Indian Journal of Gastroenterology (January–February 2024) 43(1):48–63
https://doi.org/10.1007/s12664-024-01524-2

NARRATIVE REVIEW

Perianal fistulizing Crohn's disease: Current perspectives on diagnosis, monitoring and management with a focus on emerging therapies

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Received: 20 November 2023 / Accepted: 2 January 2024 / Published online: 3 February 2024

Abstract

Crohn's disease (CD), a chronic inflammatory bowel disorder, manifests in various phenotypes, with fistulizing perianal CD (CD-PAF) being one of its most severe phenotypes. Characterized by fistula formation and abscesses, CD-PAF impacts 17% to 34% of all CD cases and with a significantly deleterious impact on patient's quality of life, while increasing the risk for anorectal cancers. The pathogenesis involves a complex interplay of genetic, immunological and environmental factors, with cytokines such as tumor necrosis factor-alpha (TNF-α) and transforming growth factor-beta (TGF-β) playing pivotal roles. Diagnostic protocols require a multi-disciplinary approach including colonoscopy, examination under anesthesia and magnetic resonance imaging. In terms of treatment, biologics alone often prove inadequate, making surgical interventions such as setons and fistula surgeries essential. Emerging therapies such as mesenchymal stem cells are under study. The South Asian context adds layers of complexity, including diagnostic ambiguities related to high tuberculosis prevalence, healthcare access limitations and cultural stigma toward perianal Crohn's disease and ostomy surgery. Effective management necessitates an integrated, multi-disciplinary approach, especially in resource-constrained settings. Despite advances, there remain significant gaps in understanding the disease's pathophysiology and a dearth of standardized outcome measures, underscoring the urgent need for comprehensive research.

Keywords Crohn's disease · Magnetic resonance imaging · Perianal fistula · Treatment outcome · Tumor necrosis factor inhibitors

Introduction

Perianal fistulizing CD (CD-PAF) is a type of Crohn's disease (CD) with penetrating presentation in the perianal area, due to fistula formation with or without abscesses and associated with frequent relapses [1]. Its incidence varies from 17% to 34% of those with CD, especially co-existent in distal CD. In 5% of CD patients, perianal fistula is the only manifestation [2]. Another 10% manifest other perianal symptoms such as stenosis, fissures and skin tags [2, 3]. Persistent symptoms and treatment processes associated with CD-PAF have been shown to negatively influence both—quality of life and overall well-being in patients, as evidenced by long-term studies, while simultaneously being associated with high healthcare costs [4]. Moreover, individuals with CD-PAF are at an increasing risk of developing cancer in the anorectal region [5, 6]. In recent years, South and South East Asia have seen a notable rise in inflammatory bowel disease (IBD) incidence. India, despite having a lower prevalence compared to Western countries, might carry the largest global burden of IBD due to its significant size of its population [7]. However, knowledge about the epidemiology and risk factors for IBD in South Asia remains limited [8]. In Asia, perianal CD prevalence ranges from 18% to 24.8%, according to Asia Pacific Crohn's and Colitis Epidemiology Study and a study from Hong Kong [9]. Indian studies

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show a 6.9% to 40% prevalence of CD-PAF [10–13]. CD-PAF is as prevalent in Asian populations as in western countries [14–16].

Pathogenesis

The pathogenesis of CD-PAF is yet to be fully clarified, but current understanding points toward genetic factors and inappropriate immune responses to gut microbes. Heightened levels of cytokines such as tumor necrosis factor-alpha (TNF-α) and transforming growth factor-beta (TGF-β and interleukin-13 (IL-13) have been implicated in fistula pathogenesis (Fig. 1) [17]. Variables contributing to increased risk include colorectal disease with rectal involvement, younger age at onset, male sex, longer disease course and extraintestinal manifestations [4, 18, 19]. The existing literature offers scant insight into the role of microbiota in CD-PAF. Preliminary studies show a unique microbial signature associated with CD-related perianal fistulas, distinct from the microbiota in mucosa and stool samples of the same patients [20]. The number and species of Gram-positive organisms are notably higher in CD-related fistulas compared to cryptoglandular fistulas [21, 22]. Advances in tissue metabolomics also point toward altered amino acid and lipid metabolism [23].

Diagnosis of perianal Crohn's disease

Classification

Multiple frameworks exist for categorizing CD-PAF, yet the Parks classification remains prevalent in clinical practice. This schema delineates the anatomical relationship of the fistulas with both internal and external anal sphincter (Fig. 2). However, it has limitations such as not delineating abscesses, secondary fistula tracts, concurrent proctitis and anorectal strictures [24]. The American Gastroenterological Association (AGA) introduced a refined classification framework in its technical review, which distinguishes perianal fistulas into simple and complex categories (Fig. 3), where complex fistulas are high fistulas (relative to levator ani), have multiple external openings or have associated perianal

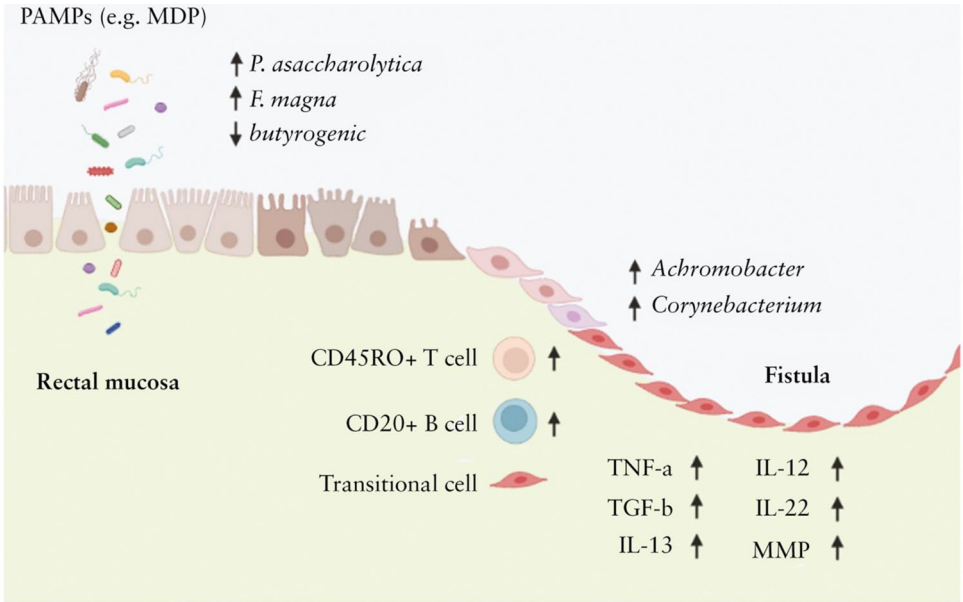


Fig. 1 The pathophysiology of perianal fistulizing Crohn's disease. A mucosal epithelial defect likely services as an initiating event, which is followed by the influx of several pathogen-associated molecular patterns (PAMPs) including muramyl dipeptide (MDP). The bacterial stimuli may lead to enrichment of CD45RO+ T cells and CD20+ B cells and activated transitional cells (myofibroblasts). Those cells produce cytokines including tumor necrosis factor (TNF)-α, transforming growth factor (TGF)-β and interleukin (IL)-13, IL-12 and IL-22 that probably sustain chronic inflammation and activate genes involved in the epithelial-mesenchymal transition (EMT). Elevated expression of matrix metalloproteinases (MMPs) enhance cell invasion and lead to fistula formation. The fistula tract preferentially harbors bacterial populations such as Achromobacter and Corynebacterium, which may contribute to the progression and maintenance of perianal fistulas. Increased abundances of *Porphyromonas asaccharolytica* and *Finegoldia magna*, two bacteria associated with opportunistic soft tissue infection and abscess formation, were found in the rectal mucosa of pediatric patients with perianal CD, compared with children without perianal disease or healthy individuals. In contrast, a decreased butyrogenic potential was found in mucosa-associated microbiome of children with perianal CD. Reproduced with permission.

