Journal of Enterocolitis

Review

Perianal Fistula Treatment in Crohn's Disease: Medical and Surgical Options

Oğuz Kağan Bakkaloğlu[1], Aykut Ferhat Çelik[2]

[1]Department of Gastroenterology,Kartal Kosuyolu High Specialization Training and Research Hospital, Istanbul, Türkiye
[2]Department of Gastroenterology, Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Istanbul, Türkiye

Cite this article as: Bakkaloğlu OK, Çelik AF. Perianal Fistula Treatment in Crohn's Disease: Medical and Surgical Options. *J Enterocolitis*. 2025;4(Suppl 1):S51-S58.

Corresponding author: Oğuz Kağan Bakkaloğlu, e-mail: o.k.bakkaloglu@gmail.com

Received: December 20, 2024 **Accepted:** March 06, 2025

DOI: 10.14744/Jenterocolitis.2025.17966

Abstract

Perianal fistulizing Crohn's disease is a challenging condition that affects up to 10% of patients at diagnosis, with prevalence increasing over time, often necessitating complex treatment strategies. Effective management requires early, aggressive combination therapy, typically incorporating antibiotics, immunomodulators, and anti-TNF agents—particularly infliximab—to control inflammation and promote fistula closure. Radiological closure, rather than clinical remission alone, is crucial for confirming fistula healing and guiding therapeutic decisions, as persistent fistula tracts may remain despite symptom relief. Optimizing anti-TNF levels and the duration of combination therapy further improves outcomes, with the goal of achieving sustained radiological remission. Routine imaging with MRI or perianal ultrasound is essential for monitoring disease response, ensuring complete closure, and minimizing the risk of recurrence. In refractory or severe cases, surgical interventions such as seton placement, fistulotomy, or diversion stoma may be necessary to manage drainage while preserving sphincter integrity. A multidisciplinary approach is critical in complex cases, requiring collaboration between gastroenterologists, surgeons, and radiologists to tailor interventions for optimal results. Clear patient communication is essential, particularly regarding the potential need for a permanent stoma if full fistula closure cannot be achieved. Despite advances in therapy, perianal fistulizing Crohn's disease remains a significant challenge, necessitating continued innovation to improve durable radiological and clinical remission and enhance overall patient quality of life.
Keywords: Crohn's disease, perianal fistula, radiological remission, stoma

INTRODUCTION

Perianal disease is present in approximately 4–10% of patients at the time of Crohn's disease (CD) diagnosis, with the cumulative risk increasing as the disease progresses.[1] In tertiary care clinics, more than 30% of patients under follow-up may have a perianal fistula (PAF).[2] The incidence of isolated perianal disease is lower, and in some cases, associated satellite luminal involvement may not be immediately recognized.

CLASSIFICATION

A commonly used anatomical classification, the Parks classification, categorizes fistulas based on their relationship to the external anal sphincter as intersphincteric, transsphincteric, suprasphincteric, or extrasphincteric (Figure 1).[3] Another classification system divides fistulas into simple and complex types:

- **Simple fistulas** are defined as low transsphincteric or intersphincteric fistulas that involve less than the distal one-third of the external anal sphincter and are located below the dentate line.
- **Complex fistulas** include high transsphincteric, suprasphincteric, and extrasphincteric fistulas, as well as horseshoe fistulas. These may be associated with multiple perianal openings, abscesses, fluid collections, or anal stenosis.[4,5]

There is no consensus on classifying perianal fistulas as either simple or complex. In the St. James's Hospital classification, a grade 2 fistula—defined as an intersphincteric fistula with an associated abscess or secondary tract—is considered simple. However, according to the AGA 2003 guidelines, the presence of an abscess or secondary tract (branching) qualifies a fistula as complex.[5,6] Similarly, in the AGA 2003 guidelines, a high-course transsphincteric fistula (TSF) (located above the distal one-third of the sphincter complex) is classified as complex. In contrast, the St. James's Hospital classification categorizes any TSF as grade 3, without specifying details regarding its course.

In clinical practice, we consider any fistula that transects the sphincter above the dentate line (above the upper one-third) as complex, while those below are classified as simple, based on the Parks classification—unless additional factors indicate complexity. The simple-complex distinction outlined in the AGA 2003 guidelines is practical for clinical use. While some ambiguities exist in its definition of complex fistulas, we believe the guideline's classification is valuable, as it considers fistulas complex if they involve rectal involvement, anal stenosis, a suprasphincteric course, an abscess, or a vaginal fistula, even if they are intersphincteric and would otherwise be classified as simple.

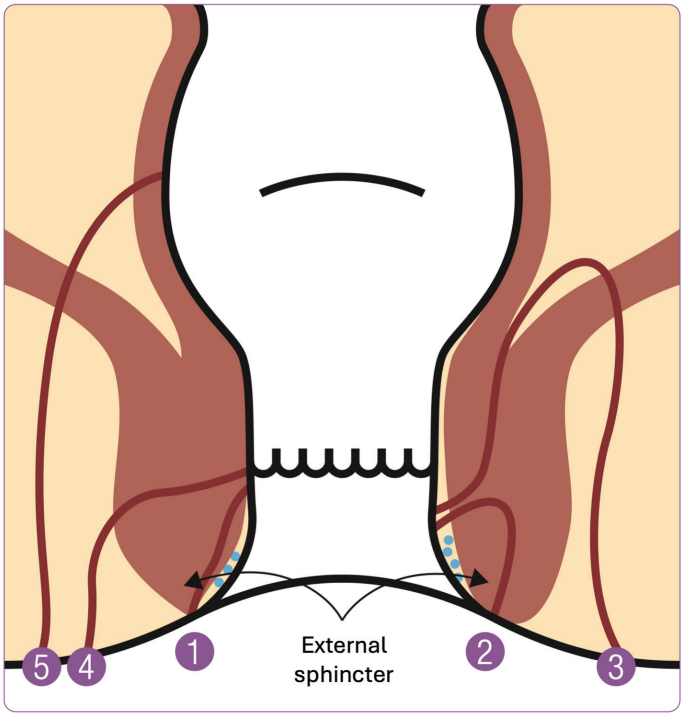

Figure 1. External spinchter.

