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Original Article

A new protocolized treatment strategy optimizing medical and surgical care leads to improved healing of Crohn's perianal fistulas

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Abstract

Background and Aims: Crohn's perianal fistula healing rates remain low. We evaluated the efficacy of a protocolized multidisciplinary treatment strategy optimizing care in adults with Crohn's perianal fistulas.

Methods: A new treatment strategy was established at a single tertiary center. The strategy comprised 3 dynamic stages of care directed toward achieving and maintaining fistula healing. Stage A, active disease, focused on early commencement and proactive escalation of biologic therapies and structured surgical reviews ensuring adequate fistula drainage and conditioning. Stage B, optimized disease with a seton *in situ*, focused on consideration for seton removal and appropriateness of definitive surgical closure and/or ablative techniques. Stage C, healed disease, focused on proactive care maintenance. Sixty patients were sequentially enrolled and prospectively followed for ≥12 months. Endpoints included clinical healing and radiologic remission in those with clinically active fistulas, and relapse in those with healed fistulas.

Results: At baseline, 52% ($n = 31$) and 48% ($n = 29$) had clinically active and healed fistulas, respectively. For patients with clinically active fistulas, 71% achieved clinical healing after 22 months, with estimated healing rates of 39% and 84% at 1 and 2 years, respectively. Radiologic remission was achieved in 25%, significantly higher than baseline inclusion rates of 6%. For patients with healed fistulas, 7% experienced clinical relapse after 23 months, with no significant change in radiologic remission, 80% versus 86% at baseline.

Conclusions: A protocolized treatment strategy proactively optimizing care resulted in high rates of clinical healing and improved radiologic remission of Crohn's perianal fistulas. Controlled-matched studies are needed.

Key words: Crohn's disease; perianal fistulas; treatment optimization.

1. Introduction

Perianal fistulas are a morbid and common manifestation of Crohn's disease,[1] negatively impacting 26% of patients after 20 years of Crohn's disease diagnosis.[2] Standard care relies on a combination of medical and surgical treatments.[3–5] Anti-tumour necrosis factor-α (anti-TNF) drugs have revolutionized medical care, with infliximab having the greatest efficacy data and representing the mainstay of medical treatment.[3,4] However, despite being the best care, the rates of sustained fistula healing remain low, with only 54% achieving clinical healing in real-world practice.[6] The reasons for this are multifactorial, reflecting an inherently aggressive phenotype of Crohn's disease with limited treatment options.

From a medical treatment perspective, standard biologic prescribing uses streamlined fixed dosing regimens adopted

from luminal Crohn's disease, which fail to meet patients' individual needs for intensified dosing schedules.[6–8] There is also heterogeneity in escalation of biologic therapies due to a paucity of evidence guiding policy development. From a surgical treatment perspective, there is a lack of structured review for definitive surgical interventions and consensus regarding the optimal intervention to use, with resultant variability in practice and outcomes. Despite increasing evidence supporting techniques focused on ablation and closure of fistula tracts,[9] international practice preferences the use of setons as definitive surgical management,[10] an approach prohibitive of fistula healing.

Collectively, due to a lack of protocolized treatment strategies, there is variability in medical treatment and prescribing practices, variability in surgical treatment and therapeutic targets, and overall heterogeneity in standard care delivery; with care often only escalated following the emergence of complications such as perianal sepsis. There is a need to standardize practice to ensure the best outcomes are achieved.

A new protocolized multidisciplinary treatment strategy, incorporating early proactive optimization of medical and surgical care, is hypothesized to improve healing rates of Crohn's perianal fistulas, by offering a more targeted and potentially sustainable approach to care. We developed a new treatment strategy and evaluated its efficacy in real-world experience.

