Crohn’s disease can manifest in many different ways including fibrostenotic (stricturing), or non-perforating, non-stricturing (inflammatory) disease or predominantly perforating (fistulizing) disease. Patients with fistulating Crohn’s disease tend to have a more aggressive disease course. The morbidity is greatly increased in those patients with fistulating disease. Perianal disease and fistulas can lead to fecal incontinence, abscess formation and anal strictures. The treatment of fistulas is dependent on many factors including location, severity, and previous surgical history.

The estimated incidence of fistulas (entero-cutaneous or perianal) in patients with Crohn’s disease is approximately 35%. Approximately 21% of patients with Crohn’s will have perianal fistulas within 10 years of diagnosis. Before the introduction of biologics, most fistulas required surgical intervention and the rate of fistula recurrence was estimated to be 34%.^1^3

Understanding the Anatomy and Pathogenesis

Our current understanding shows that fistulas in Crohn’s disease develop secondary to multiple causes. One proposed mechanism for perianal fistula formation is that fistulas begin as an ulcer within the anal canal. When feces is forced into this ulcer it causes penetration of the lesion through the wall. This track then extends over time with increased pressure from the fecal stream. Another hypothesis of fistula formation involves an abscess of one of the anal glands which can be present within the intersphincteric space. This abscess then grows and a fistula forms as a way to drain this area of purulence under pressure. The fistula can extend through the external anal sphincter (trans-sphincteric fistula), track down to the skin (inter-sphincteric fistula) or track upward to become a supra-sphincteric fistula.

A careful physical exam and endoscopic exam must be performed prior to initiating treatment for the fistulizing disease, with special attention to location of the fistula in relation to the dentate line. Fistulas can be classified many different ways. The most anatomically precise method is the Park’s classification. This classification system uses the external sphincter as a central point of reference and includes five types of perianal fistulas: intersphincteric; trans-sphincteric; suprasphincteric; extrasphincteric; and superficial. An intersphincteric fistula tracks between the internal anal sphincter (IAS) and the external anal sphincter (EAS) in the intersphincteric space. A trans-sphincteric fistula tracks from the intersphincteric space through the EAS. A suprasphincteric fistula leaves the intersphincteric space over the top of the puborectalis and penetrates the levator muscle before tracking downward to the skin. An extrasphincteric fistula tracks outside of the EAS and penetrates the levator muscle into the rectum. Finally, a superficial fistula tracks below both the IAS and EAS complexes.

Although the Parks system is most accurate method of describing fistula anatomy and helps clinicians communicate with the surgeons taking care of patients with perianal fistulas, there are several limitations to this system including the fact that associated abscesses and connections to other structures such as the vagina or bladder are not part of this schema but are clinically important.

The other methods for classifying fistulas are to divide them into simple or complex fistulas. This was proposed in 2003 by American Gastroenterological Association Technical Review Panel as an alternative and more clinically relevant classification system for perianal fistula. Within this system, a simple fistula is superficial or begins low in the rectal canal, has a single opening on the skin, is not associated with an abscess, and does not connect to other structures such as the vagina or scrotum. A fistula is complex if it begins high in the canal, is associated with an abscess, has multiple openings, or connects to an adjacent structure. Another important distinction is to determine if the fistula is associated with obvious inflammation of the colonic mucosa; if so, this too would be considered complex. This classification is clinically relevant because complex fistulas involve more of the sphincter complex, reducing the chance for fistula healing, and placing patients at increased risk for incontinence with aggressive surgical intervention.
Diagnostic Modalities for Assessing Fistulas

Occult abscesses or fistulas are difficult but important to recognize. Missing occult lesions can result in recurrent fistulas, abscesses and/or convert a simple fistula into a complex fistulizing process. Once the fistulizing process becomes complex, the chance for healing is greatly reduced. In order to prevent the development of a complex fistula and increase the chance of closure, one must identify and optimize the medical and surgical treatment early at disease onset. The fistula must be fully defined so appropriate therapy can be started. The goal is establish drainage of any abscess that may be present and control fistula healing to prevent abscess formation during treatment of fistulas. Ideally this initial assessment could be done with a simple digital rectal exam (DRE), although because of the associated induration and scarring, the accuracy of this exam in defining fistula anatomy is reportedly low, 62% in one study.

Because of the low accuracy of the DRE, imaging should be used as a means to provide a therapeutic roadmap to ensure that all potential areas are treated. The various imaging modalities that have been used to assess perianal fistulas include fistulography, computed tomography, pelvic MRI, and rectal EUS.