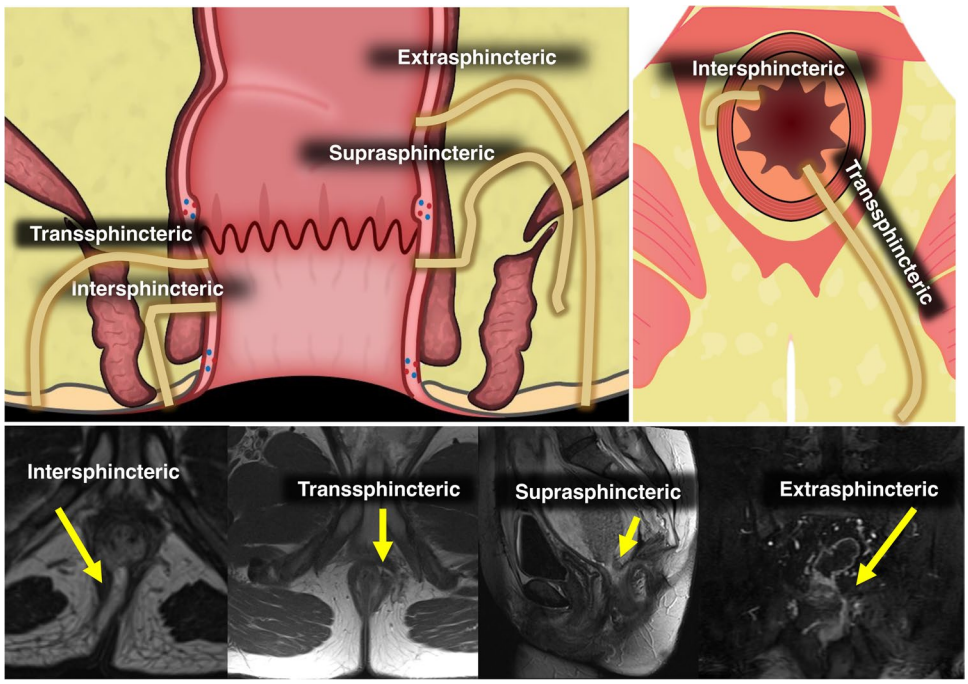


Fig. 2 Parks classification of perianal fistulizing Crohn's disease

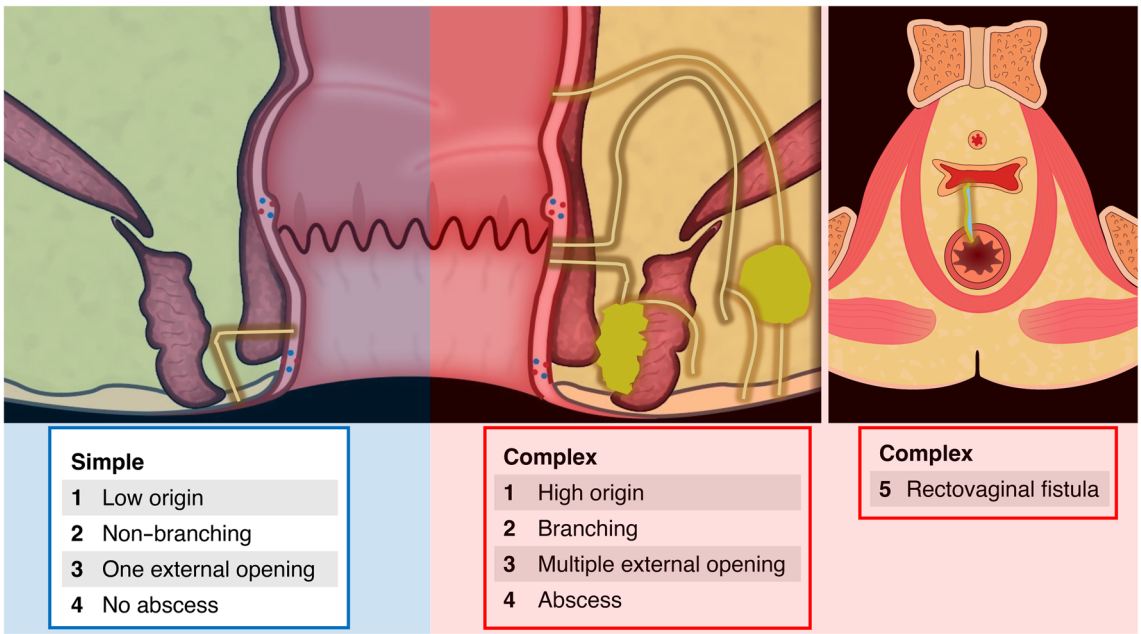
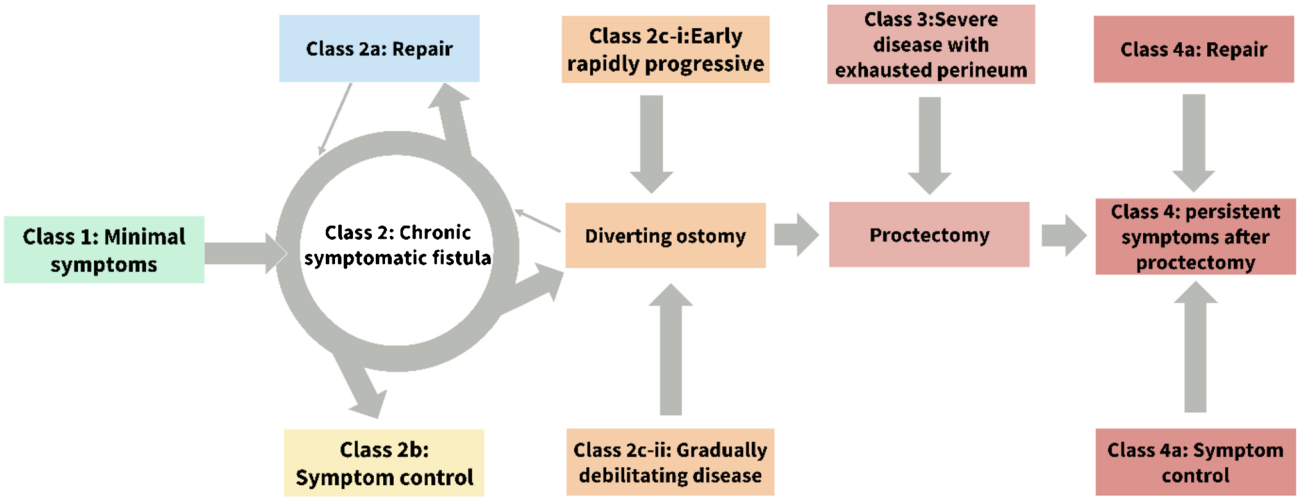


Fig. 3 American Gastroenterological Association Classification of perianal fistulizing Crohn's disease

abscess, rectovaginal fistula or anorectal stricture [25]. A new expert consensus-based classification system for CD-PAF was recently put forth by Geldof et al. to standardize clinical trial methodologies and provide recommendations for patient management. This system categorizes patients into four clusters based on factors such as disease severity, treatment outcomes and therapeutic goals (Fig. 4). This is constructed to guide both medical and surgical interventions and can be adapted as the disease course or therapeutic goals shift with an emphasis on collaborative decision-making. The system is still in the preliminary stage, awaiting validation through prospective real-world applications [26].



