

Managing perianal Crohn's fistula in the anti-TNF α era

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Abstract Perianal fistulas in Crohn's disease are common and difficult to treat. Their aetiology is poorly understood. Assessment is clinical, endoscopic and radiological, and management is undertaken by a multidisciplinary team of gastroenterologists, surgeons and radiologists. Surgical drainage of the fistula tract system with the placement of loose setons precedes combined therapy with immunosuppressant and anti-TNF α agents in most patients. Proctitis should be rigorously eliminated where possible. Definitive surgical repair is sometimes possible and diversion or proctectomy are occasionally required. Combined medical and surgical management represents a promising avenue for the future.

Keywords Perianal fistula · Crohn's disease · Surgery · Biological therapies · Anti-tumour necrosis factor- α

Epidemiology

Perianal fistulas in Crohn's disease (pCD) are a common and difficult problem. Twenty-six percent of Crohn's patients develop an anal fistula over a 20-year period [1], and perhaps a third will suffer from one at some point in their lives [2]. Those with colonic disease and in particular proctitis are more likely to develop a fistula [3]. Crohn's anal fistulas are often recurrent, complex and multiple and predict increased

disease severity with more rapid disease progression and need for medical and surgical intervention [4–6].

Aetiology

The aetiology of Crohn's anal fistulas is poorly understood. The cryptoglandular theory [7] may not be wholly applicable to the Crohn's setting in which anal ulceration may play a part [8]. As with luminal disease, an interplay of genetic predisposition, bacterial dysbiosis and host immune malfunction is implicated (reviewed in [9]) although recent work casts doubt on the relevance of bacteria in maintaining a fistula once formed [10]. The range of treatments available, their diversity and lack of efficacy speak to the poor understanding of fistula pathogenesis.

Classification

pCD may be classified according to the anatomy of the tract and in terms of disease activity. The Parks classification of anal fistulas describes primary tracts and secondary extensions [11] and may be applied to Crohn's disease. Classifications of fistula activity include the Fistula Drainage Assessment and Perianal Disease Activity Index (PDAI). MRI-based scoring [12] also exists, but as with the activity classifications is of limited value in the clinical setting [13].

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The principals of management

pCD is best managed by a multidisciplinary team. A thorough history of the patient's luminal disease, perianal symptoms, past surgery, continence and bowel habit is

crucial. Smoking should be actively discouraged. Examination should identify proctitis as well as assess the perianal disease. Imaging is discussed below but will most frequently take the form of MRI. Endoscopy may be required to assess luminal disease and in particular identify any proctitis. Examination under anaesthetic and preoperative imaging will help map the fistula and also identify any perianal collections or abscesses. Following EUA, the patient should have a fully drained system with no undrained sepsis remaining, achieved through incision and drainage (I + D) and the placement of comfortable loose setons. Anti-TNF treatment will then be instituted with or without concomitant immunosuppression (often with azathioprine) and/or a short antibiotic course. Variations to this broad outline may be needed. Figure 1 is reproduced from the 2014 global consensus statement on pCD from Geese et al. [14].

Investigation

Imaging allows accurate classification of pCD and guides surgical management. Options include magnetic resonance imaging (MRI), endoanal ultrasound (EUS) and trans-perineal ultrasound (TPUS). Evaluation of MRI and the two forms of US have shown that MRI provides a very accurate overview of the primary tract and any secondary extensions [15] but may not demonstrate the internal opening (IO). EUS has a high accuracy in determining the IO and local tracts, but the resolution diminishes with distance from the probe. TPUS suffers from the same problem with more cephalad tracts, for example supralelevator extensions, but is quick and easy to perform. Combined MRI and EUS may yield 100 % accuracy [16].

A role for MRI in monitoring response to medical treatment has also been proposed, partly because clinical assessment alone misses occult and unhealed tracts of a patient ‘in remission’. In these patients, deep healing (based on MRI appearances) has been shown to occur a median of 12 months after closure of the external openings [13, 17]. MRI volume assessment using 3D models shows promise in monitoring response to treatment [18].