Fistulography and Computed Tomography (CT)
Fistulography involves the placement of a small catheter into the cutaneous opening of a fistula tract and injection contrast under pressure. Fistulography can cause pain during the exam and the theoretical potential for dissemination of septic fistulous contents. Fistulography has a low overall accuracy for determining the tract of the fistula ranging from 16-50%. CT has been used to assess perianal disease but is limited by poor spatial resolution in the pelvis. It is not commonly used because its accuracy is low as well, ranging from 24-60%.

Endoscopic Ultrasound (EUS) and Magnetic Resonance Imaging (MRI)
The most accurate way to evaluate perianal Crohn’s fistulas is by MRI or rectal EUS. A prospective blinded study compared the accuracy of MRI, EUS and exam under anesthesia in 34 patients with suspected Crohn’s perianal fistulas. In this study, all three methods demonstrated high accuracy when compared with the consensus gold-standard, (EUS - 91%, MRI - 87%, and EUA – 91%). The consensus gold standard was determined by the co-investigators after reviewing all of the tests results and the patients history. When any of the imaging modalities are combined with EUA, the accuracy was 100% in these patients and was the most cost effective approach. The role of MRI and EUS to monitor the fistula response to medical therapy is still being explored but may help guide treatment decisions in these patients (see below).

Treatment Options
After a fistula has been properly assessed and categorized as simple vs. complex, the most appropriate treatment course can then be determined. The decision between medical therapy and surgical therapy or a combination medical and surgical therapy is determined by the type of fistula and the degree of rectal inflammation present.

Medical Treatment
Antibiotics
Multiple studies have been done utilizing antibiotics for the treatment of fistulizing Crohn’s disease, with only modest results. Most of these were open label case series involving few patients. Antibiotics are used for both their activity in perianal sepsis and for their anti-inflammatory properties. The most common antibiotics used are metronidazole at doses of 750-1,000 mg/day or ciprofloxacin at 1,000-1,500 mg/day for up to 2-4 months. Adverse events commonly associated with metronidazole include metallic taste, glossitis, nausea, and a distal peripheral sensory neuropathy. Adverse events with ciprofloxacin occur less commonly but include headache, nausea, diarrhea, and rash.

Recently a randomized, double-blinded, placebo-controlled trial was performed looking at ciprofloxacin and metronidazole for the treatment of perianal fistulas in patients with Crohn’s disease. 25 patients were randomized to ciprofloxacin 500 mg (10 patients), metronidazole 500 mg (7 patients) or placebo (8 patients) twice daily for 10 weeks. Response (≥ 50% reduction in the number of draining fistulas) at week 10 was seen in 4 patients (40%) treated with ciprofloxacin, 1 patient (14.3%) treated with metronidazole, and 1 patient (12.5%) with placebo (p=0.43). 1 patient from both the ciprofloxacin and placebo, and 5 (71.4%) treated with metronidazole dropped out of the study (p<0.02). This small study suggested that remission and response occurred more often in patients treated with ciprofloxacin but the differences were not significant.

Immunomodulators
There have been several trials of 6-mercaptopurine and azathioprine for luminal Crohn’s disease where the treatment of perianal disease was a secondary endpoint. A meta-analysis of these trials looked at fistula closure as a secondary endpoint for post hoc analysis. This analysis found that 22 of 42 (54%) of patients with perianal Crohn’s disease who received AZA/6MP responded vs. only 6 of 29 (21%) patients who received placebo (odds ratio [OR] = 4.44). Caution should be taken as the primary goal of these studies was to treat active inflammatory Crohn’s disease and was not designed primarily to look at the effect on perianal fistulas. In fact, only one of the studies stratified the patients for the presence of fistulas at randomization.
Tacrolimus

Tacrolimus has been studied for perianal Crohn’s disease in a randomized placebo controlled study.48 Patients with Crohn’s perianal fistulas were randomized to tacrolimus standard dose 0.2 mg/kg/day vs. placebo for 10 weeks. In the tacrolimus group 43% had fistula improvement (closure of ≥ 50% fistulas for > 4 weeks) compared with 8% placebo patients (p=0.004). However, complete fistula closure was only achieved in 10% of the patients who received tacrolimus. Fistula closure in the treatment group was not improved with concomitant immunosuppressive therapy with AZA/6 MP (38% closure with therapy vs. 50% without). Number of adverse events was higher in the treatment group (5.2 vs. 3.9; p = 0.009) including headache, insomnia, elevated creatinine, paresthesias, and tremor. The use of tacrolimus requires regular monitoring of renal function and drug levels which limits its ease of use.