FACTORS RELATED TO TREATMENT SUCCESS IN PERIANAL FISTULA

Perianal fistula treatment requires an aggressive, multidisciplinary approach that should begin as early as possible, as older fistulas become increasingly resistant to treatment and can lead to severe complications.[7] In addition to fistula type, the presence of complications such as anal canal stenosis, fecal incontinence, perianal maceration, and abscess formation can influence treatment decisions.[8]

Proctitis is associated with a poor treatment response and is considered an independent predictor of recurrence. Other factors linked to unfavorable outcomes include smoking, strictures, and luminal satellite involvement.[5] More complex, high-volume fistulas carry a greater inflammatory burden, making treatment more challenging and requiring a longer duration to achieve remission.[6] Initiating combination therapy in the early stages—before complications arise—can improve outcomes and reduce the likelihood of permanent stoma placement.

MAIN POINTS

- Achieving radiological fistula closure, rather than just clinical remission, is crucial for the long-term management of perianal fistulizing Crohn's disease (CD), as persistent tracts often remain despite symptom relief.
- Early and aggressive combination therapy—particularly with anti-TNF agents and antibiotics—significantly improves outcomes in perianal CD and increases the likelihood of achieving both clinical and radiological remission.
- For complex or treatment-resistant perianal fistulas, integrating surgical interventions within a multidisciplinary approach can optimize patient outcomes and reduce complications, emphasizing the need for comprehensive, individualized care in perianal CD management.

FISTULA TREATMENT GOALS – DEFINITIONS OF REMISSION

Research suggests that fibrotic changes and/or endothelialization in aging fistulas reduce treatment success and make closure more difficult. As a result, early biological therapy has become a preferred approach over the traditional step-up strategy in perianal fistula treatment.[7,9] While the ultimate goal is early and uncomplicated fistula closure, it is important to recognize that complex fistulas often require prolonged treatment and close monitoring.

The initial response of a perianal fistula to treatment—particularly dual antibiotic therapy—can provide valuable insights into its long-term behavior. Therefore, assessing the combined treatment response, especially with the addition of azathioprine (AZA) during the induction phase of anti-TNF therapy and the transition to maintenance therapy (typically 12–14 weeks), is crucial. The use of antibiotics in the early phase further supports this assessment. For each component of combination therapy—particularly anti-TNF agents—optimizing dosage and duration while closely monitoring treatment response and potential side effects are essential before determining treatment failure. Some patients should be informed from the outset that symptom control, quality-of-life maintenance, complication prevention, and continence preservation may only be possible with a stoma.[10] For patients who refuse a temporary stoma, clinicians must clearly communicate that a permanent stoma may become inevitable, along with potential morbidity and, in rare cases, mortality. The clinician's approach and communication play a crucial role, as they can significantly impact patient understanding and acceptance of treatment options.
Previously, a 50% reduction in fistula drainage was considered a clinical response. However, the focus has shifted toward radiological closure, reflecting more rational and evolved treatment expectations, even though this shift has not been accompanied by a proportional increase in treatment success.[11]

The clinical response for perianal fistulas is traditionally defined as the closure of 50% of fistulas, while clinical remission is characterized by the complete closure of all fistulas.[11] However, this is a cross-sectional and momentary evaluation that does not account for the fluctuating nature of fistula behavior. Therefore, we propose a more precise definition of clinical fistula remission: the absence of any drainage, including minimal soiling of underwear, for more than three months, with no discharge upon compression.

Assessing clinical response in perianal fistulas is a subjective, multi-parameter evaluation shaped by the treating physician's judgment. A >50% reduction in CRP levels compared to baseline can serve as a supportive indicator, provided there is no active luminal disease or if luminal disease is in remission. During physical examination, checking for discharge upon compression should be a routine verification step at every visit. To establish a more rational definition of "clinical response," we suggest incorporating a time parameter—similar to our proposal for defining clinical remission. Specifically, clinical response should be defined as a >50% reduction in fistula output and/or drainage frequency (as reported by the patient), with no significant intermittent increases in drainage, sustained for more than one month.

Studies have shown that even when a fistula appears clinically closed, the fistula tract may remain open on MRI.[12] Therefore, equating radiological closure of the fistula with the endoscopic remission of luminal disease is a reasonable approach. This reinforces the recommendation that radiological closure should be a primary treatment goal for achiev-

ing long-term remission.[13] Radiological closure can be defined as the complete absence of a fistula or the presence of fibrotic healing.[14,15] Additionally, the Van Assche and modified Van Assche index scores are valuable tools for assessing dynamic radiological changes in fistula response during clinical follow-up.[15,16]

MEDICAL TREATMENT

Perianal fistulas range from simple cases to complex, high-output forms with complications such as perianal maceration. Medical treatment strategies vary from short-term monotherapy with a single antibiotic to long-term combination therapy, which may include dual antibiotics, maximum-dose anti-TNF agents, and AZA at 2–2.5 mg/kg, sometimes in conjunction with a diverting stoma. Figure 2 illustrates treatment strategies for complex perianal fistulas. Clinical findings suggest that early anti-TNF therapy may benefit perianal disease, and a negative correlation has been observed between disease duration and anti-TNF response in fistulizing Crohn's disease.[17-19]

When treating perianal Crohn's disease, it is essential to identify and manage any underlying abscess or infection before initiating immunosuppressive therapy. Currently, there is limited evidence supporting the efficacy of biological agents other than anti-TNF therapy (especially intravenous options) for perianal fistulas. However, combination therapy with anti-TNF agents, AZA, and antibiotics has demonstrated superior clinical response and remission rates compared to anti-TNF induction therapy alone.[7]

Infliximab (IFX), due to its intravenous administration option and the ability to escalate doses when necessary, has shown higher clinical success rates. Therefore, it is recommended to initiate treatment with antibiotics upon detecting a perianal fistula, followed by the addition of AZA and IFX combination therapy within 2–4 weeks. This approach allows for assessing the hepatotoxic potential of various treatment agents (anti-TNF, AZA, and antibiotics), particularly dual antibiotic therapy, all of which have varying degrees of hepatotoxicity risk. Additionally, it ensures that any subclinical infection associated with the fistula is not overlooked.