Geldof Classification	Criteria
Class 1: Minimal symptoms	Minimal to no perianal symptom burden whose disease requiring no fistula specific intervention
Class 2a: Repair	Chronic symptomatic fistula in patients seeking definitive closure whose disease is amenable to procedural correction including seton removal, fistulotomy, fibrin glue, bioprosthetic plug, mucosal advancement flap, ligation of the intersphincteric fistula tract (LIFT), or stem cell therapy
Class 2b: Symptom control	Chronic symptomatic fistula either not amenable to definitive procedural closure or whose documented goal is symptom control and do not require more advanced procedural intervention such as diverting ostomy or proctectomy
Class 2ci: Early rapidly progressive disease	Severely symptomatic fistula defined by disease progression due to primary or secondary non-response to medical and surgical therapy within 12 months of symptom onset that require diverting ostomy or total proctectomy for symptom control
Class 2cii: Gradually debilitating disease	Severely symptomatic fistula defined by disease persistence or progression for greater than 12 months despite medical and surgical therapy greater than 12 months after symptom onset that require diverting ostomy or total proctectomy for symptom control.
Class 3: Severe disease with exhausted perineum	Uncontrolled symptomatic fistula with irreversible perineal destruction despite prior diverting ostomy requiring total proctectomy for symptom control
Class 4a: Repair	Persistent symptoms despite prior proctectomy in patients seeking definitive sinus closure whose disease is amenable to surgical closure
Class 4b: Symptom control	Persistent symptoms despite prior proctectomy either not amenable to definitive surgical closure or documented goal is symptomatic control

Fig. 4 Geldof et al. classification of perianal fistulizing Crohn's disease

Diagnostic tools

The diagnosis of CD-PAF involves a multi-disciplinary approach. During examination, signs such as erythema, induration, visible fluctuant swelling, external openings and fistula discharge can be observed. Various diagnostic modalities exist, yet accurately delineating the fistula tracts' anatomy and ruling out perianal abscesses are essential for devising targeted treatment strategies. Colonoscopy, examination under anesthesia (EUA) and magnetic resonance imaging (MRI) pelvis with fistula protocol form the diagnostic triad for CD-PAF [25, 27, 28]. Colonoscopy assesses luminal inflammation; EUA enables anatomical description and abscess management; MRI provides detailed imaging and proctitis assessment. Endoanal ultrasound and transperineal ultrasound are secondary options in centers with appropriate expertise, but otherwise limited in performance in non-expert hands [29]. Combining any of these imaging modalities with EUA enhances diagnostic accuracy [27].

MRI pelvis fistula protocol is often performed without and with intravenous contrast. The key sequences are shown in Table 1. Pelvic MRI can be performed as a stand-alone examination or paired with an MR enterography. In an MRI fistula protocol, the key sequences are the multi-planar, small field-of-view T2 turbo spin echo images focused on the anal canal. Contrast does add value with better identification of the site of communication with the internal sphincter [30]. If a patient cannot receive MRI contrast, the non-contrast sequences of an MRI pelvis fistula protocol often provide diagnostic information. MRI provides superior

Table 1 Sequences in a magnetic resonance imaging of the pelvis fistula protocol

Phases	Description
T2 (HASTE)	• HASTE - coronal and transverse • Transverse – 4-mm slice, 1-mm gap
Dixon (chemical shift)	• In- and opposed phase, water- and fat-only • Transverse
T2 (small FOV)	**Key sequences** **Turbo-spin echo** Coronal, sagittal and transverse • Coronal - cover pelvic inlet side to side, all the way through rectum • Sagittal - cover mid rectum through perineum • Transverse - cover mid rectum through perineum
Diffusion	• B50, B500, B1000 and ADC map
T2 (fat saturation)	• Transverse - cover mid rectum through perineum
Pre-contrast T1 VIBE	• Coronal – cover kidney, kidneys, ureters, and bladder
Post-contrast	Inject contrast: Dotarem @ 2 mL/s Transverse, coronal, and sagittal acquisitions. • Dynamic contrast (transverse) - arterial, portal venous and equilibrium • Subtractions of the transverse sequences
T2 3D (small FOV)	**Key sequence** **T2 SPACE** • Transverse - cover mid rectum through perineum

resolution compared to CT [31]. A patent fistula tract on CT may not be distinguishable from a linear area of soft tissue thickening. In contrast, MR can delineate the nature of the fistula tract (patent, fibrotic or patent centrally with a fibrotic outline). For CD-PAF patients with acute symptoms presenting in the emergency department, CT serves as an alternative to MRI, particularly for identifying actionable perianal abscesses [31]. In addition to contra-indications to MRI and acute presentations, CT may be used over MRI if CD-PAF patient cannot lie still in an MRI bore.

Assessment of fistula activity

The evaluation of fistula activity can be executed both clinically and radiologically. Clinically, the Perianal Disease Activity Index (PDAI) is most utilized [32]. Crohn's Anal Fistula Quality of Life (CAF-QoL) is a new validated patient-reported outcome measure (PROM) which is a 28-item questionnaire that complements objective clinical evaluation of fistula by capturing impact on the patient [33]. It has shown good internal consistency (Cronbach's alpha 0.88), excellent stability (intraclass correlation 0.98) and good responsiveness and construct validity, for use as a PROM in research and clinical practice.

MRI indices are shown in Table 2. Van Assche et al. proposed an MRI pelvis-based index incorporating fistula anatomy with MRI findings of inflammation [34]. Both these indices are partially validated and necessitate further substantiation. Recently, a newer MRI pelvis index, namely magnetic resonance novel index for fistula imaging in CD (MAGNIFI-CD), has been developed and internally validated using the ADMIRE CD study cohort with greater predictive accuracy for long-term fistula closure [35]. The Image Kids study developed a pediatric-specific MRI index called the Pediatric MRI-based perianal Crohn's disease (PEMPAC) index to evaluate CD-PAF. This index created using data from 95 pelvic MRIs (65 for derivation, 31 for validation), to assess disease activity and severity. PEMPAC effectively distinguishes between remission and active disease and has good responsiveness to change [36]. An example scoring of the three indices is shown in Fig. 5. The MRI indices are not currently used in routine clinical practice, but are more likely to be first utilized in clinical trials evaluating therapeutics in CD-PAF.