Cyclosporine

Studies with cyclosporine for fistulizing Crohn’s disease have also been performed. These are all uncontrolled small studies that showed improvement in fistula drainage but the majority of patients relapsed after transition to oral therapy or discontinuation of the drug.37-39 The toxicity profile of cyclosporine may preclude use for fistulizing disease given safer better tolerated alternatives.

Tumor Necrosis Factor alpha (TNF) Antagonists

Prior to the introduction of anti-TNF antibodies the goal of treatment was primarily control of symptoms in order to improve the patients quality of life. Long term resolution had not been demonstrated in a large group of patients. Now it is realistic to strive for complete fibrosis of the fistula when using biologic agents especially in those patients with simple fistulas.

A number of biologic therapies have been developed for the treatment of Crohn’s disease, including adalimumab (a fully human IgG1 anti-TNF-alpha monoclonal antibody), infliximab (a chimeric monoclonal antibody to TNF-alpha), and certolizumab pegol (a humanized anti-TNF Fab’ monoclonal antibody fragment linked to polyethylene glycol), which antagonize TNF-alpha and have been shown to decrease clinical severity of disease.

There have been two double blind placebo-controlled trials of an anti-TNF anti-body with a primary focus being on fistulizing Crohn’s disease. Both of these trials have been with infliximab.40,41 The initial fistula trial with an anti-TNF-alpha agent looked at the short-term effect of infliximab on fistula drainage.41 Ninety-four patients were randomized to treatment with infliximab 5 mg/kg, infliximab 10 mg/kg, or placebo. Patients were given an infusion at weeks 0, 2, and 6. The primary endpoint was a >50% reduction from baseline in the number of draining fistulas. A fistula was considered to be draining if the examiner could express purulent material with gentle pressure on the fistula tract. Results showed a 68% response rate (achievement of the primary endpoint) in the 5 mg/kg infliximab treatment arm compared with only 26% in the placebo cohort; 55% of patients who received infliximab 5 mg/kg had complete cessation of drainage (i.e., closure) of all fistulas. However, the fistulas tended to become active again once infliximab was discontinued.

This study led to the ACCENT II [A Crohn’s Disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment Regimen in Patients With Fistulizing Crohn’s Disease] trial,40 which investigated whether cessation of fistula drainage could be preserved over the course of a year with infliximab maintenance therapy given every 8 weeks. Patients who had active fistulas and who responded to the initial 3 doses of infliximab at weeks 0, 2, and 6 were randomized to receive infliximab or placebo every 8 weeks. After 54 weeks, 36% of patients in the infliximab group maintained complete fistula closure compared with 19% in the placebo arm (p=0.009).

Fistula healing was studied as a secondary endpoint in the adalimumab maintenance trial, CHARM (Crohn’s trial of the fully Human antibody Adalimumab for Remission Maintenance).42 The CHARM trial assessed the efficacy of adalimumab in the maintenance of response and remission in patients with luminal Crohn’s disease. Complete fistula closure at 56 weeks was seen in 33% of the treated group (i.e., total randomized population on therapy who had fistulas at baseline (combined 40 mg weekly and every other week adalimumab dosing arms) compared with 13% in the placebo arm (p=0.016).

Unlike other monoclonal antibodies, certolizumab pegol does not contain an Fc portion and therefore does not induce in vitro complement activation, antibody-dependent cellular cytotoxicity, or apoptosis. Fistula healing was also examined as a secondary endpoint in one of the certolizumab maintenance trials PRECISE 2, which evaluated the efficacy and tolerability of certolizumab in the maintenance of clinical response following successful induction therapy in patients with active Crohn’s disease, had a small number of patients with draining fistulas at enrollment: 14% of patients in the intention-to-treat population from this study had draining fistulas at baseline (28 patients in the treatment arm and 30 on placebo).43 Among these patients, 54% of those treated with certolizumab had fistula closure as compared to 43% of those in the placebo group. At week 26, 67% of patients who received continuous certolizumab were able to maintain complete fistula closure. The study was underpowered to examine the efficacy of certolizumab for fistula closure.
There are no head-to-head trials comparing the efficacy of these agents in the treatment of Crohn’s disease or for obtaining fistula closure. Additionally, there are no studies comparing the efficacy of surgical treatment alone to that of combination surgical intervention plus conventional medical treatment (antibiotics, immunosuppressants). However, a retrospective study involving 32 patients with perianal fistulizing Crohn’s disease examined the efficacy of infliximab alone vs. infliximab as an adjunct to seton placement. Patients with fistulizing Crohn’s disease who had EUA (exam under anesthesia) with seton placement prior to receiving infliximab had an initial response of 100% vs. 82% for patients who only received infliximab (response was defined as complete closure and cessation of drainage from the fistula). Patients who received infliximab after EUA with seton placement also had a lower recurrence rate (44% vs. 79%) and longer time to recurrence (13.5 months vs 3.6 months). In another retrospective review, Topstad et al. showed that seton placement prior to infliximab resulted in complete response in 67 percent of patients.\(^\text{44}\)

