infliximab should be used with concomitant immunomodulators such as thiopurines to achieve a better outcome is difficult to answer in the setting of perianal Crohn’s disease. It is interesting to note that the majority in remission in the Hungarian study were on a concurrent immunomodulator, most frequently Azathioprine. In the ACCENT II trial, about one third of patients were on concomitant immunomodulators. A post-hoc analysis of the ACCENT II data by Lichtenstein and colleagues published in 2009 identified that approximately one third of patients in both placebo and infliximab arms were on concomitant immunomodulators at baseline and it appeared that there was no major benefit of dual therapy\textsuperscript{45}. However, in a recent study to assess whether concomitant immunomodulators are useful in patients with Crohn’s disease, it was found that perianal complications were less frequently observed at times when patients were on concomitant immunomodulators\textsuperscript{46}. The balance of risk and benefit of dual therapy needs to be considered in individual cases. In the recent Study of Immunomodulator Naïve patients in Crohn’s disease (SONIC) trial which assessed efficacy of infliximab monotherapy,
azathioprine monotherapy and the two drugs combined in over 500 adults with moderate to severe Crohn’s disease who had not had previous immunomodulator or biologic therapy, overall about 12% of patients had perianal fistulas but no separate analysis was performed in this group to determine the relative benefits of single or dual therapy. However, across all Crohn’s patients dual therapy with infliximab and azathioprine was superior to either therapy alone with regards to steroid free remission and mucosal healing at 26 weeks.

Presence of proctitis has been shown to be a predictor of poor response to anti-TNFα. There are no other clear predictors of failure or success of anti-TNFα in Crohn’s perianal fistulas. However, it is interesting to note that perianal fistulas heal more commonly than other fistulas, particularly internal fistulas, with this treatment.

**Combined surgery and infliximab**

The combination of infliximab and surgery has been examined in a number of small trials in three ways; the application of surgery before radical infliximab treatment, the application of infliximab before surgery or using maintenance infliximab with periodic examination under anaesthetic with seton insertion as required.

The use of examination under anaesthetic, drainage of trapped sepsis and insertion of setons prior to infliximab infusion improved outcome by increasing initial response rate
by almost a fifth, lowering recurrence rate by a third and increasing time to recurrence by 
10 months \textsuperscript{49}.

A series of 226 patients undergoing various surgical procedures for Crohn’s anal fistulae 
included 79 who received preoperative infliximab \textsuperscript{50}. The groups in this study were not 
randomised and are heterogeneous. For example the combined treatment group had a 
higher proportion of transsphincteric (as opposed to intersphincteric) fistulae, a higher 
proportion of seton insertions (as opposed to fistulotomies) and a higher proportion of 
patients with proctitis. Both groups achieved healing similar rates of approximately 
60\% however there were signals in this report which suggest there is a benefit to 
combined treatment. Time to healing was reduced from 12.1 to 6.5 months and two 
subgroups, patients with transsphincteric fistulas or those treated with setons as their only 
surgical intervention, healed more frequently if treated with infliximab too. Proctectomy 
rates were similar in both groups (8-10\%) and, interestingly, although proctitis was 
reduced in the combination group, this did not correlate with healing.

A smaller series of 17 patients in which 7 underwent either fistulotomy (for low fistulae) 
or advancement flap (for higher fistulae) alone and 10 had preoperative infliximab found 
100\% initial healing in both arms with 2 recurrences (29\%) in the surgery alone group 
and 1 (10\%) in the infliximab group \textsuperscript{51}.

Several small uncontrolled case series report the successful use of combined seton 
insertion and maintenance infliximab with remission rates of between 47\% and 78\% \textsuperscript{52-54}. 
Local injection of infliximab

Two open label studies have used infliximab as a local instillation in situations where disease is limited to the anus or there are contraindications to systemic Infliximab. Poggioli and colleagues in 2005 reported the results of 3 to 12 infusions of infliximab (15 to 20mg) directly injected into the tissue surrounding both internal and external openings and into the wall of track. Healing of fistulas was noted in 10 of 15 patients.

Asteria and colleagues in 2006 reported 6 of 11 patients treated with local Infliximab achieving a clinical response and 4 of the 11 remained healed at a median of 10 months follow up.

Adalimumab

In the CHARM (Crohn's trial of the fully Human Antibody Adalimumab for Remission Maintenance) study, 113 patients with Crohn’s fistulas were given adalimumab at week 0 (80mg), week 2 (40mg) and then maintenance with either weekly or fortnightly adalimumab or placebo. Fistula response and fistula remission (cessation of drainage from all orifices) were secondary endpoints. At 26 weeks, 30% of patients treated with adalimumab had complete closure and this rose to 33% at 56 weeks compared with 13% in the placebo arm. In CLASSIC-1 (Clinical Assessment of Adalimumab Safety and Efficacy Studied as an Induction Therapy in Crohn's disease) adalimumab at 80/40 mg, 160/80 mg or
placebo was administered and short term effects were assessed. 32 of the 299 patients had draining perianal fistulae and no difference was found between placebo and any of the ADA induction doses for fistula response or remission. Other studies have considered adalimumab in patients who have already failed a biologic drug. In GAIN (Gauging Adalimumab efficacy in Infliximab Non-responders), Crohn’s disease patients who had lost response or who were intolerant to infliximab were treated with an induction regime of 160/80 mg adalimumab or placebo. 45 of the 325 patients had perianal fistulae and no difference was found between placebo and any of the ADA induction doses for fistula response or remission. In an open label trial in which 22 patients with perianal fistulae who had lost response or showed intolerance to infliximab were treated with adalimumab 160/80 mg, remission was noted in 23% at 4 weeks.

The study of fistulating Crohn’s disease, described above, in which 34 patients with fistulating perianal disease (85% anal fistulas, 15% rectovaginal fistulas) were followed up at St Mark’s hospital, also evaluated the response to adalimumab in patients who lost response to or were intolerant of infliximab. At 6 months 14% of the adalimumab treated patients (who had failed Infliximab) were in clinical remission, 43% in clinical response and 43% having had no response. The data suggest that a second biological agent is effective in patients who have failed one biological therapy already, but the effect is reduced.

The long term use of adalimumab is shown in the CHARM extension study which followed patients for a further 2 years and demonstrated that 60% of
adalimumab-treated patients maintained fistula healing although the non-responder imputation efficacy at 2 years which includes those patients who started on Adalimumab but left the trials for any reason (including stopping the drug due to lack of efficacy, adverse events, protocol violations etc.) was 31%.