Conventional management

For the management of CD-PAF, a multi-disciplinary approach is crucial to include gastroenterologists, colorectal surgeons and abdominal radiologists. This section reviews current medical and surgical approaches to managing CD-PAF at initial presentation (Fig. 6) and if refractory to initial therapy with an anti-TNF (Fig. 7), after drainage of a perianal abscess and appropriate antibiotic usage.

Antibiotics

The use of ciprofloxacin and metronidazole for six to 12 weeks in most studies play a role in fistula healing and improve the quality of life; but the supporting data comes from non-randomized small, open-label and observational studies. Prolonged administration of antibiotics heightens

Table 2 Radiological scoring indices developed for magnetic resonance imaging of the pelvis in perianal fistulizing Crohn's disease

MRI Variables	PEMPAC [2021]		MAGNIFI-CD [2019]		mVAI [2017]	
Score range	**0–41** ○ **Remission: < 10** ○ **Active: ≥ 10** ○ **Severe: ≥ 30** ○ **Response: change ≥ 4**		**0–25**		**0–19.5**	
	Item Score		Item Score			
Fistula number	None	0	None	0		
	Single	4	Single, unbranched	3		
	Multiple	8	Complex	6		
Fistula location	None	0				
	Intersphincteric	3				
	Transsphincteric	6				
	Extrasphincteric	9				
	Transsphincteric/intersphincteric	12				
Fistula length	None	0	< 2.5 cm	0		
	0.1 - 2.5 cm	2	2.5 - 5 cm	2		
	2.6 - 5.0 cm	4	> 5 cm	4		
	> 5.0 cm	6				
Extension			Absent	0	Absent	0
			Horseshoe	2	Infralevator	1.5
			Intralevator or supralevator	4	Horseshoe	3
					Supralevator	4.5
Dominant feature			Fibrous	0	Fibrous	0
			Granulation tissue	2	Granulation tissue	1.2
			Fluid or pus	4	Fluid or pus	2.4
Rectal wall involvement					Normal	0
					Thickened	1
					Increased signal intensity	2
Inflammatory mass	Absent	0	Absent	0	Absent	0
			Focal	1	Diffuse	1.2
			Diffuse	2	Focal	2.4
	Present > 3 mm	11	Small collection	3	Small collection	3.6
			Medium collection	4	Medium collection	4.8
			Large collection	5	Large collection	6
Maximal T2 hyper-intensity	None	0			Absent	0
	Mild	2			Mild	2.3
	Pronounced	4			Pronounced	4.6
Hyperintensity of primary tract on postcontrast T1-weighted images			Absent or mild	0		
			Pronounced	2		

Bold entries shows the total number of score ranges before the description of each component and emphasizes which number shows remission, active, severe, and response

the potential for adverse outcomes [37–40]. However, on cessation of antibiotics, recurrence of most fistula has been observed, suggesting against the use of antibiotics alone in the management of CD-PAF [41]. However, antibiotics have a role when used in combination with thiopurines [38]. AGA guidelines similarly recommend using biologic agents in combination with oral antibiotics (during the induction phase), rather than relying solely on biologics, for achieving fistula remission in CD-PAF based on randomized double-blind, placebo-controlled trials and meta-analysis, including various anti-TNFs [39, 40, 42–44].

Immunomodulators

A recent systematic review and meta-analysis of RCTs suggest a limited benefit of immunomodulators. However,

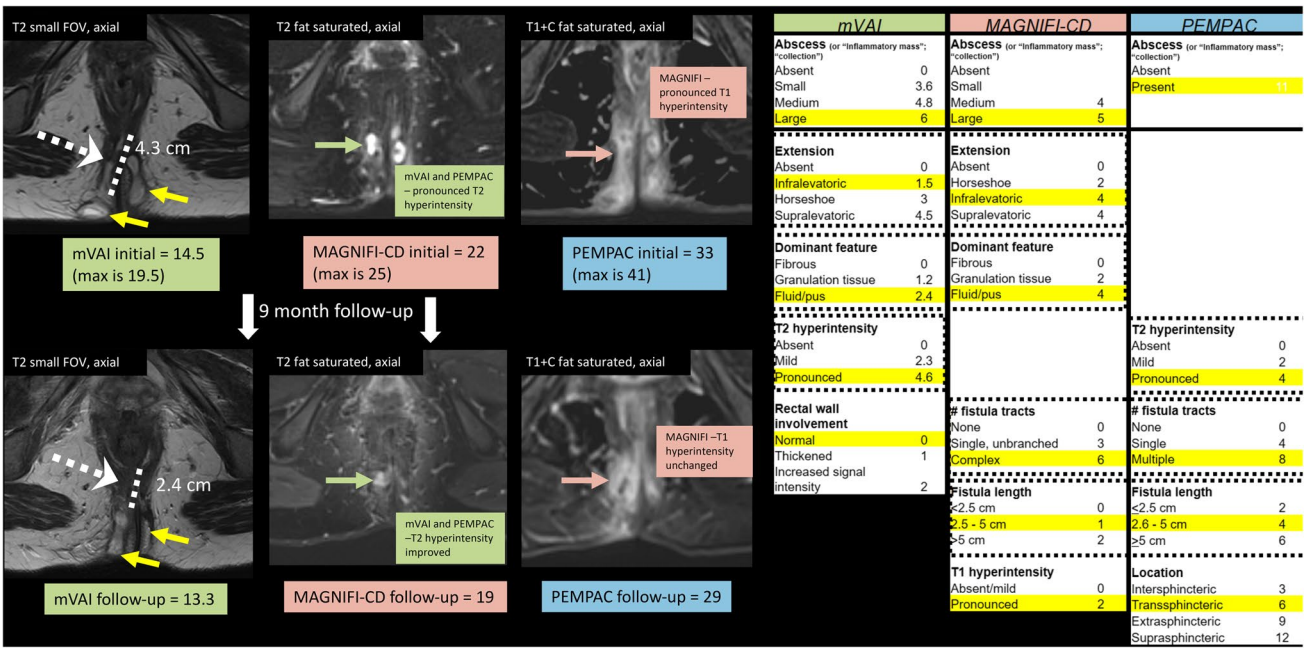


Fig. 5 Application of perianal fistulizing Crohn's disease magnetic resonance imaging (MRI) pelvis scoring systems. Left panel: initial MR images (top row) demonstrate a 4.3-cm trans-sphincteric perianal fistula feeding bilateral perineal abscesses. Initial MR scores for this baseline MR are mVAI = 14.5, MAGNIFI-CD = 22, and PEMPAC = 33. Follow-up MR images (bottom row) demonstrate smaller length of a now 2.4-cm trans-sphincteric perianal fistula feeding bilateral perineal abscesses. The bilateral perineal abscesses are both larger, but the largest already qualified as a "large" abscess for mVAI and MAGNIFI-CD. As the fistula appearance has changed from primarily fluid/pus to more peri-fistula fibrosis with a central patent tract (granulation tissue appearance), the MR scores for all three scoring systems decreased compared to prior. Follow-up MR scores for this nine-month MR are mVAI = 13.3, MAGNIFI-CD = 19 and PEMPAC = 29. Right panel: factors in the three highlighted MR scoring systems. Common factors between the scoring systems are highlighted with solid and dashed black boxes. Yellow highlighted factor indicates which score was chosen for the initial MR