We have learned a great deal about the treatment of fistulizing Crohn’s disease since the initial infliximab trials nearly a decade ago. Data indicate that most patients with fistulizing disease will need maintenance therapy, as brief exposure to TNF antagonists does not stop drainage of fistulas initially but recurrence is common after cessation of therapy. Indeed, after 1 year of maintenance therapy with infliximab complete closure of fistula tracks is rare as evidenced by evidence on magnetic resonance imaging (MRI) and/or endoscopic ultrasound (EUS) exam of persistent fistula activity even when the fistula drainage stops.\(^\text{29}\)

The Use of Imaging to Monitor Fistula Healing

Retrospective and small prospective trials have shown outcomes can be optimized by using imaging (EUS/MRI) to guide combination medical and surgical therapy in these patients.\(^\text{45,46}\) Schwartz et al. looked at using EUS to assess and guide therapy for fistulas. Twenty-one patients with Crohn’s perianal fistula underwent serial EUS exams. The findings were used to guide therapy (i.e., the presence of fistula healing on EUS was used to decide the appropriate time for seton removal. In this study, no abscess developed during treatment in any patient. EUS evidence of persistent fistula activity was seen in 10 patients (48%) which would not have been appreciated with physical exam alone. This study showed using EUS to guide therapy for Crohn’s perianal fistulas resulted in high short and long-term fistula response rate.\(^\text{46}\)

Spradlin et al. prospectively studied EUS related to outcomes for patients with perianal fistulizing Crohn’s disease. In this study ten patients with perianal Crohn’s disease were prospectively enrolled in a randomized study. All patients underwent a rectal EUS to delineate fistula anatomy followed by an EUA by a colorectal surgeon with seton placement and/or incision and drainage, as indicated. The surgeon was blinded to the initial EUS results of patients in the control group. Patients in the EUS group underwent scheduled EUS and surgical interventions based on the findings. Those in the control group underwent additional interventions at the discretion of the surgeon (without EUS guidance). After 54 weeks, all patients had a repeat EUS performed to determine the fistula status. One of 5 (20%) in the control group and 4 of 5 (80%) in the EUS group had complete cessation of drainage.\(^\text{45}\)

In a study by Tougeron et al., MRI was used to assess and follow patients with fistulas. Patients with perianal fistulizing Crohn’s disease had base line clinical and MRI characteristics recorded and were treated with infliximab. They did not find a MRI characteristics that was predictive of therapy response. The study did find that the presence of proctitis was associated with a lack of response to treatment.\(^\text{47}\)

Ng and colleagues prospectively followed with MRI 34 patients with Crohn’s perianal fistulas over the course of a year.\(^\text{48}\) They demonstrated again that fistulas remain active well after drainage stops. Also, MRI was able to identify a subset of patients in whom complete fistula healing had occurred. The risk of fistula recurrence in these patients was very low even after stopping the anti-TNF antibody.

Surgical Therapy

Surgical treatment is an integral part of treating fistulizing Crohn’s disease. The reported incidence of perianal fistulas that require surgery in patients with Crohn’s disease varies from 25-30%.\(^\text{49}\) It has been shown that the combination of medical and surgical therapy result in the best outcome for these patients.\(^\text{10,44,50,51}\) Surgical evaluation with EUA and seton placement allow for control of fistula healing during medical treatment. It is thought that the rapid closure of the cutaneous openings of the fistula tracks which may be seen with anti-TNF drugs can lead to abscess formation in the middle of the fistula track. In the two infliximab fistula trials, abscess formation during treatment was 11-15%, respectively.\(^\text{40,41}\)

The most common surgical treatment options include exam under anesthesia (EUA) which involves probing of the fistula tract, seton placement, incision and drainage, or fistulotomy in which the fistula tract is incised open. The placement of a draining seton maintains fistula drainage until the tract becomes inactive on medical treatment. A non-cutting seton or draining seton is threaded through the fistula tract and is tied outside the anal canal. The seton can be removed when the fistula track has healed, or can remain in situ for an extended period if healing has not occurred.
Patients with superficial or low perianal fistulas who do not have active inflammation in their rectum (i.e., simple fistulas) can be safely treated by fistulotomy alone with resolution of fistula symptoms in up to 85% patients.\(^{32}\) Advancement-flap procedures have been attempted as treatment for perianal fistulas with good initial healing rates of up to 89% but recurrence was found in 34% of these patients during follow-up.\(^{33}\)