Table 1. Randomised Controlled Trials (RCT) or meta-analyses of established medical treatments of Crohn’s-related perianal fistulas

<table>
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<tr>
<th>Drug</th>
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<th>Fistula remission</th>
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<td>Metronidazole</td>
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<td>0% 12.5%</td>
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<tr>
<td>Ciprofloxacin</td>
<td>Thia 2009[34]</td>
<td>RCT</td>
<td>10</td>
<td>10 weeks</td>
<td>30% 12.5%</td>
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<tr>
<td>Aza/6-MP</td>
<td>Pearson 1995[35]</td>
<td>Metaanalysis</td>
<td>41</td>
<td>-</td>
<td>*54% *21%</td>
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<tr>
<td>Tacrolimus</td>
<td>Sandborn 2003[28]</td>
<td>RCT</td>
<td>42</td>
<td>10 weeks</td>
<td>10% 8%</td>
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<td>Infliximab</td>
<td>Present 1999[27]</td>
<td>RCT induction</td>
<td>94</td>
<td>14 weeks</td>
<td>55% 13%</td>
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<tr>
<td>Infliximab</td>
<td>Accent II 39[39]</td>
<td>RCT maintenance</td>
<td>282</td>
<td>54 weeks</td>
<td>36% 19%</td>
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<td>Adalimumab</td>
<td>CHARM #57</td>
<td>RCT maintenance</td>
<td>113</td>
<td>56 weeks</td>
<td>33% 13%</td>
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* = remission and response included together
# = In CHARM patient with luminal and perianal Crohn’s disease were assessed

**Other medical options**
Other immunomodulators including Tacrolimus, Thalidomide, Methotrexate and Ciclosporin have been considered. Alternative options include GMCSF, absorptive carbon and hyperbaric oxygen.

**Tacrolimus, Thalidomide, Methotrexate, Ciclosporin**

**Tacrolimus**

Tacrolimus was assessed in a placebo-controlled trial in which it was given orally for 10 weeks in 42 Crohn’s anal fistula patients. There was significant clinical improvement in the tacrolimus group (45%) compared with placebo (9%) but no significant improvement in fistula remission rates was seen. Gonzalez Lama and colleagues in 2005 showed that longer term therapy may be required to achieve healing. Topical tacrolimus has been used in a placebo controlled trial in which 19 patients were stratified according to whether they had ulcerating or fistulating disease. There was a benefit in the ulcerating but not the fistulating group. There was no systemic detection of tacrolimus and side effects were not encountered. This lack of systemic absorption was also noted in a case series of children with oral or perianal (6/8) Crohn’s and in whom the topical preparation was effective in improving fistulas after failure of numerous other therapies.

**Thalidomide**
Thalidomide has been used in the context of perianal Crohn’s disease. Vasiliauskas and colleagues in 1999 reported an open series of 12 male patients with Crohn’s disease of whom six had fistulas and 5 out of 6 demonstrated significant improvement. Ehrenpreis and colleagues in 1999 reported an open label study of 13 patients with fistulating Crohn’s disease. Six out of 13 achieved complete remission of their fistulas at 12 weeks. Plamondon and colleagues in 2007 reported an open label study of 11 patients with fistulating Crohn’s disease treated with Thalidomide. Nine out of the 11 responded to the Thalidomide and 3 out of 9 had a complete response. The data suggest that Thalidomide can heal fistulas in patients naïve or refractory to biological drugs.

Methotrexate

There is little evidence to support the use of methotrexate as monotherapy to treat perianal Crohn’s disease. There are no randomised data, only small case series. In one case series, 56% of patients with Crohn’s anal fistulas on methotrexate showed a complete or partial response to therapy. Schroder and colleagues used infliximab induction as a bridge to methotrexate (20 mg/week) in 12 consecutive patients of whom four (33%) had complete closure and three (25%) had partial response.

Ciclosporin
There have been small case series using intravenous ciclosporin, usually at a dose of 4mg/kg, to treat perianal Crohn’s disease. Although about three quarters of patients initially responded, the treatment was limited in that following oral transition or discontinuance of ciclosporin, a majority of patients relapsed 71.

GM-CSF

Human granulocyte-macrophage colony-stimulating factor (GM-CSF) has been examined in luminal Crohn’s disease in a small number of studies, including a double blind RCT where it was used as a steroid sparing agent in steroid dependent Crohn’s disease. The primary end point was steroid free remission which was achieved in 18.6% of treatment patients vs. 4.9% of those taking placebo (p = 0.03) 72. Evidence of improvement in perianal fistulas is limited and a small case series of heterogeneous and complex patients published in 2010 failed to find any improvement in fistulas in Crohn’s disease after GM-CSF treatment 73.

Hyperbaric Oxygen Therapy (HBOT)

The mechanism of action of HBOT is thought to be multifactorial including raising the oxygen tension in damaged tissue, improving oxygen-burst mediated phagocytosis, decreasing circulating LPS-stimulated pro-inflammatory cytokines such as IL-1, IL-6 and TNFα levels and inhibiting neutrophil-associated...
inflammation\textsuperscript{74,75}. Several studies during the 1980s and 1990s described cases or small case series of patients with severe perianal Crohn’s disease which partially or completely responded to HBOT\textsuperscript{76-78}.

In these trials, side effects of HBOT included tympanic membrane perforation and blurred vision (which resolved after treatment finished). Patients spent between 30 and 130 hours in the HBOT chamber in 1.5-2 hour sessions. It is difficult to draw firm conclusions from these heterogeneous studies on efficacy or side effects in the absence of randomized controlled data.

**Oral absorptive carbon**

Fukuda and colleagues reported a randomised controlled trial of oral absorptive carbon in which 57 patients received either activated absorptive carbon or a non-absorptive carbon molecule as placebo\textsuperscript{79}. The treatment group achieved 37% improvement and 30% remission of anal fistulas after 8 weeks treatment compared to 10% and 7%, in the placebo group. The authors suggested that the mechanism of action might be a combination of firming of stool, absorption of toxins or intestinal stimulation factors (such as serotonin and histamine) and restoration of the normal luminal environment and flora.

**Monitoring response to therapy**
The improved medical treatment for Crohn’s perianal fistulas has prompted new questions: how to monitor patients, how long to treat them with drugs which have serious side effects and are expensive, and when or perhaps if to stop treatment.