ANTIBIOTICS IN TREATMENT

The optimal duration of antibiotic therapy remains unclear due to varying patient responses and the frequent recurrence of drainage after discontinuation. As a result, antibiotic treatment should be individualized. While antibiotics are not currently standardized as first-line therapy,[9] most patients present for medical evaluation due to active fistula drainage and are initially prescribed antibiotics. Ciprofloxacin (which has high tissue penetration) and metronidazole (which covers anaerobic bacteria) are the preferred first-line antibiotics for managing perianal fistulas and uncomplicated abscesses. However, for complex fistulas, antibiotic monotherapy is insufficient, and recurrence is common after discontinuation.[20,21] Single-antibiotic therapy may be an option for patients with minimal, low-frequency drainage and no complications. If metronidazole-related gastrointestinal side effects occur, alternative antibiotics with anaerobic coverage (e.g., amoxicillin + clavulanic acid) or moxifloxacin as a substitute for ciprofloxacin may be considered.

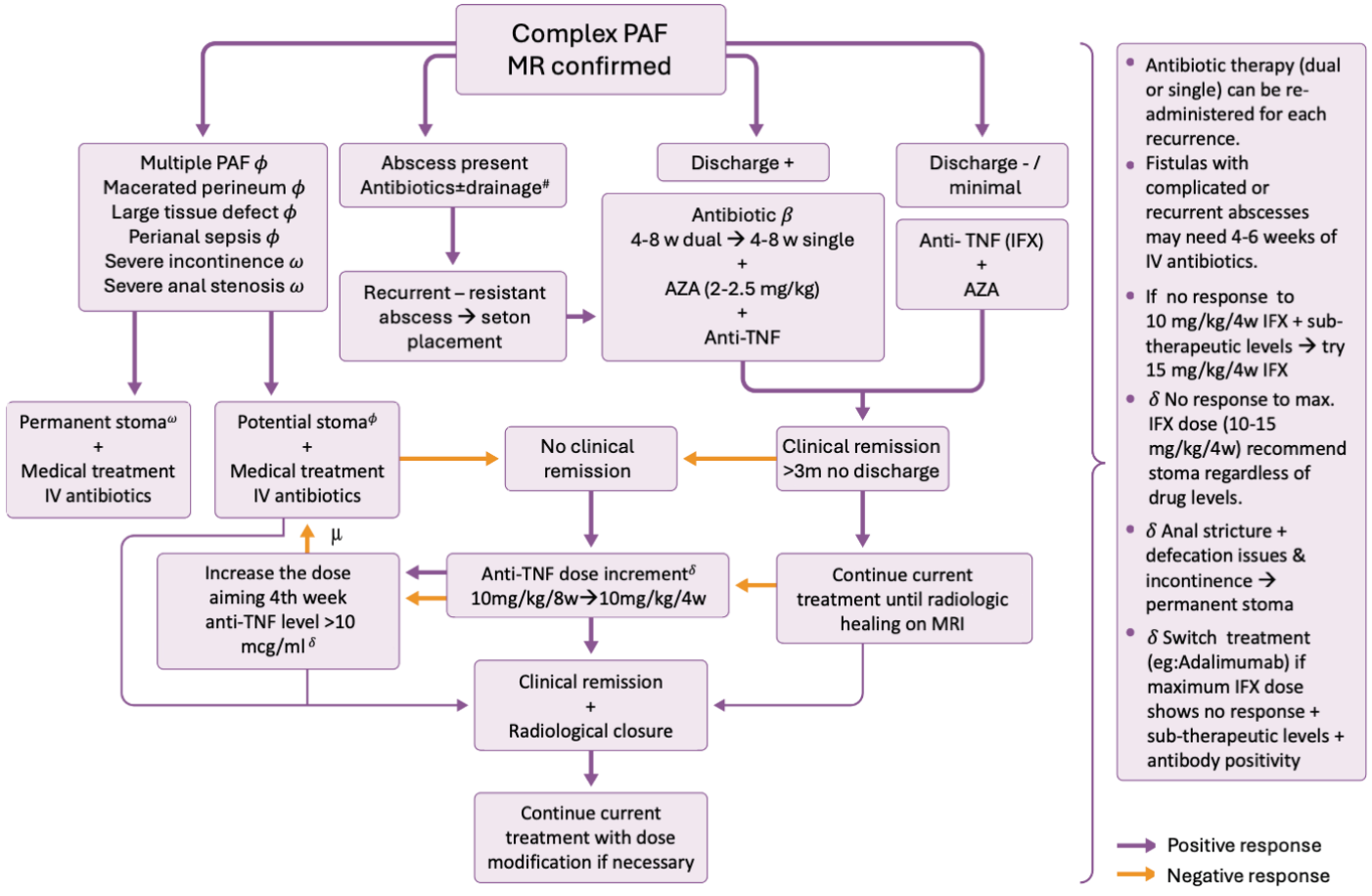

Figure 2. Treatment strategies for complex perianal fistulas

Clinical response should be reassessed after 2–4 weeks of antibiotic therapy to determine the need for AZA and anti-TNF therapy, as well as to evaluate overall treatment response. This strategy is particularly relevant for patients with simple perianal fistulas, mild luminal disease characterized by aphthous ulcerations, or isolated perianal involvement. In such cases, fistula management with AZA alone—without anti-TNF agents or prolonged antibiotic use—may be feasible. In more complex situations, AZA and anti-TNF therapy should be introduced alongside antibiotic treatment as early as possible.

For patients presenting with clinical remission (no drainage for >3 months) and no signs of abscess, we do not recommend initial antibiotic therapy. In such cases, if MR fistulography indicates the presence of an abscess, it is advisable to reassess whether it is a <1 cm abscess or an enlarged fistula tract using clinical and laboratory findings (CRP, leukocytes) and, if necessary, evaluate further with anal ultrasonography.

Our recommendation, under the conditions mentioned above, is to initiate dual antibiotic therapy for 4–8 weeks and then, in patients who respond, continue with a single agent for the following 4–8 weeks. This duration can be modified based on early and late treatment success, extending to 8–12 weeks or shortening as needed.