2. Materials and methods

2.1. Study design

An investigator-initiated prospective real-world single-arm cohort study was used to evaluate the efficacy of a new treatment strategy optimizing medical and surgical care. A new protocolized, multidisciplinary care model for adults with Crohn's perianal fistulas was established at a single tertiary referral center with a preexisting inflammatory bowel disease (IBD) service. The service included specialist IBD and colorectal surgery clinics, weekly IBD multidisciplinary meetings (gastroenterologists, colorectal surgeons, radiologists, and IBD nurses), weekly therapeutic drug monitoring multidisciplinary meetings (gastroenterologists, IBD nurses, and pharmacists), and an IBD nurse dedicated to overseeing the implementation of the new treatment strategy.

Ethics approval was obtained from *St Vincent's Hospital (Melbourne) Human Research Ethics Committee* (HREC-72046).

2.2. Patient selection

Adult patients with Crohn's perianal fistulas seen through the new care model, at the single tertiary referral center, were sequentially invited to participate, between March 1, 2021, and April 30, 2022. Patients were included irrespective of disease activity, disease duration, treatment experience, or duration of attendance through the baseline preexisting service. Patients with rectovaginal or rectovesical fistulas, complete proctectomies, or those pregnant or breastfeeding were excluded.

2.3. Intervention

The new treatment strategy implemented structured 3 monthly clinician reviews and a protocolized algorithm for managing patients with Crohn's perianal fistulas. The algorithm centralized around 3 stages of care, which were predetermined prior to study commencement after expert meetings involving specialist gastroenterologists, colorectal surgeons, and radiologists. Multiple focused meetings and discussions were undertaken during algorithm development, with decisions finalized using a consensus-based approach. The stages of care were based on clinical disease activity at a given time point, with the focus of care and recommended treatments changing as patients transitioned between stages (Figure 1).

Stage A patients had clinically active disease, defined as sepsis or actively draining perianal fistulas. Treatment focused on early optimization of medical and surgical therapies. Medical treatment optimization incorporated a systematic approach, whereby: (1) biologic therapies were commenced if not on treatment, with a preference for anti-TNF therapy, specifically infliximab, with ustekinumab and vedolizumab representing second- and third-line therapy in patients with anti-TNF refractory disease, respectively; (2) biologic therapies were dose escalated, initially using proactive drug levels for anti-TNF agents and subsequently using combined drug levels and clinical response, with clinical response assessed at the 3 monthly clinician reviews; and (3) biologic therapies were switched if continued inadequate response despite maximal dose escalation, with patients discussed at multidisciplinary meetings prior to switch. Patients prescribed an anti-TNF agent had drug levels requested every 12–16 weeks depending on the dosing interval. Infliximab trough levels <10.1 μg/mL and adalimumab levels <8.1 μg/mL were deemed suboptimal, leading to proactive dose escalation; with optimal target drug levels predetermined based on available retrospective and post-hoc analyses.[6–8] Escalated biologic dosing referred to any dosing regimen above conventional dosing, whether an increase in administered dose or a decrease in dosing interval. Maximally escalated biologic dosing referred to infliximab 10 mg/kg 4 weekly, adalimumab 80 mg weekly, ustekinumab 90 mg 4 weekly, and vedolizumab 300 mg 4 weekly. Surgical treatment optimization included structured colorectal surgeon reviews to facilitate: (1) early detection and drainage of sepsis, with insertion of setons; and (2) surgical conditioning of fistulas with the removal of granulation tissue and seton manipulation, where deemed appropriate at the discretion of the treating colorectal surgeon.

Stage B patients had clinically optimized disease, defined as minimally draining perianal fistulas with setons *in situ* after undergoing optimization of medical and surgical therapies. Treatment focused on consideration for seton removal and appropriateness of definitive surgical closure and/or ablative techniques, with patients discussed at multidisciplinary meetings and consensus recommendation guided by clinical and radiologic disease characteristics. Final surgical intervention was at the discretion of the treating colorectal surgeon in consultation with the patient. Medical treatment was proactively maintained throughout.