Studies have shown that although clinical healing (in the form of a closed external opening or cessation of drainage) has occurred in the short term, imaging modalities including MRI indicate that the fistula track may remain for some time with deep and true healing of the fistula lagging behind clinical remission by months or with reactivation after cessation of treatment or during maintenance treatment. In those in whom healing does take place, determining the moment of tissue healing using MRI and stopping treatment at this point, rather than based on clinical remission, ought to mean a lower risk of later recurrence.

Sequential MRI scanning may also select those patients who are non-responders at an earlier stage, permitting an early change to another biological therapy or the decision to stop altogether or continue on maintenance treatment. This early diagnostic impact on decision making should improve treatment efficiency and patient safety.

The prospective study of 34 patients with fistulating Crohn’s disease at St Mark’s Hospital, discussed above, also evaluated the impact of MRI on clinical decision making. Patients were treated with infliximab and if there was a lack or loss of
response or if the patient was intolerant to infliximab, they were treated with an alternative agent (adalimumab or thalidomide). Patients were assessed clinically and by MRI at 6, 12, 18 and 24 months, and yearly thereafter with a median follow up of 83 weeks (range 52 to 131 weeks).

At 6 months, 58% of the Infliximab treated patients and 14% of adalimumab treated patients were in clinical remission. They found that deep tissue healing as assessed by MRI was slower to occur than clinical healing and the rate of deep tissue healing varied between patients. The presence of proctitis, but neither the complexity nor the duration of fistula, was associated with a lack of response.
Imaging may also be useful in guiding surgical intervention during medical treatment and thereby improve outcome. A small study by Spradlin and colleagues (2008) showed that serial EUS during maintenance infliximab treatment, which was used to time seton removal and repeat abscess drainage and seton insertion, reduced fistula recurrence and treatment failure \(^8\).
Surgery for perianal Crohn’s disease

The surgeon’s role in Crohn’s perianal fistulae has changed and management is now performed in combination with the physician. Some fistulas can be definitively cured surgically, usually by lay open or advancement flap whilst other patients need palliation of their symptoms or even a proctectomy. Palliation usually comes in the form of drainage of any trapped infection and thereafter a long term, comfortable loose seton (figure 2b.).

Examination under anaesthetic, drainage of sepsis and insertion of comfortable setons now forms the first stage in the truly combined surgical-medical eradication of anal fistulas using infliximab as described above. If pre-treatment surgical drainage is inadequate, abscess formation during the infliximab course may be more likely and could cause the treatment to fail. In the ACCENT II trial of maintenance infliximab in patients with fistulating Crohn’s disease, there was no signal that infliximab-treated patients were more likely to develop new perianal sepsis. Twenty-one (15%) patients in the infliximab maintenance group had at least one newly developed fistula-related abscess compared with 27 (19%) in the placebo maintenance group (P = 0.526). The number of fistula-related abscesses diagnosed over time did not differ between groups.

Loose seton insertion seeks to palliate, reducing pain and discharge and in particular preventing recurrent abscess formation. In addition to the described
role with infliximab treatment, it remains a key tool in the surgeon’s arsenal for the long term management of Crohn’s perianal fistulas, stubbornly resistant to all attempts at eradication.

![Figure 2. a. A bulky silastic seton and b. a low profile ethibond seton with just three throws and the ‘whiskers’ tied back with silk.](image)

**Lay open**

Some Crohn’s fistulas can be laid open and cured. As a general rule, surgeons are more cautious in Crohn’s disease and will not lay open fistulas that in the idiopathic setting they would be happy to treat. Not only are there concerns regarding future fistula formation and problems with healing, but the increased bowel frequency and the tendency for this to worsen with disease activity or future resection makes incontinence a greater threat.

**Advancement flaps**
Advancement flaps can be used as a sphincter preserving technique for some higher fistulas in Crohn’s disease with a success rate of around 50%. Patients are chosen who do not have active proctitis or extensive cavitating ulceration in the anal canal. A defunctioning stoma is sometimes used in an attempt to improve the chance of success, although there is little evidence suggesting an improved success rate. An adjunctive Martius flap may be helpful. An advancement flap is easier when there is perineal descent or internal intussusception.

Two studies from the Cleveland Clinics of Florida and Ohio, published in 2002, demonstrated a worse outcome for advancement flap surgery in Crohn’s anal and rectovaginal fistulas than those of cryptoglandular origin in more than 100 patients each. Mizrahi and colleagues showed an increased recurrence rate after surgery from 33% in non-Crohn’s fistulas to 57% in the Crohn’s patients which was similar to the findings of Sonoda and colleagues with 30% recurrence rising to 50% in Crohn’s disease. This latter study also demonstrated a lower success rate in rectovaginal than anal fistulas and found that early surgery on a well drained fistula complex increased the chance of success. Smoking has been shown to increase the risk of failure in cryptoglandular fistulas although in this as well as most studies of advancement flap surgery, patients with Crohn’s disease were excluded.
Glues and plugs

Fistula infill materials, such as fibrin or collagen glues and collagen plugs, have not maintained the same initial enthusiasm and excellent results that their first published trials enjoyed. None-the-less they remain a low risk (albeit expensive) option in the management of idiopathic anal fistulas. Many of the trials of both glue (table b) and plugs (table c) have included small numbers of Crohn’s patients, although independent analysis of efficacy in the Crohn’s cohorts is often not possible due to these small numbers and the absence of MRI validation of healing.

Vitton and colleagues studied 14 Crohn’s fistulas (superficial, inter- trans and suprasphincteric and anovaginal) and observed complete clinical healing in 8 of them at a median of 23 months follow up. The fistulas were described as refractory, although the complexity of the fistulas and extent of Crohn’s disease is not described.86

A recently published study of fibrin glue in Crohn’s perianal fistulas, an open label, randomised controlled trial, demonstrated initial success (clinical remission at week 8) in 38% (13 of 34) of the fibrin glue group compared to 16% in the observation only group.87 Twenty of the 37 patients in the observation only group crossed over to fibrin glue treatment at week 8 and 9 of these patients went into remission at week 16. Unfortunately, of the 54 who underwent fibrin glue treatment at some point in the trial, only 11 (20%) were in remission at long
term follow up (median 37 months for initial fibrin glue group and 17 months for cross over group). No imaging was used to assess deep tissue healing in this study.