In cases where patients have not received antibiotics initially but have responded clinically during the induction phase and the transition to maintenance (12–14 weeks) with the anti-TNF + AZA combination, and in fistulas that rarely drain, we suggest antibiotics could be used later to help achieve clinical remission.

Short-term and/or non-combined antibiotic therapy may prevent us from fully understanding the behavior of the fistula and could lead to unstable and frequently repeated antibiotic use. Recurrence in clinical response following the discontinuation of antibiotics, while continuing combination therapy, is a common occurrence.

If clinical remission is not achieved within the expected time frames using combination therapy, it may be necessary to consider extending or repeating dual antibiotic therapy, independent of any dose modifications of anti-TNF or AZA, while ensuring close monitoring.

It is crucial to remember that all drugs used in the treatment of inflammation, particularly in combined fistula therapy, carry a potential for hepatotoxicity. This risk can be amplified, especially with dual antibiotic therapy, and patients should be closely monitored for toxicity.

In cases of chronic kidney disease, in children or young patients whose bone development is incomplete, and in pregnant or breastfeeding patients, the use of ciprofloxacin or other antibiotics from the same class should be avoided.

For elderly patients with a history of frequent hospitalizations, particularly those on long-term combination immunosuppressive therapy, it is recommended to check for *Clostridium difficile* toxin A/B positivity in stool samples. However, aside from close monitoring, we do not recommend that toxin A/B positivity necessarily change the treatment plan unless there is a clear indication.

IMMUNOMODULATORS IN TREATMENT

While immunomodulators such as thiopurines (AZA, 6-mercaptopurine [6-MP]) can improve symptoms, their effects on fistulas are limited, and closure rates are low. Recurrences are common. Although they can be partially effective in treating perianal fistulas,[22] the main expectation from these drugs lies in their synergistic effects when used in combination therapy. Experience with methotrexate in the treatment of perianal fistulas is more limited compared to AZA. It is primarily used in the treatment of luminal disease or to enhance the efficacy of anti-TNF therapy rather than specifically for fistulas.[12,23]

Although some studies suggest no advantage of combining immunomodulators with anti-TNF compared to anti-TNF alone, observational studies highlight that the combination is associated with higher clinical response rates.[24,25] In these studies, the lack of data on anti-TNF levels makes it unclear whether the contribution of immunomodulators is related to reducing anti-TNF immunogenicity or maintaining therapeutic drug levels. Given the refractory and complication-prone nature of perianal fistulas associated with Crohn's disease, the use of immunomodulators in combination with anti-TNF therapy, along with dose optimization, should be considered the best available treatment until better alternatives are found. Even though AZA is considered the weakest link in combination therapy, we do not recommend discontinuing or reducing the dose of AZA before 12 months in refractory fistulas or before radiological closure in responding cases, unless there are contraindications such as toxicity.

ANTI-TNF IN TREATMENT

Data regarding the effectiveness of current biologics in fistula treatment come from subgroup analyses of phase trials, which were not specifically designed for perianal fistula treatment.[25,26] These cross-sectional results primarily assess response rates and may not fully reflect success in real-world clinical practice.

Among the anti-TNF agents, IFX stands out due to the advantage of intravenous administration and weight-based dosing. Induction therapy with IFX has been shown to be associated with a reduction in drainage and clinical response,[27] and maintenance therapy has been linked to the continuation of remission.[25] These findings suggest that IFX is a key agent in both the induction and long-term management of perianal fistulas in CD.

At different stages of treatment (post-induction / during maintenance), varying IFX serum levels (6–15 μg/ml) have been associated with treatment response in fistulas.[28,29] One challenge with IFX levels is that the recommended levels generally define remission but provide little guidance on the initial treatment levels required to induce fistula closure. Additionally, the IFX serum levels reported for fistula response are often higher than those for luminal disease success. Therefore, no clear upper limit has been defined for supra-therapeutic IFX levels in patients demonstrating clinical response or remission. Also, similarly for Adalimumab, serum drug levels associated with fistula response and closure appear to be higher than those described for endoscopic response and remission.[28,30,31]

Anti-TNF agents have been considered the cornerstone in treating perianal fistulas for over 25 years. Therefore, it is recommended not to abandon a new regimen without sufficient observation, especially when dose escalation or increased dosing frequency is still an option. In perianal fistula treatment, we recommend assessing the efficacy of each dose after at least three applications following the induction phase. For an 8-week interval regimen, this assessment should occur at 6 months, while for a 4-week interval regimen, it should occur at 3 months.

In cases where clinical response is absent or minimal, extending the duration of treatment should be considered. The decision to continue

treatment should be based on patient adherence, the degree of response, improvement over time, and the consistency of combination therapy. For patients who do not achieve clinical remission after at least three doses of anti-TNF, we recommend checking serum anti-TNF levels to ensure they are within the therapeutic range (>10 µg/ml) before making any decisions about dose escalation or modifications. Before increasing the dose to 10 mg/kg every 4 weeks, it may be recommended to first increase the dose to 15 mg/kg every 8 weeks as an intermediary dose. This offers a lower intermediate dose and allows for a transition to 10 mg/kg every 4 weeks. However, this decision should be made based on how close the serum level at week 8 on the 10 mg/kg dose is to the target. Additionally, it may be more difficult to justify this intermediate dose in terms of cost-effectiveness compared to the 10 mg/kg/4-week regimen under reimbursement systems.

Although testing for anti-TNF antibodies is dependent on resources, it is recommended in clinical practice to check for antibodies in patients with unexpectedly low levels who are non-responsive or not in clinical remission. If there is anti-TNF antibody positivity, especially in patients with insufficient clinical response, changing the anti-TNF agent may yield better results. For patients who do not achieve clinical response or remission at 10 mg/kg/4 weeks and are below the therapeutic anti-TNF level, increasing to 15 mg/kg every 4 weeks should be considered.

If anti-TNF antibody positivity is present along with sub-therapeutic levels, switching to subcutaneous adalimumab (40 mg weekly after induction) may be recommended, particularly for patients who have shown clinical response but not clinical remission. The question of whether 80 mg weekly adalimumab will yield better results in patients who do not respond well to 40 mg weekly is based on individual clinical observations, even in luminal disease treatment. Therefore, in patients who are responding clinically but have sub-therapeutic drug levels, it may be worth trying this approach as the only known effective treatment option to optimize anti-TNF use.