Stage C patients had clinical healing, defined as the absence of draining perianal fistulas with no seton *in situ*, whereby treatment focused on proactive care maintenance. Patients maintained 3 monthly clinician reviews irrespective of the duration of sustained clinical healing or radiologic remission, with the reemergence of symptoms or signs triggering early re-assessment of disease relapse. Patients prescribed an anti-TNF agent continued to have drug levels requested every 12–16 weeks, with suboptimal levels reviewed at

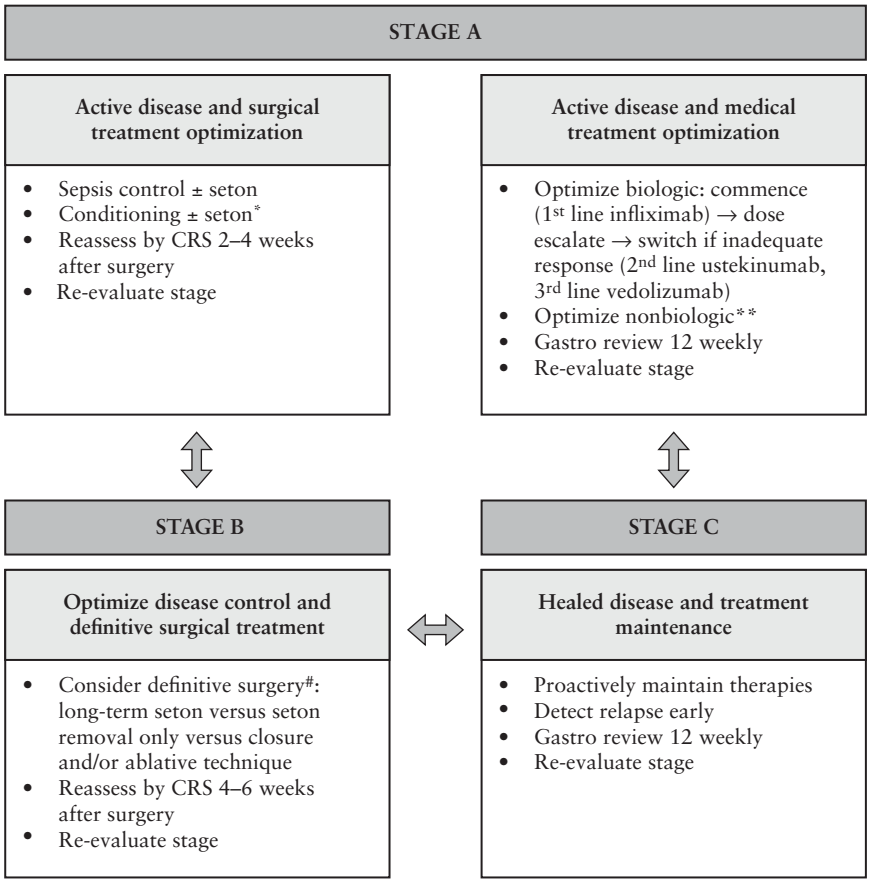

Figure 1. Schematic diagram of the new protocolized treatment strategy centralized around 3 stages of care. Abbreviations: CRS, colorectal surgeon; Gastro, gastroenterologist. *Tract curettage with removal of granulation tissue and manipulation of setons. **Optimize combined immunosuppressant therapy, particularly in the setting of anti-TNF agents, and consider antibiotics during biologic commencement. #Review clinical and radiologic disease characteristics at multidisciplinary meeting involving colorectal surgeons, gastroenterologists, and radiologists, to achieve consensus recommendation regarding definitive surgery.

multidisciplinary meetings for consideration of proactive dose escalation.

2.4. Patient assessment and data collection

Patients underwent baseline assessment including: (1) physical examination by the treating clinician to determine clinical disease activity; (2) pelvic magnetic resonance imaging (MRI) to assess radiologic disease activity; and (3) completion of questionnaires evaluating patient-reported outcomes. Thereafter, physical examinations were completed every 3 months by the treating clinicians, MRI was completed annually, and repeat patient questionnaires were disseminated at the final review. Patients were followed up for a minimum of 12 months.