Table 2. Studies of fistula glue in anal fistula including Crohn’s patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>FU (months)</th>
<th>Routine preop seton</th>
<th>Total n</th>
<th>Crohn’s n</th>
<th>Overall success rate</th>
<th>Crohn’s success rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abel+</td>
<td>1993</td>
<td>3-12</td>
<td>No</td>
<td>10</td>
<td>3</td>
<td>6/10 (60%)</td>
<td>1/3 (33%)</td>
</tr>
<tr>
<td>Venkatesh#</td>
<td>1999</td>
<td>12</td>
<td>No</td>
<td>30</td>
<td>6</td>
<td>18/30 (60%)</td>
<td>0/6 (0%)</td>
</tr>
<tr>
<td>Cintron#</td>
<td>2000</td>
<td>12</td>
<td>No</td>
<td>79</td>
<td>6</td>
<td>48/79 (61%)</td>
<td>2/6 (33%)</td>
</tr>
<tr>
<td>Lindsey</td>
<td>2002</td>
<td>17.1</td>
<td>No</td>
<td>19</td>
<td>2</td>
<td>12/19 (63%)</td>
<td>2/2 (100%)</td>
</tr>
<tr>
<td>Zmora</td>
<td>2003</td>
<td>12.1</td>
<td>No</td>
<td>24</td>
<td>5</td>
<td>8/24 (33%)</td>
<td>2/5 (40%)</td>
</tr>
<tr>
<td>Sentovich</td>
<td>2003</td>
<td>22</td>
<td>Yes</td>
<td>48</td>
<td>5</td>
<td>33/48 (69%)</td>
<td>4/5 (80%)</td>
</tr>
<tr>
<td>Loungnarath</td>
<td>2004</td>
<td>26</td>
<td>No</td>
<td>39</td>
<td>13</td>
<td>12/39 (31%)</td>
<td>4/13 (31%)</td>
</tr>
<tr>
<td>Singer#</td>
<td>2005</td>
<td>27</td>
<td>No</td>
<td>75</td>
<td>3</td>
<td>25-44%</td>
<td>0/3 (0%)</td>
</tr>
<tr>
<td>Vitton#</td>
<td>2005</td>
<td>23.4</td>
<td>No</td>
<td>14</td>
<td>14</td>
<td>8/14 (57%)</td>
<td>8/14 (57%)</td>
</tr>
<tr>
<td>Chung$</td>
<td>2010</td>
<td>3</td>
<td>No</td>
<td>(81)</td>
<td>2</td>
<td>23/79 (29%)</td>
<td>0/1 (0%)</td>
</tr>
<tr>
<td>de Parades#</td>
<td>2010</td>
<td>11.7</td>
<td>Yes</td>
<td>30</td>
<td>11</td>
<td>15/30 (50%)</td>
<td>7/11 (63.6%)</td>
</tr>
<tr>
<td>Grimaud#</td>
<td>2010</td>
<td>2</td>
<td>No</td>
<td>34</td>
<td>34</td>
<td>13/34 (38%)</td>
<td>13/34 (38%)</td>
</tr>
</tbody>
</table>

#Includes some rectovaginal fistulas
+The one success in the CD group had a rectovaginal fistula (RVF) which healed after 2 treatments
$Idiopathic results from contemporary but separately published results by same authors
The anal fistula plug has been used in trials of Crohn’s perianal disease with success rates between 25% and 100% (table c) including the two largest studies (of 14 and 20 patients) which were at opposite ends of this spectrum of success (26.6% and 80%). Failure occurred due to extrusion of the plug, abscess formation or ongoing discharge. Long term follow up or radiological proof of fistula healing in an adequately powered randomised control trial is required to establish efficacy of this expensive treatment.

Table 3. Studies of the fistula plug in anal fistula including Crohn’s patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>FU (months)</th>
<th>Routine preop seton</th>
<th>Total n</th>
<th>Crohn’s n</th>
<th>Success rate</th>
<th>Crohn’s success rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Connor*</td>
<td>2006</td>
<td>10</td>
<td>depends</td>
<td>20</td>
<td>20</td>
<td>16/20 (80%)</td>
<td>16/20 (80%)</td>
</tr>
<tr>
<td>van Koperen</td>
<td>2007</td>
<td>7</td>
<td>No</td>
<td>17</td>
<td>1</td>
<td>7/17 (41%)</td>
<td>1/1 (100%)</td>
</tr>
<tr>
<td>Ky</td>
<td>2008</td>
<td>6.5</td>
<td>No</td>
<td>44</td>
<td>14</td>
<td>24/44 (54.6%)</td>
<td>4/14 (26.6%)</td>
</tr>
<tr>
<td>Schwandner</td>
<td>2008</td>
<td>9</td>
<td>No</td>
<td>18</td>
<td>7</td>
<td>12/18 (61%)</td>
<td>6/7 (85.7%)</td>
</tr>
<tr>
<td>Christofordis</td>
<td>2008</td>
<td>6.5</td>
<td>No</td>
<td>47</td>
<td>3</td>
<td>20/47 (43%)</td>
<td>NR</td>
</tr>
<tr>
<td>Schwandner†</td>
<td>2009</td>
<td>9</td>
<td>No</td>
<td>9</td>
<td>9</td>
<td>7/9 (77%)</td>
<td>7/9 (77%)</td>
</tr>
<tr>
<td>Safar</td>
<td>2009</td>
<td>4</td>
<td>No</td>
<td>36</td>
<td>4</td>
<td>5/36 (13.9)</td>
<td>1/4 (25%)</td>
</tr>
<tr>
<td>Zubaidi</td>
<td>2009</td>
<td>12</td>
<td>No</td>
<td>22</td>
<td>2</td>
<td>19/22 (86%)</td>
<td>1/2 (50%)</td>
</tr>
<tr>
<td>Chung$</td>
<td>2010</td>
<td>3</td>
<td>No</td>
<td>50</td>
<td>4</td>
<td>27/46 (59%)</td>
<td>3/4 (75%)</td>
</tr>
<tr>
<td>Owen</td>
<td>2010</td>
<td>15</td>
<td></td>
<td>35</td>
<td>3</td>
<td>13/35 (37%)</td>
<td>1/3 (33%)</td>
</tr>
</tbody>
</table>

*The O’Connor study included one pouch patient, 2 anovaginal fistulas and 4 patients on concomitant infliximab. Single rather than multiple tracts were significantly associated with successful closure. Preoperative setons were used if the tract was too wide for the plug to sit snugly.

NR – not reported or cannot be concluded form the data presented.
†In this study, 2 of the 10 patients enrolled were defunctioned and one was lost to follow up.