At the 3rd and 6th months of anti-TNF therapy, clinical evaluation should be conducted, and if clinical response or remission is achieved, a radiological evaluation (perianal MR fistulography) at the 6th month may be appropriate for managing dose escalation or combination therapy components. Otherwise, in the absence of complications like perianal abscess, we do not recommend perianal MR fistulography without achieving clinical remission. Documenting each newly developed perianal abscess or fistula tract with MR fistulography helps redefine the clinical situation and assists the surgeon with decisions on drainage or seton placement.

In patients without clinical response, MR fistulography has limited impact on clinical decisions, aside from evaluating abscesses. If clinical remission is present, healing can be confirmed and monitored with MR fistulography. It should also be noted that even when inflammation is reduced in clinical remission, full healing on MR fistulography may take 12-24 months or longer.

Perianal ultrasound (US), especially when performed with an anal probe in IBD clinics, could serve as an alternative to perianal MR fistulography. However, since it is operator-dependent and requires preparation, it may not be suitable for high-volume clinics. In clinics where these issues are not a concern, US can be an effective alternative for monitoring the progress of fistulas identified on MR fistulography and in follow-up evaluations.

OTHER BIOLOGICAL TREATMENTS

The role of vedolizumab (VED) in perianal fistula treatment is not as prominent as IFX and ADA studies have primarily focused on anti-TNF non-naive patients, there is still insufficient data to recommend widespread use of VED in perianal CD after anti-TNF failure.[32]

Another relatively new biological agent used in the treatment of CD is ustekinumab (UST). Experience with UST in perianal fistula treatment is limited.[33] While s have reported reductions in drainage or low closure rates that are not objectively measurable, and while it has been suggested that UST may be beneficial for anti-TNF-refractory perianal fistula patients with treatment optimization, the magnitude of this response and its true efficacy remain unconvincing for now.

Upadacitinib (UPA) is a selective JAK1 inhibitor that has recently found a place in the clinical treatment of both UC and CD. The evaluation parameters of fistula-related outcomes from subgroup analyses of phase trials are not convincing enough for clinicians, and the long-term follow-up results do not provide significant findings (the proportion of patients achieving clinical remission of the fistula and a ≥50% reduction in fistula drainage at week 12 was higher with UPA compared to placebo).[34]

SURGICAL TREATMENT

Despite medical therapy, including biologics, up to 60% of patients with perianal fistulas require perianal surgical intervention. A multidisciplinary approach and surgical techniques play a crucial role in managing these cases.[2]

The majority of complex fistulas are located in such a way that fistulectomy or fistulotomy would likely result in fecal incontinence. Therefore, the choice of surgical procedure is based on the complexity and location of the fistula, with an emphasis on minimizing the risk of sphincter damage. Due to the potential for complications, particularly in the perianal area, the presence of an experienced IBD surgeon is critical in determining the chances of successful surgical treatment.

For complex perianal fistulas that have fistulized to the bladder or vagina, medical therapy should follow surgical intervention. Although there have been isolated successes in achieving clinical response with combined medical therapy, relapses are not uncommon. High-output vaginal or bladder fistulas should be promptly evaluated for elective surgical treatment, with post-operative medical therapy considered.

SETON

Approximately 80% of fistulas are associated with perianal abscesses, making incision and drainage the most common initial surgical intervention.[35] In addition to drainage, non-cutting setons are used to reduce the recurrence of abscesses and the formation of new fistula tracts.[36] However, setons alone are not curative and typically require further intervention, which underscores the importance of concurrent medical therapy.[37,38]

In cases where MR fistulography reveals abscesses smaller than 2 cm, and if no additional complications are present, we believe that these abscesses can be managed with close monitoring and combined antibiotic therapy without drainage. Although the theoretical concern of unnecessary abscess drainage potentially creating artificial fistulas is somewhat speculative, it is still worth considering.

The timing for seton removal should be individualized for each patient. There are concerns that leaving the seton in place for too long could de-

lay closure, however, it may be necessary to prevent recurrent abscesses. For patients without a history of recurrent abscesses, those who have had their first drainage, or those who have experienced spontaneous drainage, observing without placing a seton may provide an opportunity to assess the early behavior of the abscess and fistula, allowing for better evaluation of treatment effectiveness and management expectations during follow-up.

In patients with a seton placed under complicated conditions, once infection, inflammation, and drainage are under control (low output, drainage every other day or less), removal of the seton can be considered. If a seton placed during abscess drainage has led to no reformation of the abscess under the seton, we believe it is appropriate to remove the seton at the start of maintenance therapy to facilitate faster closure.

The lack of consensus on seton removal timing is related to the highly variable anatomical and clinical behavior of perianal fistulas. In cases of uncertainty, allowing a loose seton to fall out spontaneously is a common and acceptable approach in most patients.

In patients with horseshoe fistulas and/or branching fistulas with multiple external openings, the seton placed in the most clinically significant tract can guide the timing of seton removal. For fistulas with multiple tracts and setons, each tract should be evaluated individually following the above principles. In such cases, it is recommended to remove each seton in a controlled manner, allowing sufficient time to evaluate clinical outcomes. For multiple long-standing fistulas (>6 months), the first seton to be removed should be the one in a tract where MR fistulography shows reduced or resolved activity.

It is important to remember that in some patients who are unresponsive to treatment and exhibit frequent abscess formation, leaving the seton in place long-term or even permanently may be the only treatment option. Therefore, in patients who have experienced recurrent complications after previous seton removal, or those who have no drainage or controlled drainage while living without issues under the seton, permanent seton placement with periodic monitoring and replacement may be the most appropriate treatment approach.