Abscess associated with fistula must be drained in order to achieve healing. The surgical approach can include local incision and drainage, catheter drainage, or seton placement. According to the recommendations of the American Society of Colon and Rectal Surgeons, anal abscesses should be drained in a timely manner. Lack of fluctuance should not be a reason to delay treatment. Perianal abscesses can often develop into a chronic fistula.\(^{54}\)

### Treatment Algorithm

In counseling patients about the treatment of fistulizing Crohn’s disease, the most important decision is when to start biologic therapies. The “top down” approach to starting anti-TNF therapy advocates the earlier use of biologic therapy earlier in the disease course in order to prevent the complications associated with the disease.\(^{23}\) In this paradigm, rather than “ramping up” therapy in the traditional “step-up” or sequential approach, proceeding from the “weakest” (i.e., lowest efficacy [e.g., 5-aminosalicylic acid or 5-ASA]) to the “strongest” (anti-TNF-alpha agents) therapeutic interventions, with each subsequent therapy being added due to lack of response or toxicity, one would “reverse” the treatment pyramid and start with the most effective therapy at the beginning (early in the disease course) in order to change the natural history of the disease and prevent complications. This type of treatment schema can be applied to fistulizing Crohn’s disease as well. Indeed, the presence of fistulizing disease is one of the factors predictive of severe disabling Crohn’s disease.\(^{54}\)

Because fistulizing disease is one of the predictive markers of severe disease, initiating therapy with anti-TNF agents early on in these patients is preferential for several reasons. Studies have shown that once a fistula becomes “complex” the chance for complete closure of that fistula drops dramatically.\(^{46}\) Therefore, by employing the most efficacious treatment available we hope to prevent this transformation. In addition, sub-analysis of the certolizumab and adalimumab maintenance trials demonstrates significantly increased response rates to these agents in patients treated earlier in their disease course.\(^{35}\) For instance, in the CHARM trial, patients with Crohn’s disease \(< 2\) years had remission rates with maintenance adalimumab at week 56 of 51% compared to remission rates of only 35% in patients with Crohn’s disease \(> 5\) years (p=0.001).\(^{36}\)

Treatment must be individualized for each patient on the basis of the type of fistula present. Thus, the approach to treating patients with fistulas begins by first stratifying the perianal disease into 1 of 3 fistula types: simple fistulas without proctitis, simple fistulas with proctitis, or complex fistulas. This is generally done by imaging the perianal disease with either MRI or EUS exam and endoscopy.

In patients with simple fistulas without proctitis, treatment consists of medical therapy and involves a trial of antibiotics and immunosuppressants, with or without anti-TNF-alpha agents. The use of surgical treatment in this subset of patients is not mandatory, as healing rates with isolated medical therapy are generally good. If no response is observed, then a combined surgical and medical approach with an anti-TNF-alpha agent is recommended.\(^{57}\)

Patients with simple fistulas and concomitant proctitis should be treated with a combined surgical and medical approach using anti-TNF-alpha agents as first line to decrease inflammation and allow fistula closure. A short trial of rectal 5-ASA or rectal steroids to reduce inflammation may represent a reasonable alternative. Clinicians typically begin with a top-down approach, using an anti-TNF-alpha agent early to prevent the fistulizing process from becoming complex. We generally wait to start immunomodulators and anti-TNF treatment until after the EUA is completed in order to reduce the risk of abscess formation.

Complex fistulas absolutely require surgical intervention with the placement of draining setons, followed by treatment with a combination of antibiotics, immunosuppressants, and anti-TNF-alpha therapy, as the goal of therapy in this setting changes from complete fibrosis of the tract to control of fistula drainage and prevention of abscess formation.\(^{46}\)

### Conclusion

Fistulas are a frequent manifestation of Crohn’s disease and can result in significant morbidity and often lead to the need for surgical intervention. Historically, it has been more difficult to obtain complete fistula closure in patients with perianal Crohn’s disease. The advent of anti-TNF-alpha agents and the use of more accurate imaging modalities such as MRI and rectal EUS has greatly enhanced our ability to manage fistulizing Crohn’s disease. A combined medical and surgical approach is usually the best option for most patients.
REFERENCES

108 IC: Advances in Inflammatory Bowel Disease