$Idiopathic results from contemporary but separately published results by same authors

**Modified infill materials**

The waning published efficacy of glues and plugs over time has led to the addition of agents designed to improve healing rates. Preclinical work at St Mark’s has demonstrated that the addition of autologous fibroblasts to a collagen glue improved the histological appearance of the healed track compared to glue alone and clinical studies are in progress\(^{107}\). A single case report of autologous fibroblasts on a biologic scaffold (HYAFF) has been described in a Crohn’s patient with a transphincteric fistula\(^ {108}\). The patient had a seton inserted and three doses of intravenous infliximab administered before fistulectomy and then insertion of the scaffold with autologous fibroblasts into the track until it was completely filled. The patient was free of recurrence throughout a 20 month follow up period, but MRI validation of healing was not performed.

In 2008 Garcia-Olmo and colleagues reported the administration of adipose derived stem cells (ASCs) in fibrin glue vs. glue alone in a randomised controlled trial of 49 patients (14 with Crohn’s disease) and found a significant increase in healing from 16% without ASCs to 71% with them\(^ {109}\). ASCs are living adult stem cells of mesenchymal origin which are extracted from subdermal adipose tissue obtained through liposuction. The study’s authors suggest that the ASCs may
have both an initial anti inflammatory effect and also aid tissue repair through differentiation into epithelial cells.

This approach of adding constituents to correct specific aspects of the pathology in persisting anal fistula tracts is extremely attractive and could in the future lead to personally tailored treatments in both idiopathic and Crohn's related anal fistulas incorporating aspects of immunology and microbiology specific to an individual.

**Defunctioning and proctectomy**

Some patients have either failed medical therapy and undergone several operations finding nothing that helps to alleviate their symptoms and gain the quality of life they want, or are subdued by the systemic effects of their colorectal disease to such an extent that a stoma becomes a realistic option. Proctectomy (+/- colectomy depending on the extent of disease) in the patient with severe rectal and/or perianal disease can leave patients with an improved quality of life in spite of a recurrence (of luminal disease) rate of around 20% and a similar risk of reoperation. The principle risks of this operation include damage to the pelvic nerves and the delayed or unhealed perineal wound, which affects around 30% of patients up to 6 months and 10% beyond that time. A small group of these will require further surgical procedures to aid healing of the wound, including curettage or (usually myocutaneous) flap reconstruction.
Defunctioning with an ileostomy provides temporary relief of symptoms but disease often recurs and most of these stomas will never be reversed. Yamamoto and colleagues reported their series of 31 patients who underwent defunctioning alone in Crohn’s disease for perianal or anovaginal disease. Only 8 (26%) went into long standing remission and only 3 patients (10%) had their stoma reversed. Hong and colleagues reported a series of 21 patients who were defunctioned for perianal Crohn’s disease and found the chance of having continuity restored was not influenced by infliximab. At median follow up of 22 months (4-121), 4 patients (19%) had undergone stoma closure, 11 had had a proctocolectomy, and 6 had both a stoma and their rectum in situ. The effect of the procedure on severity of perianal disease was no effect in 4 (19%), temporary improvement in 6 (29%), initial improvement with a sustained benefit in 7 (33%), and healing in 4 (19%).

As a general rule, if a patient needs their large bowel Crohn’s disease excised, defunctioning alone will leave ongoing ill-health with little or no chance of reversal in the longer term and should be avoided. In a recent series of Crohn’s anal fistulae managed with a variety of medical and surgical interventions, around 10% ultimately underwent proctectomy (Gaertner 2007).

**Fistula-associated carcinoma in Crohn’s disease**
It is important to note that malignancies can arise in Crohn’s related perianal disease. Although it is uncommon, a recent literature review revealed 61 cases of carcinomas arising in perineal fistulas in Crohn’s disease. Sixty-one percent of the patients were females and females were significantly younger than males at the time of diagnosis of cancer, and had a shorter duration of fistulating perianal disease prior to cancer transformation. Adenocarcinoma was the most common histology followed by squamous cell carcinoma.

An approach for managing anal fistulae in Crohn’s disease

Based on current best practice at St Mark’s Hospital, we present an approach to the management of the patient with anal fistulae in Crohn’s disease and an algorithm for the use of infliximab to heal their fistulae.

It should be remembered that the finding of anal fistulae in Crohn’s disease usually predicts a high risk of a severe and disabling disease course; luminal disease should be managed aggressively and fistulae treated by the approach described below.

Initial management
A full assessment of both luminal and perianal disease should be made. Perianal abscess should be clinically excluded. Luminal assessment will consist of colonoscopy and small bowel imaging according to local expertise. Fistula assessment should be by MRI in the first instance. Luminal assessment provides information on the extent of disease. MRI of the pelvis will guide surgical review and early examination under anaesthetic (EUA) and provide a template for future comparison.

The initial treatment of anal fistulae in Crohn’s disease is with antibiotics and immunomodulators. If this treatment fails to produce remission, infliximab should be considered. The therapy needs to be considered in the context of any luminal disease elsewhere according to NICE guidelines.

**Surgical assessment and infliximab induction (week zero)**

All patients should have a surgical review to assess the nature of the fistula*, the patient’s general health and any appropriate surgical approach. Most commonly, EUA will be performed with adequate surgical drainage of the fistula complex, with or without seton insertion, prior to treatment with biologic agents. However, curative surgery should also be considered at this point although few patients are suitable* and in the patient in poor general health and severely disabled by their disease, ablative surgery may be most appropriate§.
If surgical drainage and medical treatment is the optimal option, as in most
cases, infliximab should be commenced with a standard induction protocol of
5mg/kg at 0, 2 and 6 weeks. Setons should be removed around week 6 if there
is clinical evidence of improvement, to enable healing of the tract. If anal fistulae
and luminal disease are present, adalimumab can be considered as an
alternative.

Twelve week assessment

At approximately 12 weeks, clinical assessment of response should be
performed. Primary non-responders can be identified as those who have
achieved no response to infliximab induction and they should be changed onto
an alternative biologic drug (adalimumab). If clinical response occurs then
maintenance treatment should commence with 5mg/kg doses every 8 weeks with
assessment of adverse events and response with each dose.

Any clinical improvement at 12 weeks, even if not meeting the criteria of clinical
response described above, should prompt maintenance treatment.