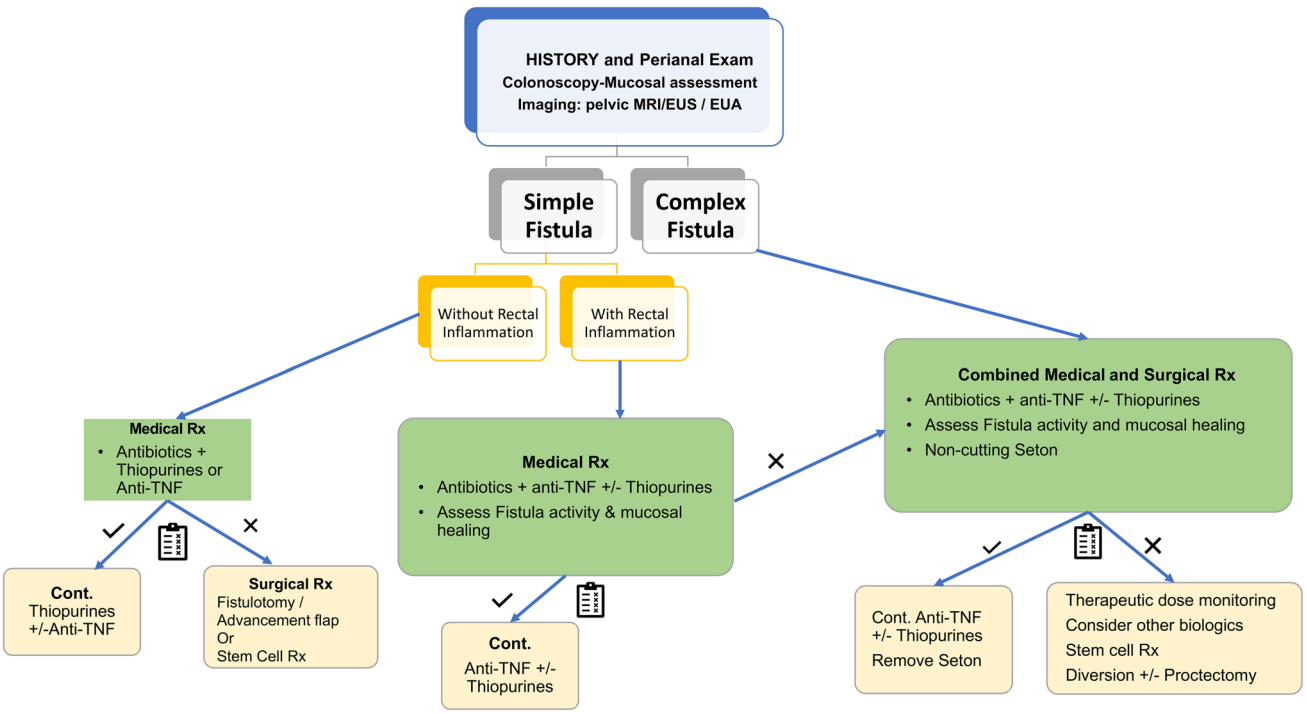


Fig. 6 Flowchart for the initial management of a new patient with perianal fistulizing Crohn's disease

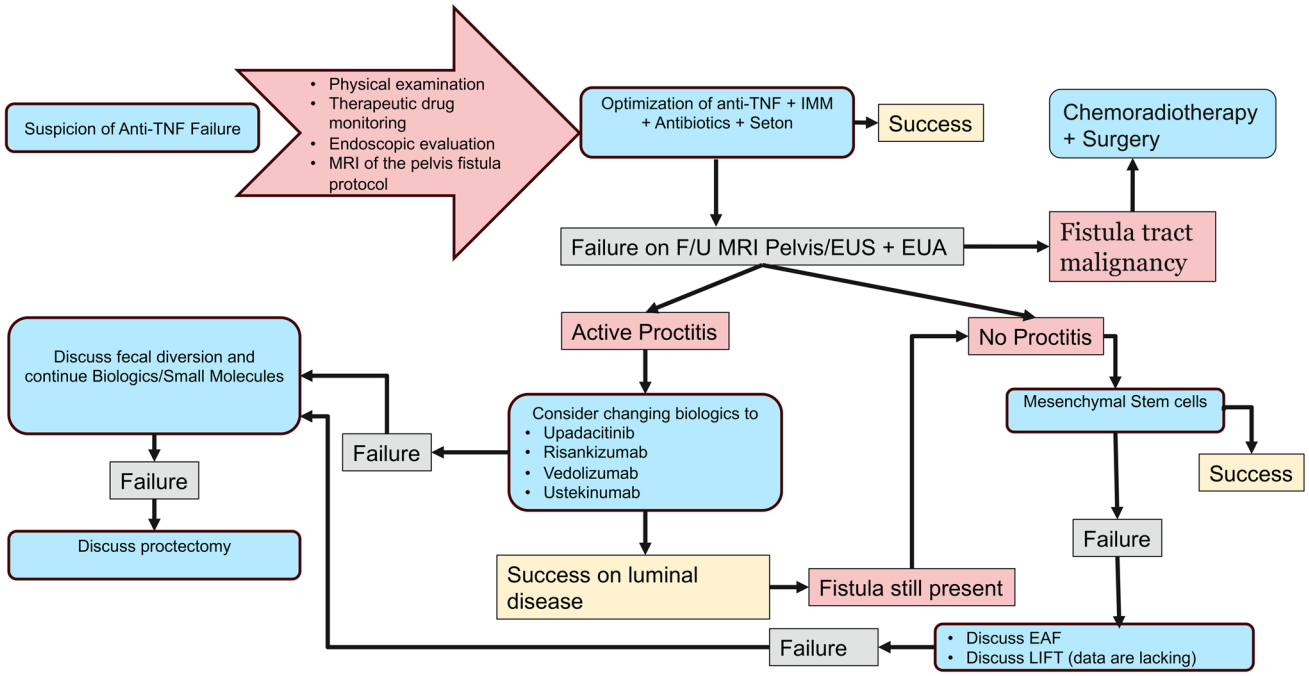


Fig. 7 Flowchart for management of a patient with perianal fistulizing Crohn's disease refractory to anti-TNFs

evidence from cohort studies and case series presents a more optimistic view of thiopurines' potential in the management of CD-PAF [44, 45]. A pediatric CD cohort reported fistula closure in 40% of patients [46], while real-world data from India noted fistula closure rates of 25% with immunomodulators (azathioprine, 6-MP or methotrexate [MTX]) [47]. A study by Mahadevan et al. reported that intra-muscular MTX weekly for 12 weeks resulted in fistula closure in 25% (4/16) of the patients and fistula improvement in 31% (5/16). It is noteworthy that many experienced fistulae relapse when switching to oral MTX or when the dose was lowered [48].