Medical treatments

The aim of medical treatment is to reduce symptoms and heal fistulas whilst protecting continence and avoiding ablative surgery in the form of proctectomy. Data regarding the efficacy of medical treatments in the management of pCD are sparse. Steroids and 5-ASA agents are of no benefit in pCD. Antibiotics, mostly metronidazole [19, 20] and ciprofloxacin [21, 22], have been claimed (in small,

uncontrolled series) to reduce discharge and improve symptoms, although relapse is common after cessation and side effects limit long-term use. A randomised controlled trial comparing each to placebo, however, found no significant differences in outcome [23]. Thiopurines in pCD have mainly been studied as a secondary end point in RCTs and results conflict. One meta-analysis of these RCTs has demonstrated increased response in the treatment group versus placebo (54 vs 21 %) [24], but a more recent Cochrane review failed to demonstrate any benefit [25]. Thiopurines are often used in combination with other agents where increased efficacy has inconsistently been demonstrated [26–28].

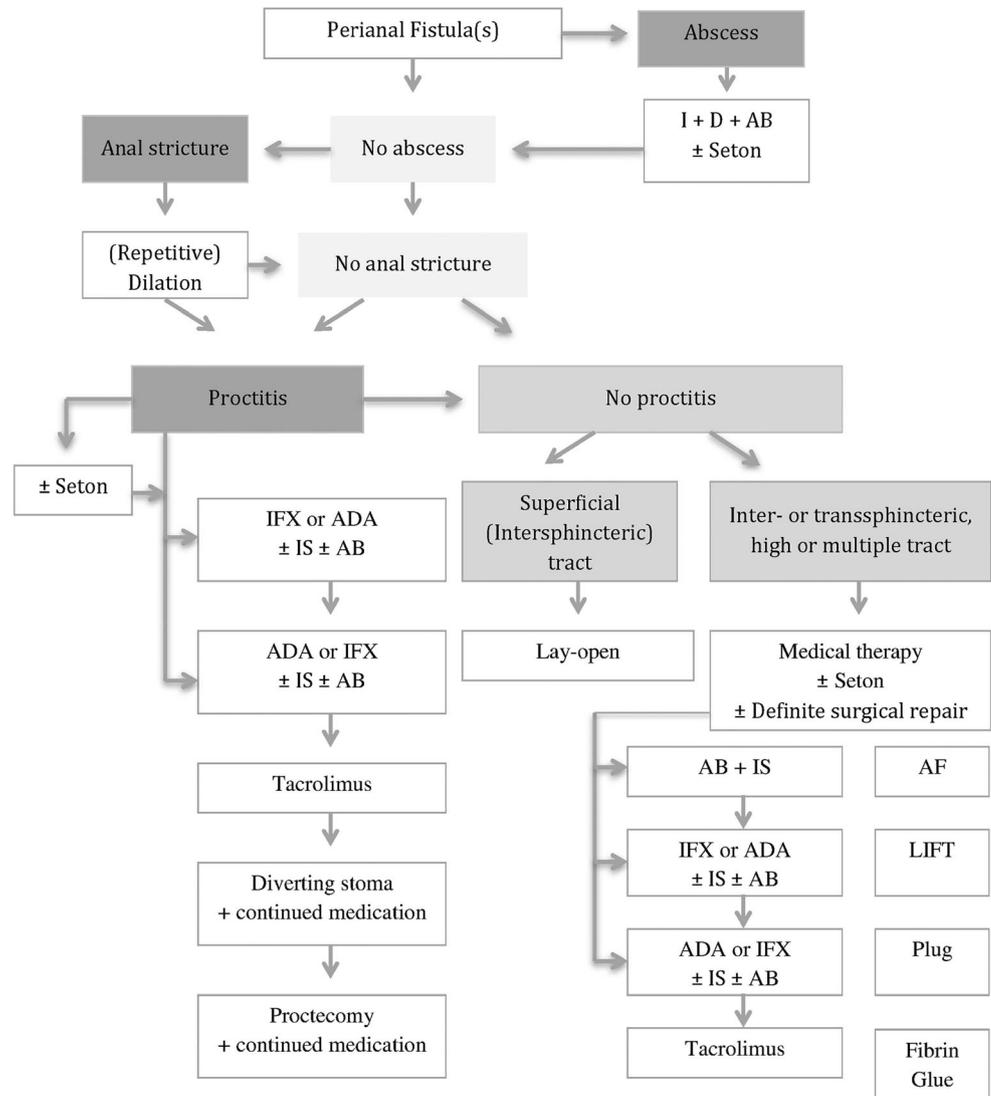
Cyclosporin can lead to rapid, but short-lived, improvement in fistulas, and relapse on cessation and side effects limit longer-term use [29]. Tacrolimus appears to induce early clinical improvement, but healing of all fistulas has not been consistently shown, and evidence for long-term improvement is lacking [30, 31]. Methotrexate also suffers from a lack of evidence. Thalidomide, despite its well-documented side effects, may have a role in those refractory to anti-TNF drugs. Small series have shown both improvement and remission [32], but large-scale evidence is lacking.