One year assessment
At 1 year a full clinical and radiological (MRI pelvis) assessment of fistula response should take place as well as assessment of luminal disease. Clinically, the patient can either have remission (closure of all external openings), response (closure of ≥50% of external openings) or lack of response. Radiologically, the patient can be healed, improved by comparison with baseline or have lost response (either by returning to baseline appearance or, if an intercurrent scan has occurred, by comparison with the last scan). The patient will thus fall into one of the five categories outlined below:

1. If there is clinical remission and the fistula has radiologically fully healed, and there is no other indication for continuing infliximab treatment such as luminal disease, consider stopping infliximab but thiopurines should be maintained. A further MRI scan should be performed in 6 months to confirm persistent radiological healing or prompt reinstatement of infliximab if evidence of recurrence is seen.

2. If there is clinical remission but only radiological improvement over baseline and not full healing, maintenance infliximab should be continued and reassessment performed 6 monthly for a year and annually thereafter.

3. If clinical improvement and radiological improvement persist then the patient should continue on maintenance infliximab.
4. If there is clinical loss of response but radiologically some improvement over the baseline scan, infliximab treatment should be optimised (increase dose to 10mg/kg or decrease interval between doses) or consider switching to adalimumab.

5. If the patient has clinically lost response and the fistula has radiologically returned to the pre-treatment situation, the need for further surgical intervention to drain trapped sepsis inhibiting response should be considered†. If there is no trapped sepsis to drain then infliximab should be optimised (as described above) or consider switching to adalimumab.

Fistula recurrence should be treated by restarting this algorithm from the beginning
Algorithm for the management of anal fistulae in Crohn’s disease

1. **Anal fistula in Crohn’s disease**
2. **Clinical assessment: exclude abscess**
   - Treat with antibiotics and thiopurines unless indication for urgent biologic agent
3. **MRI pelvis and luminal assessment**
   - Surgical review; EUA +/- drainage +/- setons, curative or ablative procedure*

   - **Induction of infliximab:** 5mg/kg at weeks 0, 2 and 6, remove seton at approximately week 6 if clinical improvement
   - (if anal fistula and luminal disease, consider infliximab or adalimumab)

4. **Clinical assessment**
   - Primary non-responders
     - **Clinical response/remission or any symptomatic improvement**
     - **Continue infliximab 8 weekly, clinical assessment, as required or at least 6 monthly**

5. **Clinical assessment, MRI pelvis, luminal assessment if appropriate**
   - **Clinical remission**
     - **MRI scan**
     - Complete radiological healing
     - **Consider stopping**
     - **Continue thiopurine, MRI in 6 months**
   - **Clinical response**
     - **MRI scan**
     - Partial radiological improvement
     - **Continue infliximab, reassess in 6 months (then annually)**

6. **Loss of response**
   - **MRI scan**
   - **No radiological improvement**
     - **MRI scan**
     - **Consider surgical intervention**, optimise infliximab, switch to adalimumab

---

*Indications for surgical intervention**

- EUA +/- drainage +/- setons, curative or ablative procedure
- Indications for urgent biologic agent

---

**Notes:**

- Induction of infliximab: 5mg/kg at weeks 0, 2 and 6, remove seton at approximately week 6 if clinical improvement
- (if anal fistula and luminal disease, consider infliximab or adalimumab)
- Primary non-responders
  - **Clinical response/remission or any symptomatic improvement**
  - **Continue infliximab 8 weekly, clinical assessment, as required or at least 6 monthly**
- **Clinical remission**
  - **MRI scan**
  - Complete radiological healing
  - **Consider stopping**
  - **Continue thiopurine, MRI in 6 months**
- **Clinical response**
  - **MRI scan**
  - Partial radiological improvement
  - **Continue infliximab, reassess in 6 months (then annually)**
- **Loss of response**
  - **MRI scan**
  - **No radiological improvement**
    - **MRI scan**
    - **Consider surgical intervention**, optimise infliximab, switch to adalimumab

---

**Algorithm for the management of anal fistulae in Crohn’s disease**
**Curative surgery**
A few patients with moderate Crohn’s disease may be candidates for curative surgery:

- advancement flap (good rectum, perineal descent/internal intussusception helpful, consider temporary stoma);
- coloanal pull through (rectal internal opening, good anus, good colon, loop ileostomy);
- Turnbull-Cutait‡ (internal opening at dentate line, good anus, good colon, loop ileostomy);
- fistulotomy +/- delayed sphincter repair (consider temporary stoma).

Some patients with severe and debilitating disease may benefit from ablative surgery§

**Temporary stoma**
Temporary ileostomy/colostomy:

- will not of itself lead to fistula resolution
- may be an adjunct to surgical or medical therapy
- should not be used when proctectomy or proctocolectomy is needed

‡ **Turnbull-Cutait procedure**
Two stage coloanal.

- 1st stage leaves colon extruded anally for one week;
- 2nd stage trims the colon back to the anus.

† **Surgery in loss of response**
MRI may indicate undrained sepsis leading to lack or loss of response

- drainage of sepsis should be obtained and further setons inserted
- infliximab maintenance should then recommence
- further clinical assessment in 6 months

§ **Ablative surgery**
Perianal fistulae alone are unlikely to lead to very poor general health with restriction of work or social activities; colorectal disease is likely to be to blame. In this case:

- medical management should be optimised;
- if this fails, proctectomy or proctocolectomy (dependent on the extent of disease) should be considered;
- advice regarding the risk of delayed or poor perineal wound healing should be given.
**Incidental cryptoglandular fistulae**
Rarely, a cryptoglandular fistula will occur in a patient with Crohn’s disease:
• the anorectum will be entirely normal and unaffected by Crohn’s disease;
• there will be very limited luminal disease;
• treatment should be surgical, as for other cryptoglandular fistulae, except with greater sphincter preservation because of the risk of diarrhoea in the future.

**Summary**

Anal fistulas are a common, unpleasant and treatment-resistant manifestation of Crohn’s disease. Medical treatments with antibiotics and immunomodulators have been limited but the advent of biologic drugs has had a dramatic effect on the prognosis of these fistulas, offering the patient a realistic chance at response and indeed remission. However, loss of response and side effects are all too common. Local administration, combinations of drugs and new biologics all offer potential improvements.

Surgery likewise can have a high rate of recurrence for most procedures and the risks of stomas, impairment of continence, unhealed wounds and repeated operations are ever present.