Biologics

Infliximab

Infliximab (IFX) was the first biologic and anti-TNF agent approved for CD [49]. Present et al. showed that IFX significantly reduced fistula drainage in 68% of Crohn's disease patients, compared to 26% in a placebo group [50]. Additionally, 55% achieved full fistula healing, with an NNT of 2.4, emphasizing its clinical utility in CD-associated perianal fistulas. In the context of sustaining response, as demonstrated in the ACCENT II RCT, the administration of IFX showed an elevated probability of maintaining a response for a year [51]. One crucial aspect of IFX is loss of treatment response, affecting nearly 50% of the patients, which is proven in recent PISA studies. There was a need for re-intervention in 42% of patients in the RCT group and 48% in the registry group, underscoring a decline in treatment response [52]. While most patients experienced alleviation of inflammation surrounding the fistula tracts, improved symptoms and reduced drainage, the fistula tracts remained open, seen both on MRI pelvis and anal endosonography [53, 54].

To maintain IFX effectiveness, strategies involve the use of thiopurines or methotrexate to prevent anti-IFX antibody formation, higher trough-level, combination with antibiotics during induction phase and multi-disciplinary management with a colorectal surgeon [55].

Adalimumab

Adalimumab (ADA) has not been studied in an RCT for its use in CD-PAF; however, numerous post-hoc analysis suggest its efficacy in CD-PAF. The CHARM trial found significant fistula closure at 26 and 56 weeks (30% vs. 13%, $p = 0.043$; 33% vs. 13%, $p = 0.016$) [56]. A one-year follow-up, open-label study showed 90% maintained healing at week 56 (ADHERE study) [57]. A meta-analysis reported 36% complete and 31% partial fistula closure with adalimumab [58]. ADA is more effective in anti-TNF-naïve patients, but also remains effective for CD-PAF even after IFX failure (CHOICE trial) [59].

Therapeutic drug monitoring of anti-TNFs

Newer research indicates higher serum anti-TNF levels may improve both clinical and radiological outcomes in CD-PAF

[60–62]. In a study involving 193 patients with CD-PAF on maintenance IFX or ADA, achieving radiologic healing had higher median drug levels (IFX: 6.0 vs. 3.9 µg/mL; ADA: 9.1 vs. 6.2 µg/mL) and those in radiologic remission also had higher median drug levels (IFX: 7.4 vs. 3.9 µg/mL; ADA: 9.8 vs. 6.2 µg/mL). Notably, as drug levels increased, there was a clear incremental improvement in radiologic outcomes, highlighting a positive correlation between anti-TNF drug concentration and radiologic healing in CD-PAF for both IFX and ADA [62]. In the absence of a clear cut-off, it is suggested to use therapeutic drug monitoring to achieve radiological fistula closure going beyond clinical fistula closure [63].

Ustekinumab

Data supporting the use of ustekinumab (UST) in CD-PAF comes from post-hoc analysis. In UNITI and CERTIFI studies, by week 22, those receiving UST had a 47% rate of clinical fistula healing, surpassing the 30% rate observed in the placebo group ($p = 0.33$) [64]. Moreover, a systematic review and meta-analysis illustrated UST's efficacy in inducing clinical fistula response, with rates of 40% at week eight and 56% at week 52, while maintaining a constant 17% clinical remission rate [65]. Additionally, UST showcased promising results in a French multi-center retrospective study (BioLap), where 40% of anti-TNF-experienced patients achieved fistula healing [66]. Currently, there is no data available on the trough drug levels of UST in relation to fistula response and remission rates.

Vedolizumab

In the post-hoc analysis of data from GEMINI II vedolizumab (VDZ) showed its effectiveness in fistula closure (31%) compared to placebo (11%) by week 52 (absolute risk reduction [ARR]: 19.7%; 95% CI, -8.9 to 46.2) [67]. In an open-label study, patients with moderate-severe CD with one to three perianal fistulae on MRI were randomized to two VDZ regimens, one with standard dosing at weeks 0, two, six, 14 and 22 and another with an additional week-10 dose. The primary endpoint was a ≥ 50% reduction in draining fistulae by week 30. Overall, 53.6% met this goal: 64.3% in the standard group and 42.9% in the week-10 dose group. Both regimens yielded sustained improvement, but the extra week-10 dose had no significant effect on outcomes. Safety profiles remained consistent with previous VDZ studies [68]. In a recent meta-analysis of four studies, encompassing 198 patients with active CD-PAF (87% failed anti-TNF therapy), pooled complete healing rate was 27.6% (95% CI, 18.9%–37.3%) with moderate heterogeneity ($I^2 = 49.4\%$) and pooled partial healing was 34.9% (95% CI, 23.2%–47.7%) with high heterogeneity ($I^2 = 67.1\%$) [69]. The combination of VDZ with UST or IFX has also demonstrated efficacy in inducing fistula healing, as evidenced by retrospective cohort studies and case reports [70–72]. The ideal trough levels for VDZ in luminal or perianal fistulizing disease are still unknown.

A network meta-analysis of 28 randomized controlled trials (RCTs) with 2239 patients evaluated treatments for fistulizing CD. IFX (5 mg/kg) demonstrated significant efficacy, with a relative risk (RR) reduction of 2.30 (95% CI, 1.40–3.77) at 16–24 weeks. UST emerged as the most effective treatment at 44 weeks, showing a 2.38-fold increase in efficacy (RR, 2.38; 95% CI, 1.24–4.56) over placebo. ADA also showed promise (RR, 2.06; 95% CI, 1.06–3.99). The results indicate potential roles for UST and ADA as alternatives to IFX, underscoring the need for future standardized RCTs for direct comparison [73].

Janus Kinase inhibitors

Upadacitinib

Upadacitinib (UPA) is the only Janus Kinase inhibitor approved for moderate-severe CD in the United States, Canada and in the E.U. In U-EXCEL and U-EXCEED trials, 1021 CD patients were randomized to UPA 45 mg or placebo (PBO) for 12 weeks. Responders entered a 52-week U-ENDURE trial on UPA 30 mg or 15 mg or PBO. Of enrollees, 143 had fistulas (86.7% perianal) and 54 had fissures at baseline. UPA outperformed placebo in fistula closure, draining resolution and fissure healing at 12 and 52 weeks. UPA yielded superior outcomes with no new safety concerns [74]. UPA appears to be a promising second-line therapy in those who have failed either IFX or ADA and do not have contra-indications for starting this therapy.

Filgotinib in the phase III DIVERSITY and phase II DIVERGENCE 2 trials did not meet their co-primary endpoints, despite promising phase-II results in the FITZROY trial [75–77]. Hence, it is not recommended to use filgotinib in the treatment of CD-PAF. Similarly, tofacitinib is also not approved for the treatment of moderate-severe Crohn's disease and consequently not recommended in the treatment of CD-PAF.

Hyperbaric oxygen therapy

The efficacy of Hyperbaric oxygen therapy (HBOT) has been evaluated in systematic review and meta-analysis, where it exhibited complete healing of the fistula in fistulizing Crohn's disease in 47.64% (22.05–74.54), while partial healing was noted in 34.29% (17.33%–56.50%) [78]. It may potentially have a role as a complementary therapy in

CD-PAF secondary to anti-inflammatory properties, with increased expression of growth factors and the mobilization of stem cells [79]. There are varying protocols with the most common method involving the inhalation of 100% oxygen at pressures exceeding the standard atmospheric level, on daily session, five days a week for four to eight weeks. However, there is risk of barotrauma.