Anti-TNF α agents (infliximab, adalimumab and certolizumab pegol) have changed the landscape for medical treatment of pCD. Infliximab has been shown to induce external closure of all fistulas in 55 % [33] and maintenance treatment delays relapse with one-third of patients in clinical remission at 1 year [28]. A separate study demonstrated that deep tissue healing demonstrated on MRI lagged behind clinical healing (closure of tracts externally) by a median of 12 months [17]. Combination infliximab and azathioprine may improve response rate further, although reports on this are conflicting. Adalimumab has not been shown to produce a similar effect at induction, but in a maintenance study one-third of those who had initially responded to adalimumab maintained clinical remission at 1 year [34] and 90 % of these patients remained healed at 2 years [35]. There is also a role for adalimumab in patients who have lost response or become intolerant to infliximab, one-quarter of whom gain benefit. Certolizumab pegol-induced remission in one-third of patients at 6 months of treatment, although improvement short of full remission occurred at a similar rate to placebo [36].

Surgical treatments

The role of the surgeon as a part of the multidisciplinary team managing pCD patients is threefold: to provide adequate drainage of perianal sepsis before medical treatment;

Fig. 1 Treatment algorithm for perianal fistulising Crohn’s disease reproduced from a global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulising Crohn’s disease. Gecse et al. [14] with permission from BMJ Publishing Group Ltd



to attempt definitive surgical repair (and rarely lay open), where appropriate, whilst maintaining continence; and to offer ablative surgery (proctectomy) when required. The initial EUA with drainage of abscess and placement of loose setons precedes anti-TNF treatment but may need to be repeated if new abscesses develop during or between courses of treatment. Setons seek to prevent recurrent abscess formation by preventing closure of the external opening and will need to be removed if adjuvant medical treatment is to lead to healing. This is probably best done at 6 weeks (at the last induction dose of infliximab) or thereafter, if signs of improvement are seen, although the optimal timing is currently unknown.

Definitive surgical repair is difficult with widely varying reported outcomes across several surgical techniques (reviewed in [37]). Fistulotomy involving any part of the sphincter complex may lead to impairment of continence, particularly in view of concurrent or future episodes of

loose stool due to luminal disease or following resectional surgery. Sphincter-preserving options such as fistula glue, plugs, LIFT and advancement flaps are poorly studied in Crohn’s disease but may fare worse than in non-Crohn’s fistulas.

Mucosal advancement flaps achieve healing in around 50 % with a systematic review from 2010 suggesting 64 % success across 35 studies [38–40]. The LIFT procedure is a sphincter-preserving technique in which a single, mature, trans-sphincteric tract is approached in the intersphincteric plane, ligated and divided, disconnecting the gut from the residual tract [41]. The procedure shows promise, but most studies have recruited cryptoglandular fistula patients only and evidence of efficacy in Crohn’s fistulas is lacking.