The primary goal of treating Crohn’s anal fistulas should be eradication without recurrence. This may sometimes be achieved by surgery in the form of laying open in low fistulas, or alternatives such as advancement flaps or fistula plugs...
(although the evidence for these latter is scant and contradictory). Healing is more likely to occur using biological treatments. Surgery and imaging remain absolutely crucial to this mode of management with EUAs with drainage of trapped sepsis and insertion of setons before and sometimes during treatment, and high quality radiological monitoring of response so that appropriate decisions on interventions such as surgery, cessation of medical treatment or dose or drug change can be made.

**Future focus**

At the moment, during medical treatment the timing of fistula healing is estimated from observation of the external opening in many cases and the exact appearance of a healed fistula on MRI is unclear, which puts patients at risk of early cessation of treatment and resurgence of an unhealed fistula. Similarly, patients who spend years on costly biologics (with significant side effects) but never heal may be identifiable early in their treatment course on the basis of the speed and extent of their initial response, for example, and could then be protected from the potential risks of these drugs by early cessation. Such prognostic correlations should be sought in order to maximize the benefits and minimise risks of these treatments.

The search for a consistently effective treatment of perianal fistulas in Crohn’s disease is likely to combine medical and surgical elements and will need to
address the multiple aetiological factors that drive and maintain the process of anal fistulation. A fuller understanding of these aetiological factors is crucial.

This may lead to treatments based on the “biogluce” model. A treatment combining complete removal of all epithelialisation and granulation tissue followed by instillation of an infill material (glue) loaded with factors to reduce inflammation, tackle infection, correct cytokine abnormalities and promote healing may represent the future of anal fistula treatment.

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References


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54. Topstad DR, Panaccione R, Heine JA, Johnson DR, MacLean AR, Buie WD. Combined seton placement, infliximab infusion, and maintenance

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Tables for CPD Mx review

Table 1. Randomised Controlled Trials (RCT) or meta-analyses of established medical treatments of Crohn's-related perianal fistulas

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study</th>
<th>Type of study</th>
<th>n</th>
<th>FU at end point</th>
<th>Fistula remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole</td>
<td>Thia 2009 (93)</td>
<td>RCT</td>
<td>7</td>
<td>10 weeks</td>
<td>0% 12.5%</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Thia 2009 (93)</td>
<td>RCT</td>
<td>10</td>
<td>10 weeks</td>
<td>30% 12.5%</td>
</tr>
<tr>
<td>Aza/6-MP</td>
<td>Pearson 1995 (64)</td>
<td>Metaanalysis</td>
<td>41</td>
<td>-</td>
<td>*54% *21%</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Sandborn 2003 (75)</td>
<td>RCT</td>
<td>42</td>
<td>10 weeks</td>
<td>10% 8%</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Present 1999 (68)</td>
<td>RCT induction</td>
<td>94</td>
<td>14 weeks</td>
<td>55% 13%</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Accent II (78)</td>
<td>RCT maintenance</td>
<td>282</td>
<td>54 weeks</td>
<td>36% 19%</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>CHARM # (20)</td>
<td>RCT maintenance</td>
<td>113</td>
<td>56 weeks</td>
<td>33% 13%</td>
</tr>
</tbody>
</table>

* = remission and response included together
# = In CHARM patient with luminal and perianal Crohn’s disease were assessed
Table 2. Studies of fistula glue in anal fistula including Crohn’s patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>FU (months)</th>
<th>Routine preop seton</th>
<th>Total n</th>
<th>Crohn's n</th>
<th>Overall success rate</th>
<th>Crohn's success rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abel+ (1)</td>
<td>1993</td>
<td>3-12</td>
<td>No</td>
<td>10</td>
<td>3</td>
<td>6/10 (60%)</td>
<td>1/3 (33%)</td>
</tr>
<tr>
<td>Venkatesh# (100)</td>
<td>1999</td>
<td>12</td>
<td>No</td>
<td>30</td>
<td>6</td>
<td>18/30 (60%)</td>
<td>0/6 (0%)</td>
</tr>
<tr>
<td>Cintron# (16)</td>
<td>2000</td>
<td>12</td>
<td>No</td>
<td>79</td>
<td>6</td>
<td>48/79 (61%)</td>
<td>2/6 (33%)</td>
</tr>
<tr>
<td>Lindsey (47)</td>
<td>2002</td>
<td>17.1</td>
<td>No</td>
<td>19</td>
<td>2</td>
<td>12/19 (63%)</td>
<td>2/2 (100%)</td>
</tr>
<tr>
<td>Zmora (105)</td>
<td>2003</td>
<td>12.1</td>
<td>No</td>
<td>24</td>
<td>5</td>
<td>8/24 (33%)</td>
<td>2/5 (100%)</td>
</tr>
<tr>
<td>Sentovich (86)</td>
<td>2003</td>
<td>22</td>
<td>Yes</td>
<td>48</td>
<td>5</td>
<td>33/48 (69%)</td>
<td>4/5 (80%)</td>
</tr>
<tr>
<td>Loungnarath (48)</td>
<td>2004</td>
<td>26</td>
<td>No</td>
<td>39</td>
<td>13</td>
<td>12/39 (31%)</td>
<td>4/13 (31%)</td>
</tr>
<tr>
<td>Singer# (87)</td>
<td>2005</td>
<td>27</td>
<td>No</td>
<td>75</td>
<td>3</td>
<td>25-44% (0%)</td>
<td>0/3 (0%)</td>
</tr>
<tr>
<td>Vitton# (101)</td>
<td>2005</td>
<td>23.4</td>
<td>No</td>
<td>14</td>
<td>14</td>
<td>8/14 (57%)</td>
<td>8/14 (57%)</td>
</tr>
<tr>
<td>Chung$ (14)</td>
<td>2010</td>
<td>3</td>
<td>No</td>
<td>(81)</td>
<td>2</td>
<td>23/79 (29%)</td>
<td>0/1 (0%)</td>
</tr>
<tr>
<td>de Parades# (23)</td>
<td>2010</td>
<td>11.7</td>
<td>Yes</td>
<td>30</td>
<td>11</td>
<td>15/30 (50%)</td>
<td>7/11 (63.6%)</td>
</tr>
<tr>
<td>Grimaud# (31)</td>
<td>2010</td>
<td>2</td>
<td>No</td>
<td>34</td>
<td>34</td>
<td>13/34 (38%)</td>
<td>13/34 (38%)</td>
</tr>
</tbody>
</table>