Surgical management

Despite significant advancements in the medical treatment of perianal CD, surgical intervention continues to constitute a vital component of the therapeutic strategy. There is a likely advantage in synergistically employing surgical and medical therapies for CD-PAF, over the exclusive utilization of either method.

Seton

Following incision and drainage (I&D) of a perianal abscess, which in approximately 80% of cases is concomitantly present with the fistula formation, a non-cutting seton is often employed [80]. This seton serves to facilitate fistula maturation while concomitantly enhancing the efficacy of medical treatment. It also aims at minimizing the likelihood of recurrent abscess development and the emergence of new fistulous tracts [81].

Many studies have demonstrated proven benefits of placing a non-cutting seton prior to initiating a biologic and this is recommended by the current guidelines from the American College of Gastroenterology. It is advisable to place the seton prior to commencing IFX therapy and retain it throughout the induction of remission [82]. However, PISA-I demonstrated that seton treatment alone is not advisable for CD-PAF in a multi-center, pragmatic, randomized controlled trial that compared chronic seton drainage to long-term anti-TNF or surgical closure after anti-TNF induction. The seton treatment group had the highest re-intervention rate (10/15), compared to 6/15 in the anti-TNF group and 3/14 in the surgical closure group ($p = 0.02$). In PISA-II, patients with CD-PAF were randomized to a four-month anti-TNF therapy with surgical closure or a one-year anti-TNF therapy post-seton insertion. The primary endpoint was radiological healing at 18 months, measured by MRI (defined as a complete fibrotic tract or a MAGNIFI-CD score 0). Results demonstrated that 32% of patients in the anti-TNF plus surgical closure group achieved radiological healing, compared to 9% in the anti-TNF-only group ($p = 0.005$). While clinical closure rates were not statistically different between the groups, the need for reintervention was lower in the surgical group (13% vs. 43%, $p = 0.005$). In conclusion, short-term anti-TNF therapy with seton insertion, coupled with surgical closure, led to higher rates of long-term MRI healing than anti-TNF therapy alone with seton insertion, suggesting the advisability of this approach for eligible patients [52, 83]. It is crucial to note that both trials included patients with a single internal orifice and no proctitis. Therefore, the results may not apply to patients with multiple orifices or proctitis, which are common in clinical practice. The optimal timing for seton removal remains undefined; however, average fistula healing typically spans a duration of six to 12 weeks and may be subject to patient preference.

Fistulotomy

Fistulotomy entails the longitudinal opening and subsequent obliteration of the epithelialized fistula tract. It proves particularly efficacious in treating superficial and selective low inter-sphincteric and trans-sphincteric fistulas affecting less than one-third of the sphincter and without concomitant proctitis. Reported healing rates exceed 80%, with recurrence rates around 15%, irrespective of concurrent medical treatment; however, this only involved 35 patients [84, 85]. However, substantial incontinence risks persist for patients with specific conditions such as short anal canals or anterior fistulas in women, with persistent diarrhea and if there is significant external sphincter involvement [86].

Endorectal advancement flap

The endorectal advancement flap serves as an alternate surgical approach that preserves the integrity of the sphincter complex while eliminating the necessity for an external wound. The technique entails tract curettage, oversewing and the application of a flap to seal the internal fistula opening, thereby allowing for autonomous external healing [87]. In 64 patients with CD-PAF patients, overall success rates were similar for advancement flap (AF) and ligation of the inter-sphincteric fistula tract (LIFT) at 61% and 53%, respectively. However, incontinence rates were higher post-AF 7.8% compared to post-LIFT 1.6% with recurrence data being limited. The coexistence of proctitis and small bowel disease predicts an unfavorable post-operative prognosis, characterized by elevated rates of recurrence [88].

Other surgical options

The ligation of inter-sphincteric fistula tract (LIFT) procedure entails ligation of the fistula tract in the inter-sphincteric space, close to its internal opening, followed by excision and curettage of the tract. The external sphincter defect is then sutured. The method, initially introduced in 2007, shows a roughly 65% healing rate in CD-PAF over a 33-month follow-up period. Lateral incisions and longer fistulas appear to enhance long-term healing outcomes [89–91]. Video-assisted anal fistula treatment (VAAFT)

employs a fistula scope for direct visualization and cautery of the fistula tract, with minimal incontinence risk due to non-dissection of the sphincter complex [92]. However, the method is costly and time-consuming. Emerging in 2011, the method has reported success rates above 80% in brief, initial studies and is currently restricted to select facilities [93]. Each approach has merits, but further data is needed in CD-PAF for comprehensive efficacy assessment.

Diversion and proctectomy

In refractory cases, full healing is rarely achievable, necessitating fecal diversion or proctectomy. Fecal diversion acts as a short-term alternative, with only 10% to 17% achieving restoration despite early response rates of 60% to 80% [94, 95]. In a systematic review of 1578 refractory CD-PAF patients who underwent temporary fecal diversion, 61% showed clinical improvement—50% in the biologic era. Stoma reversal was attempted in 34% of patients, succeeding in 63% of these cases. Overall, 21% achieved successful bowel restoration, 24% in the biologic era, while 34% required permanent proctectomy. Factors such as post-diversion biologic use and absence of proctitis positively influenced successful bowel restoration. Thus, temporary diversion improved symptoms in half and restored bowel continuity in a quarter of patients in the biologic era [96].

Up to 20% of CD-PAF patients ultimately receive a proctectomy with a permanent stoma [97, 98]. Surgical risks involve wound healing complications, pelvic nerve damage and abscess formation [87]. Myocutaneous advancement flaps are commonly used for large perineal defects. Long-term success rates for proctectomies stand at 64%, with a potential for quality-of-life improvement [99].

Future perspectives in perianal fistulizing Crohn's disease

Mesenchymal stem cells (MSC) (Table 3) are multipotent cells with anti-inflammatory, anti-apoptotic, pro-angiogenic, proliferative and immunomodulatory properties, sourced from autologous or allogenic adipose tissue and bone marrow, which have shown promising results for fistula treatment [100–103]. Adipose tissue-derived MSCs are favored for their ease of harvest and elevated replication [104]. The ADMIRE-CD trial, which was completed in Europe, showed long-term closure rates of 56% at 104 weeks of follow-up with allogenic adipose-derived MSCs Darvadstrocel [105, 106]. Administration is through the removal of seton, curettage of tract, closure of internal opening of fistula and then injection of darvadstrocel. Darvadstrocel consists of 120 million cells formulated in 24 mL of culture medium in four vials of 6 mL. The formulated product can be stored between 15°C and 25°C for a maximum of 48 hours. The product is injected using a 20-G long needle, where the first half of the dose

Table 3 Summary of studies reporting stem cell therapy for perianal fistulizing Crohn's disease