Fistula glue and plug studies have included small groups with success rates varying dramatically within short-term follow-up (reviewed in [37]). Some of the larger and longer follow-up studies put success rates between 20 and 50 %

[42–46]. Factors predicting success have been identified, and proponents claim that a higher success rate may be achievable although more robust evidence is required. Additionally, plug insertion does not damage the sphincter complex or contraindicate any subsequent medical or surgical management in the event of recurrence.

In recent years, several authors have reported on their experience with cell-based therapies to treat fistulae-in-ano both of cryptoglandular and CD origin. Following an initial case of successful treatment of a recto-vaginal fistula in a patient with perianal CD using a combination of adipose-derived in vitro enhanced mesenchymal stem cells (ASCs) in fibrin glue [47], the authors reported fistula closure in more than 70 % for CD patients [48, 49]. Although their later-reported long-term follow-up showed that more than half of the initial successes developed recurrence of their fistulae within 3 years [50], others have reported similar rates of initial success in 80 % using autologous ASCs [51]. Whilst these techniques employed a combination of ASC in fibrin glue scaffold, injection of the fistula tract wall with in vitro enhanced allogenic ASCs without obliteration of the lumen may be also effective; successful fistula closure in more than 50 % of cases could further indicate the possible importance of the local immunomodulatory effects of the cells [52].

The potential systemic therapeutic effect of locally injected autologous bone marrow-derived mesenchymal stem cells into the fistula has been postulated by a study on 10 patients with perianal CD, where not only seven patients (70 %) achieved complete closure of the tract at 1 year, but the authors also demonstrated significant increases in the circulating T cells as well as a significant reduction in the CDAI in all patients [53]. Whilst these studies are small and the high recurrence rate is troubling, with a number of ongoing trials on the efficacy of cell-based therapies both in Crohn's disease and cryptoglandular fistulae, such therapeutic options may hold some potential in the future.

Small, retrospective studies have shown that a defunctioning stoma is an option to gain improvement in severe perianal sepsis and is successful in 80 % of cases in the short term. However, disease often recurs, with sustained benefit occurring in fewer than 50 % of cases, and the majority of stomas formed in this way are never reversed [54–58].

Proctectomy may be less frequently required in the anti-TNF era [54, 59] and is now considered a failure of combined medical/surgical treatment by many, as well as carrying risks including pelvic nerve damage, pelvic adhesions leading to reduced fecundity and delayed perineal wound healing in up to one-third. However, a minority of patients, their lives blighted by a combination of perianal disease and proctitis, are best served by this approach.

Proctitis

Proctitis is associated with a poorer outcome with both medical [13] and surgical [60] treatment. It is also associated with a higher proctectomy rate [54] and should be assiduously eliminated if possible. Recent consensus guidelines suggest that proctitis is a relative contraindication to definitive surgical repair because of an increased risk of failure and poor wound healing [14].

Optimised combination medical and surgical treatment

More recently, several studies have sought to demonstrate the benefit of combined medical and surgical management. The benefits of careful drainage and seton insertion before infliximab induction [61] and infliximab induction before definitive surgical procedures [59] have been considered. A recent systematic review found that across 797 patients, complete remission was higher and failure to respond, lower, in patients undergoing combined medical and surgical treatment versus either alone [62]. Further, robust studies are required.

Summary

Perianal fistulas in Crohn's disease are distressing for patients and hard to treat. A coordinated approach from a multidisciplinary team is best placed to provide optimal care. Careful assessment of the fistula, control of luminal (particularly rectal) disease and drainage of the fistula tract complex (with seton insertion where appropriate) precede medical treatment with immunosuppression, antibiotics and anti-TNF agents for most patients. A few may benefit from definitive surgical repair, and a small number ultimately require proctectomy. Further research into combined medical therapy, novel surgical treatments (such as using adipose-derived stem cells) and combined medical and surgical approaches are required and are underway.

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Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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