FISTULOTOMY

Fistulotomy involves opening the fistula along its length and removing the epithelialized tract. It is highly effective in treating superficial, low intersphincteric, and low transsphincteric fistulas that involve less than 33% of the sphincter.[39] Although high healing rates (up to 80%) have been reported, recurrence rates can reach up to 15%. Special attention should be paid to the risk of incontinence in patients with a short anal canal, significant external sphincter involvement, or ongoing diarrhea.[40]

OTHER APPROACHES

Ligation of the Intersphincteric Fistula Tract (LIFT): This is another surgical option for treating transsphincteric fistulas and certain complex fistulas passing through the intersphincteric area. A cut is made in the intersphincteric groove, and the internal and external openings of the fistula are identified and ligated.[41] However, complex fistulas are often not candidates for this approach.

Endorectal Advancement Flap: This is a surgical option that does not create cutaneous wounds and preserves the sphincter complex. The procedure involves curettage of the tract and suturing, followed by creating a flap to cover the internal opening of the fistula, allowing the external opening to drain and heal on its own.[39] While success rates of up to 60% have been reported in suitable patients, there is a risk of incontinence, especially when thick flaps are used. Flaps are not suitable for every patient and should be considered individually in cases where there is healthy mucosa available for the flap, often in patients with a single tract and orifice, whose drainage and inflammation are partially controlled with medical therapy.

LOCAL PERIANAL TREATMENTS

Local stem cell therapy (Darvadstrocel) has been used in studies for patients where the internal opening of the fistula can be closed. The unexpectedly high placebo response in these studies has raised concerns that the success could be attributed to the accompanying surgical procedure, and that the outcomes seen in routine practice may not be achievable without surgery (clinical remission at 104 weeks: 40% vs. 56%).[42]

DIVERSION AND PROCTECTOMY

Achieving complete healing in perianal fistulas is not always possible, making diversion and proctectomy viable treatment options for more severe, resistant cases. In patients who do not respond adequately to maximized combination medical therapy, creating a stoma may increase clinical and radiological closure rates of perianal fistulas. In cases of severe disease, diversion with a stoma can buy time to prevent proctectomy. This period provides an opportunity to manage infectious complications and optimize medical therapy. For patients with perianal fistulas who also require intestinal resection due to satellite involvement, considering a stoma is particularly important, as it helps control fistula drainage that may increase due to the output surge caused by primary anastomosis.

While diversion often results in a high rate of early clinical response, recurrences of perianal fistulas are not uncommon when continuity of the colon is restored without radiological closure of the fistula. In patients with frequent perianal abscesses, convincing the patient to accept an early stoma can reduce the risk of anal fibrosis and increase the chances of radiological fistula closure.[43] We believe that radiological closure, not just clinical closure, of the perianal fistula (i.e., no activity seen on MR fistulography) should be the key indicator for deciding when to reverse the stoma. This period typically ranges from 6 to 24 months but may be longer. For patients who have not yet achieved radiological remission on MR fistulography, it is important not to close the stoma and to explain to the patient how this decision impacts the future success of the treatment. In patients with radiological fistula closure, the anti-TNF dose may be reduced based on response, but we do not recommend discontinuing therapy entirely. We also suggest continuing MR fistulography follow-up at least once 6 months after radiological fistula closure to confirm sustained remission before ceasing MR fistulography monitoring.

In complicated cases where the perianal region is highly prone to complications such as maceration, abscesses, and/or multiple fistula tracts, making the stoma the first step of treatment—along with IV antibiotics, local antifungal treatments, anti-inflammatory agents (e.g., oxidized zinc), and negative pressure therapy combined with the previously discussed medical regimen—may be the only way to stabilize the patient. This clinical situation should be managed collaboratively by dermatologists, experienced Crohn's surgeons, and/or plastic surgeons.

In patients with a partial diversion stoma who do not exhibit clinical response or achieve full clinical remission despite optimal combination medical therapy and antibiotics, converting the stoma to a full diversion may be effective in achieving clinical response and remission,

especially if frequent passage of stool through the rectum persists. For patients with a stoma created to control complications, the decision to close the stoma should be based on whether radiological closure has been achieved, complications have been controlled, and the extent of the negative impact of complications on the patient's quality of life (e.g., incontinence, rectal stricture). In cases of resistant perianal fistulas, despite a stoma and maximal medical therapy, proctectomy and permanent stoma may be unavoidable. Continuous combination medical therapy following stoma creation should be maintained, and further evaluations should follow the treatment principles.

CONCLUSION

Perianal fistula treatment is a combined aggressive therapy that should begin as soon as possible after evaluation (perianal MR fistulography, perianal ultrasound, and examination under anesthesia). In patients with perianal fistulas complicated by abscess, drainage and combination antibiotic therapy should be prioritized.

For perianal fistulas complicated by an abscess for the first time, if the abscess is not developing in the pelvic floor, showing multiple external openings, or leading to maceration or complications, seton placement can be delayed until the abscess recurs. This approach may shed light on the behavior of the fistula and avoid issues related to seton-induced closure delays and the timing of seton removal.

Initial treatment of the fistula with dual antibiotic therapy for 2-4 weeks, followed by evaluation of clinical response (based on response or lack of response to antibiotics), can serve as a positive indication of the potential success of combination therapy. Following this, anti-TNF and AZA should be added, with efficacy evaluated at 12-14 weeks. If necessary, increasing the anti-TNF dose and/or shortening the dosing interval should be considered.

Starting antibiotic therapy as a dual regimen for 4-8 weeks and, if there is a response, continuing with single-agent therapy for the next 4-8 weeks can help control the negative effects of early antibiotic discontinuation while maintaining the continuous efficacy of combination antibiotic therapy. This duration can be adjusted based on the individual patient's needs. This treatment strategy emphasizes timely intervention, personalized therapy, and careful monitoring of the response, aiming for long-term resolution of perianal fistulas while minimizing complications.

Given the wealth of experience with IFX and its advantage of weight-based dosing, IFX is often the first choice as an anti-TNF agent for perianal fistula treatment. Due to the lack of evidence on other biologics and current treatment agents outside of anti-TNF for perianal fistula treatment, the primary goal should be the optimization of anti-TNF therapy to achieve clinical response and remission. Before transitioning to a different biological agent or treatment, it is important to ensure that sufficient time has been given to the maximum possible dose of IFX (10-15 mg/kg every 4 weeks) combined with AZA (2.5 mg/kg) and antibiotics. Measuring serum drug levels and considering clinical response can help prevent abandoning combination therapy prematurely.