Author	Year	Type of stem cell	Route	Primary outcomes
Reenaers et al. [108]	2023	Bone marrow-derived mesenchymal	Local injection	Clinical and MRI evolution in perianal fistulas
Lightner et al. [103]	2023	Allogeneic bone marrow derived	Phase IB/IIA study	Treatment efficacy for perianal fistulizing Crohn's disease
Garcia-Olmo et al. [106]	2022	Mesenchymal (Darvadstrocel)	Long-term safety and efficacy	ADMIRE-CD phase 3 trial results
Buscail et al. [100]	2021	Adipose derived	IV/injection	Clinical efficacy in perianal Crohn's fistulas
Lightner et al. [102]	2019	Autologous mesenchymal	Direct injection	Efficacy in refractory rectovaginal Crohn's fistulas
Herreros et al. [104]	2019	Stem cell therapy	Compassionate use stromal vascular fraction (SVF) was used in 31/52 (60%) cases, autologous expanded adipose-derived stem cells (Au-eASC) were employed in 9/52 (17%) and allogenic expanded adipose-derived stem cells (Allo-eASC) were employed in 12/52 (23%).	Efficacy in perianal fistula treatment
Dietz et al. [107]	2017	Autologous mesenchymal	Bio-absorbable matrix	Clinical efficacy in treatment of perianal fistulas
Panés et al. [105]	2016	Allogeneic adipose-derived mesenchymal	Phase 3 randomized trial	Efficacy for complex perianal fistulas

is injected via the anal canal into the tissue surrounding the sutured internal opening or openings; then, the other half is injected through the external opening or openings into the fistula walls (no deeper than 2 mm) all along the fistula tract or tracts, making several micro-blebs [105]. Other approaches, such as the STOMP trial, explore using MSC-coated fistula plugs, showing up to 80% early healing rates [107]. Despite variations in delivery and dosage, safety and efficacy are consistent. While darvadstrocel has European approval, the Phase 3 ADMIRE-CD II study evaluating darvadstrocel for complex CD-PAF failed to meet its co-primary 24-week remission endpoint. However, its safety profile remained consistent with previous studies, with no new safety concerns emerging. Real-world studies from Europe using darvadstrocel have matched the European trial experience. In a small study of 16 patients, at weeks 12 and 48, 9/16 and 8/16 patients had complete fistula[e] closure, respectively, whereas 11/16 patients had at least partial closure [108]. Radiological correlate was also observed where the degree of fibrosis increased significantly after MSC injection in MRI of the pelvis, where 86% of patients with > 80% of fibrosis of the fistula tract at week 48 had fistula closure. Additionally, fistula closure at week 12 was predictive of fistula closure at week 48.

Existing MSC studies in the context of CD-PAF often exclude those with active proctitis, even though over 50% of real-world cases manifest this condition. The treatment's effectiveness in this sub-group is unclear.

Challenges in CD-PAF care in South Asia context

Addressing IBD management in South Asia (SA) requires multi-faceted strategies to navigate clinical, economic and cultural barriers. Monitoring can be cost-effectively adapted by utilizing less expensive assays like C-reactive protein and fecal calprotectin, along with transperineal ultrasound imaging of CD-PAF, which is cheaper and avoids radiation risk [109, 110].

Treatment challenges in SA include limited specialized care, particularly for IBD, leading many patients to rely on corticosteroids or surgery. Availability and cost of advanced therapies such as biologics are further hurdles, made worse by poor health insurance coverage [109]. Treatment in SA often leans toward immunomodulators over biologics due to economic constraints. In a study of 807 CD-PAF patients, immunomodulators showed promise as an affordable first-line treatment, particularly where biologicals are not accessible. They demonstrated a 25% response rate, with a higher relapse rate observed in surgical interventions. The absence of perianal abscess was a positive predictor of treatment success [47]. NUDT15 Genotyping could enhance treatment safety, but is not yet widely accessible. Bio-similars offer a cost-saving alternative, warranting further research to assess their economic and clinical impact. Latent TB complicates the choice of biologics; oral therapies such as Janus kinase inhibitors emerge as less expensive, albeit with some risk for TB re-activation [111].

Cultural factors such as stigma of ostomy and the high use of Complementary and Alternative Medicine (CAM) contribute to delays in effective care and lower adherence to standard treatments [109]. Delayed care and lower adherence to therapies for refractory fistulizing IBD often necessitate surgical diversion, a strategy hampered by cultural resistance to surgery and stigmas surrounding ostomies, thereby increasing morbidity and mortality [112]. Additionally, there is a scarcity of surgeons specialized in IBD relative to the growing patient population [109].

South Asian American patient voice on CD-PAF

Recent studies highlight rising rates of CD-PAF among South Asian American patients [15, 16]. One of the authors on this (TAO), a patient with CD for 18 years, exemplifies this, experiencing multiple perianal and recto-vaginal fistulae. Initially diagnosed with ulcerative colitis, her condition progressed, leading to a total colectomy and temporary ileostomy. Cultural stigma influenced her treatment choices, with an emphasis on maintaining marriage prospects. Despite numerous surgeries and treatments, she faced persistent complications such as fistulae and abscesses. Her mental health suffered due to the stigma and medical trauma [113]. In 2015, she found relief with (UST), which brought her into remission. Similarly, in the IBDesis community (inferences drawn from a patient-driven online community that may not be generalizable), women with Crohn's prefer therapies with setons, less visible than an ostomy, to maintain marital prospects, sometimes leading to unforeseen difficulties post-marriage. This preference and associated stigma are also echoed in Middle Eastern/North African and LGBTQ+ communities. These narratives underscore the significant impact of cultural factors on treatment choices and outcomes for Crohn's patients.

In summary, CD-PAF profoundly impacts patients' personal and social well-being and poses a risk for malignancies. Despite these implications, treatment is often insufficient, partly due to unresolved questions about its pathophysiology. Efficacy data largely stems from luminal CD studies, highlighting the need for focused randomized controlled trials (RCTs) with standardized fistula remission definitions. Effective management requires a multi-disciplinary team for optimal clinical outcomes.

Author contribution Jalpa Devi: concept, initial draft and approval of final draft. David H. Ballard: concept, editing of draft and approval of final draft, Tina-Aswani Omprakash: editing of draft and approval of final draft, Alyssa M. Parian: editing of draft and approval of final draft. Parakkal Deepak: concept, initial draft and approval of final draft, study supervision and guarantor of article.

Data availability NA.

Declarations

Ethics approval and consent to participate NA.

Consent for publication NA.

Competing interests Jalpa Devi: no relevant conflicts of interest exist. David H. Ballard: research support from an Investigator-Initiated Study from Takeda Pharmaceuticals. Tina-Aswani Omprakash: no relevant conflicts of interest exist. Alyssa M. Parian: no relevant conflicts of interest exist. Parakkal Deepak: consultant or on an advisory board for Janssen, Pfizer, Prometheus Biosciences, Boehringer Ingelheim, AbbVie, Arena Pharmaceuticals, Boehringer Ingelheim, CorEvitas LLC and Scipher Medicine Corporation. He has also received funding under a sponsored research agreement unrelated to the data in the paper from Takeda Pharmaceutical, Arena Pharmaceuticals, Bristol Myers Squibb-Celgene and Boehringer Ingelheim.

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