#Includes some rectovaginal fistulas
+The one success in the CD group had a RECTOVAGINAL FISTULA (RVF) which healed after 2 treatments
$Idiopathic results from contemporary but separately published results by same authors
Table 3. Studies of the fistula plug in anal fistula including Crohn’s patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>FU (months)</th>
<th>Routine preop seton</th>
<th>Total n</th>
<th>Crohn’s n</th>
<th>Success rate</th>
<th>Crohn’s success rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Connor*</td>
<td>2000</td>
<td>10</td>
<td>depends</td>
<td>20</td>
<td>20</td>
<td>16/20 (80%)</td>
<td>16/20 (80%)</td>
</tr>
<tr>
<td>van Koperen (97)</td>
<td>2007</td>
<td>7</td>
<td>No</td>
<td>17</td>
<td>1</td>
<td>7/17 (41%)</td>
<td>1/1 (100%)</td>
</tr>
<tr>
<td>Ky (42)</td>
<td>2008</td>
<td>6.5</td>
<td>No</td>
<td>44</td>
<td>14</td>
<td>24/44 (54.6%)</td>
<td>4/14 (26.6%)</td>
</tr>
<tr>
<td>Schwandner (83)</td>
<td>2009</td>
<td>9</td>
<td>No</td>
<td>18</td>
<td>7</td>
<td>12/18 (61%)</td>
<td>6/7 (85.7%)</td>
</tr>
<tr>
<td>Christofordis (13)</td>
<td>2008</td>
<td>6.5</td>
<td>No</td>
<td>47</td>
<td>3</td>
<td>20/47 (43%)</td>
<td>NR</td>
</tr>
<tr>
<td>Schwandner † (82)</td>
<td>2009</td>
<td>9</td>
<td>No</td>
<td>9</td>
<td>9</td>
<td>7/9 (77%)</td>
<td>7/9 (77%)</td>
</tr>
<tr>
<td>Safar (72)</td>
<td>2009</td>
<td>4</td>
<td>No</td>
<td>36</td>
<td>4</td>
<td>5/36 (13.9)</td>
<td>1/4 (25%)</td>
</tr>
<tr>
<td>Zubaidi (106)</td>
<td>2009</td>
<td>12</td>
<td>No</td>
<td>22</td>
<td>2</td>
<td>19/22 (86%)</td>
<td>1/2 (50%)</td>
</tr>
<tr>
<td>Chung$ (14)</td>
<td>2010</td>
<td>3</td>
<td>No</td>
<td>50</td>
<td>4</td>
<td>27/46 (59%)</td>
<td>3/4 (75%)</td>
</tr>
<tr>
<td>Owen (62)</td>
<td>2010</td>
<td>15</td>
<td></td>
<td>35</td>
<td>3</td>
<td>13/35 (37%)</td>
<td>1/3 (33%)</td>
</tr>
</tbody>
</table>

*The O’Connor study included one pouch patient, 2 anovaginal fistulas and 4 patients on concomitant infliximab. Single rather than multiple tracts were significantly associated with successful closure. Preoperative setons were used if the tract was too wide for the plug to sit snugly.

NR – not reported or cannot be concluded form the data presented.
Figures for CPD Mx review

Figure 1. T2 weighted pelvic MRI images with fat suppression showing improvement of anal fistula from baseline (a) at six months (b) and 21 months (c).
Figure 2. a. A bulky silastic seton and b. a low profile ethibond seton with just three throws and the ‘whiskers’ tied back with silk.
Algorithm for the management of anal fistulae in Crohn’s disease

1. Anal fistula in Crohn’s disease
2. Clinical assessment: exclude abscess
3. Treat with antibiotics and thiopurines unless indication for urgent biologic agent
4. MRI pelvis and luminal assessment
5. Surgical review; EUA +/- drainage +/- setons, curative or ablative procedure*

**Week 0**
- Induction of infliximab: 5mg/kg at weeks 0, 2 and 6, remove seton at approximately week 6 if clinical improvement (if anal fistula and luminal disease, consider infliximab or adalimumab)

**Week 12**
- Clinical assessment
  - Clinical response/remission or any symptomatic improvement
    - Discontinue infliximab, commence adalimumab
  - Continue infliximab 8 weekly, clinical assessment, as required or at least 6 monthly

**Week 52**
- Clinical assessment, MRI pelvis, luminal assessment if appropriate
  - Clinical remission
    - MRI scan
      - Complete radiological healing
        - Consider stopping
      - Continue thiopurine, MRI in 6 months
  - Clinical response
    - MRI scan
      - Partial radiological improvement
  - Loss of response
    - MRI scan
      - No radiological improvement
      - Consider surgical intervention², optimise infliximab, switch to adalimumab
    - MRI scan
      - Continue infliximab, reassess in 6 months (then annually)
* Curative surgery
A few patients with moderate Crohn’s disease may be candidates for curative surgery:
* advancement flap (good rectum, perineal descent/internal intussusception helpful, consider temporary stoma);
* coloanal pull through (rectal internal opening, good anus, good colon, loop ileostomy);
* Turnbull-Cutait‡ (internal opening at dentate line, good anus, good colon, loop ileostomy);
* fistulotomy +/- delayed sphincter repair (consider temporary stoma).
Some patients with severe and debilitating disease may benefit from ablative surgery§

Temporary stoma
Temporary ileostomy/colostomy:
* will not of itself lead to fistula resolution
* may be an adjunct to surgical or medical therapy
* should not be used when proctectomy or proctocolectomy is needed

‡ Turnbull-Cutait procedure
Two stage coloanal.
* 1st stage leaves colon extruded anally for one week;
* 2nd stage trims the colon back to the anus.

† Surgery in loss of response
MRI may indicate undrained sepsis leading to lack or loss of response
* drainage of sepsis should be obtained and further setons inserted
* infliximab maintenance should then recommence
* further clinical assessment in 6 months

§ Ablative surgery
Perianal fistulae alone are unlikely to lead to very poor general health with restriction of work or social activities; colorectal disease is likely to be to blame. In this case:
* medical management should be optimised;
* if this fails, proctectomy or proctocolectomy (dependent on the extent of disease) should be considered;
* advice regarding the risk of delayed or poor perineal wound healing should be given.
Incidental cryptoglandular fistulae

Rarely, a cryptoglandular fistula will occur in a patient with Crohn’s disease:

- the anorectum will be entirely normal and unaffected by Crohn’s disease;
- there will be very limited luminal disease;
- treatment should be surgical, as for other cryptoglandular fistulae, except with greater sphincter preservation because of the risk of diarrhoea in the future.