Clinical remission only represents the first sustained response achieved with combination therapy at the current dose. It may not reflect deep healing and anatomic closure of the fistula. Thus, radiographic remission should be the primary goal before considering tapering or extending treatment intervals. It is recommended that MR fistulography be repeated based on clinical indicators during follow-up, with MR fistulography only requested if there is significant clinical improvement, worsening, or complications. Once radiological remission is confirmed via MR fistulography, a second MR within 6 months is advised to avoid incomplete evaluations and to detect early radiological recurrences.

In cases where perianal fistulas present with severe complications (multiple abscesses, maceration, tissue defects, severe incontinence, or anal stricture), prioritizing a stoma will positively impact all outcomes.[8] For high-output fistulas where medical combination therapy is limited or ineffective, convincing the patient to undergo stoma creation and keeping the stoma in place until radiological closure is achieved should be the principle.

For patients with a stoma created to manage complications, the decision to close the stoma should be based on whether radiological closure has occurred, whether complications are controlled, and the extent to which the complications negatively impact the patient's quality of life (e.g., incontinence, rectal stricture). In patients with a partial diversion stoma who are not responding to optimal combination medical therapy and have frequent rectal stool passage, converting the stoma to a full diversion with patient consent may be effective in achieving clinical response and remission.

A clear and rational discussion about the pros and cons of stoma closure, emphasizing the potential consequences, is crucial. This is particularly important in patients with coexisting anal fibrosis and/or fecal incontinence. Any perianal fibrosis present before or developed during the stoma period should be carefully identified and discussed with the patient.

Even if radiological closure of perianal fistulas is achieved, the potential problems of a newly developed fibrotic anal canal should be discussed in detail with the patient, emphasizing the possibility of requiring a permanent stoma. It is essential to ensure that the patient fully understands this necessity.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – O.K.B., A.F.Ç.; Design – O.K.B.; Data Collection and/or Processing - O.K.B.; Literature Review – O.K.B.; Writing – O.K.B., A.F.Ç.; Critical Review – A.F.Ç.

Use of AI for Writing Assistance: Not declared.

Conflict of Interest: The authors have no conflicts of interest to declare.

Funding: The authors declared that this study received no financial support.

REFERENCES

1. Munster LJ, Mönnink GLE, van Dieren S, et al. Fistulizing perianal disease as a first manifestation of Crohn's disease: A systematic review and meta-analysis. *J Clin Med*. 2024;13(16):4734. [CrossRef]
2. Brochard C, Rabilloud ML, Hamonic S, et al. Natural history of perianal Crohn's disease: Long-term follow-up of a population-based cohort. *Clin Gastroenterol Hepatol*. 2022;20(2):e102-e110. [CrossRef]
3. Parks AG, Gordon PH, Hardcastle JD. A classification of fistula-in-ano. *Br J Surg*. 1976;63(1):1-12. [CrossRef]
4. Banasiewicz T, Eder P, Rydzewska G, et al. Statement of the expert group on the current practice and prospects for the treatment of complex perirectal fistulas in the course of Crohn's disease. *Pol Przegl Chir*. 2019;91(1):38-46. [CrossRef]
5. Sandborn WJ, Fazio VW, Feagan BG, Hanauer SB; American Gastroenterological Association Clinical Practice Committee. AGA technical review on perianal Crohn's disease. *Gastroenterology*. 2003;125(5):1508-1530. [CrossRef]
6. Morris J, Spencer JA, Ambrose NS. MR imaging classification of perianal fistulas and its implications for patient management. *Radiographics*. 2000;20(3):623-637. [CrossRef]

7. Lionetti P, Bronzini F, Salvestrini C, et al. Response to infliximab is related to disease duration in paediatric Crohn's disease. *Aliment Pharmacol Ther*. 2003;18(4):425-431. [CrossRef]
8. Parian AM, Obi M, Fleshner P, Schwartz DA. Management of perianal Crohn's disease. *Am J Gastroenterol*. 2023;118(8):1323-1331. [CrossRef]
9. Torres J, Bonovas S, Doherty G, et al. ECCO Guidelines on therapeutics in Crohn's disease: Medical treatment. *J Crohns Colitis*. 2020;14(1):4-22. [CrossRef]
10. Geldof J, Iqbal N, LeBlanc JF, et al. Classifying perianal fistulising Crohn's disease: An expert consensus to guide decision-making in daily practice and clinical trials. *Lancet Gastroenterol Hepatol*. 2022;7(6):576-584. [CrossRef]
11. White I, Karki C, Geransar P, Leisle L, Junker S, Fleshner P. Impact of seton use on clinical, patient-reported, and healthcare resource utilization outcomes in complex Crohn's perianal fistulas: A systematic literature review. *Inflamm Bowel Dis*. 2024:izae186. [CrossRef]
12. Rayen J, Currie T, Gearry RB, Frizelle F, Eglinton T. The long-term outcome of anti-TNF alpha therapy in perianal Crohn's disease. *Tech Coloproctol*. 2017;21(2):119-124. [CrossRef]
13. Sangwan YP, Rosen L, Riether RD, Stasik JJ, Sheets JA, Khubchandani IT. Is simple fistula-in-ano simple?. *Dis Colon Rectum*. 1994;37(9):885-889. [CrossRef]
14. Ng SC, Plamondon S, Gupta A, et al. Prospective evaluation of anti-tumor necrosis factor therapy guided by magnetic resonance imaging for Crohn's perineal fistulas. *Am J Gastroenterol*. 2009;104(12):2973-2986. [CrossRef]
15. Vuyyuru SK, Solitano V, Singh S, et al. Scoring indices for perianal fistulising Crohn's disease: A systematic review. *J Crohns Colitis*. 2024;18(6):836-850. [CrossRef]
16. Van Assche G, Vanbeckevoort D, Bielen D, et al. Magnetic resonance imaging of the effects of infliximab on perianal fistulizing Crohn's disease. *Am J Gastroenterol*. 2003;98(2):332-339. [CrossRef]
17. Adler J, Lin CC, Gadepalli SK, Dombkowski KJ. Association between steroid-sparing therapy and the risk of perianal fistulizing complications among young patients with Crohn disease. *JAMA Netw Open*. 2020;3(6):e207378. [CrossRef]
18. Savoye-Collet C, Savoye G, Koning E, Dacher JN, Lerebours E. Fistulizing perianal Crohn's disease: Contrast-enhanced magnetic resonance imaging assessment at 1 year on maintenance anti-TNF-alpha therapy. *Inflamm Bowel Dis*. 2011;17(8):1751-1758. [CrossRef]
19. Bell SJ, Halligan S, Windsor AC, Williams AB, Wiesel P, Kamm MA. Response of fistulating Crohn's disease to infliximab treatment assessed by magnetic resonance imaging. *Aliment Pharmacol Ther*. 2003;17(3):387-393. [CrossRef]
20. Lee MJ, Parker CE, Taylor SR, et al. Efficacy of medical therapies for fistulizing Crohn's disease: Systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2018;16(12):1879-1892. [CrossRef]
21. Klag T, Goetz M, Stange EF, Wehkamp J. Medical therapy of perianal Crohn's disease. *Viszeralmedizin*. 2015;31(4):265-272. [CrossRef]
22. Pearson DC, May GR, Fick GH, Sutherland LR. Azathioprine and 6-mercaptopurine in Crohn disease. A meta-analysis. *Ann Intern Med*. 1995;123(2):132-142. [CrossRef]
23. Mahadevan U, Marion JF, Present DH. Fistula response to methotrexate in Crohn's disease: A case series. *Aliment Pharmacol Ther*. 2003;18(10):1003-1008. [CrossRef]
24. Bouguen G, Siproudhis L, Gizard E, et al. Long-term outcome of perianal fistulizing Crohn's disease treated with infliximab. *Clin Gastroenterol Hepatol*. 2013;11(8):975-981.e814. [CrossRef]
25. Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med*. 2004;350(9):876-885. [CrossRef]
26. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: The CHARM trial. *Gastroenterology*. 2007;132(1):52-65. [CrossRef]
27. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med*. 1999;340(18):1398-1405. [CrossRef]
28. Gu B, Venkatesh K, Williams AJ, et al. Higher infliximab and adalimumab trough levels are associated with fistula healing in patients with fistulising perianal Crohn's disease. *World J Gastroenterol*. 2022;28(23):2597-2608. [CrossRef]
29. Yarur AJ, Kanagala V, Stein DJ, et al. Higher infliximab trough levels are associated with perianal fistula healing in patients with Crohn's disease. *Aliment Pharmacol Ther*. 2017;45(7):933-940. [CrossRef]
30. Miranda EF, Nones RB, Kotze PG. Correlation of serum levels oaf anti-tumor necrosis factor agents with perianal fistula healing in Crohn's disease: A narrative review. *Intest Res*. 2021;19(3):255-264. [CrossRef]
31. Plevris N, Jenkinson PW, Arnott ID, Jones GR, Lees CW. Higher anti-tumor necrosis factor levels are associated with perianal fistula healing and fistula closure in Crohn's disease. *Eur J Gastroenterol Hepatol*. 2020;32(1):32-37. [CrossRef]
32. Ayoub F, Odenwald M, Micic D, et al. Vedolizumab for perianal fistulizing Crohn's disease: Systematic review and meta-analysis. *Intest Res*. 2022;20(2):240-250. [CrossRef]
33. Nagano K, Tsuchiya H, Asano T, Yamazaki H, Tominaga S, Matsumoto T. Safety and effectiveness of ustekinumab for Crohn's disease with perianal manifestations: Ad hoc analysis data from 1-year post-marketing surveillance study in Japan. *Crohns Colitis 360*. 2024;6(2):otae035. [CrossRef]
34. Shehab M, De Marco D, Lakatos PL, Bessissow T. The potential for medical therapies to address fistulizing Crohn's disease: A state-of-the-art review. *Expert Opin Biol Ther*. 2024;24(8):733-746. [CrossRef]
35. Fichera A, Michelassi F. Surgical treatment of Crohn's disease. *J Gastrointest Surg*. 2007;11(6):791-803. [CrossRef]
36. Feroz SH, Ahmed A, Muralidharan A, Thirunavukarasu P. Comparison of the efficacy of the various treatment modalities in the management of perianal Crohn's fistula: A review. *Cureus*. 2020;12(12):e11882. [CrossRef]
37. Wasmann KA, de Groof EJ, Stellingwerf ME, et al. Treatment of perianal fistulas in Crohn's disease, seton versus anti-TNF versus surgical closure following anti-TNF [PISA]: A randomised controlled trial. *J Crohns Colitis*. 2020;14(8):1049-1056. [CrossRef]
38. Tanaka S, Matsuo K, Sasaki T, et al. Clinical advantages of combined seton placement and infliximab maintenance therapy for perianal fistulizing Crohn's disease: When and how were the seton drains removed? *Hepatogastroenterology*. 2010;57(97):3-7.
39. Gecse KB, Bemelman W, Kamm MA, et al. A global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulising Crohn's disease. *Gut*. 2014;63(9):1381-1392. [CrossRef]
40. Murtaza G, Shaikh FA, Chawla T, Rajput BU, Shahzad N, Ansari S. Fistulotomy versus fistulectomy for simple fistula in ano: A retrospective cohort study. *J Pak Med Assoc*. 2017;67(3):339-342.
41. Rojanasakul A, Pattanaarun J, Sahakitrungruang C, Tantiphlachiva K. Total anal sphincter saving technique for fistula-in-ano; the ligation of intersphincteric fistula tract. *J Med Assoc Thai*. 2007;90(3):581-586.
42. Garcia-Olmo D, Gilaberte I, Binek M, et al. Follow-up study to evaluate the long-term safety and efficacy of darvadstrocel (mesenchymal stem cell treatment) in patients with perianal fistulizing Crohn's disease: ADMIRE-CD phase 3 randomized controlled trial. *Dis Colon Rectum*. 2022;65(5):713-720. [CrossRef]
43. Lightner AL, Click B, Yamamoto T, Spinelli A, Kotze P. Management of isolated anal strictures in Crohn's disease. *Dis Colon Rectum*. 2020;63(12):1639-1647. [CrossRef]