Physical examinations were completed by treating clinicians (gastroenterologists or colorectal surgeons) experienced in the management of Crohn's perianal fistulas, either during clinic consultation or examination under anesthesia. Imaging was centrally reviewed by a radiologist experienced in perianal fistulizing disease, blinded to clinical disease activity.

2.5. Endpoints

The primary endpoint was clinical healing at the end of follow-up in patients with clinically active fistulas at baseline. Clinical healing was defined as the absence of draining perianal fistulas on physical examination despite gentle finger compression and no seton *in situ*.[3]

Secondary endpoints included: (1) radiologic remission and response on MRI in patients with clinically active fistulas at baseline; (2) predictors of clinical healing in patients with clinically active fistulas at baseline; (3) clinical and radiologic relapse in patients with clinically healed fistulas at baseline; (4) patient-reported outcome measures; and (5) proportion of patients requiring medical and surgical treatment optimization.

Radiologic disease activity was assessed using validated scoring indices: Van Assche Index (VAI); VAI-inflammatory subscore (VAI_{infl}); Magnetic Resonance Index for Assessing Fistulas in Patients with Crohn's Disease (MAGNIFI-CD); and Fibrosis Score (FS).[7,11–14] Radiologic remission was defined as a VAI = 0, VAI_{infl} = 0, MAGNIFI-CD = 0, or FS = 6. Radiologic response was defined as a reduction in VAI of >3, a reduction in MAGNIFI-CD of >4, or an increase in FS of ≥1.

Patient-reported outcome measures were assessed using validated questionnaires for health-related quality of life and mental health: Inflammatory Bowel Disease Questionnaire-32 (IBDQ-32),[15] with higher scores indicative of better health-related quality of life; and Depression Anxiety and Stress Scale-21 (DASS-21),[16] with higher scores indicative of more severe states of distress.

2.6. Statistical analysis

Independent categorical data were presented as frequencies and percentages and compared using the Chi^2 test or Fisher-exact test, with paired data compared using the McNemar test. Independent continuous or ordinal data were presented as medians and interquartile ranges (IQRs) and compared using the Mann–Whitney *U* test, with paired data compared using the Wilcoxon signed-rank test.

The Kaplan–Meier survival method was used to analyze time to clinical healing and clinical relapse for patients with clinically active and clinically healed fistulas at baseline, respectively. For patients with clinically active fistulas at baseline, clinical healing was only deemed achieved if sustained until the end of follow-up.

For patients with clinically active fistulas at baseline, the relationships between achieving clinical healing and baseline demographics, disease characteristics, radiologic disease activity, and care model treatments were assessed on univariable and multivariable logistic regression analyses. The multivariable analysis was completed using a backward stepwise selection method. Variables with $P < .200$ on univariable analysis were included in the multivariable analysis and results were presented as odds ratios (ORs) with exact 95% confidence intervals (95% CIs). There was minimal missing data, restricted to pathology only, and this was managed with case-wise deletion. As this was a small cohort, there was no loss to follow up. Analyses were performed using Stata17.

All authors had access to the study data and reviewed and approved the final manuscript.

3. Results

3.1. Study population

Sixty patients were included. At baseline, 52% ($n = 31/60$) had clinically active fistulas and 48% ($n = 29/60$) had clinically healed fistulas, prior to implementation of the new protocolized treatment strategy.

Fifty-two percent ($n = 31/60$) were male and the median age was 40 years (IQR 32–49). Patients with active fistulas at baseline had shorter duration of Crohn's disease, 9 (IQR 4–20) versus 15 years (IQR 9–24) ($P = .047$), and shorter duration of perianal disease, 5 (IQR 2–13) versus 15 years (IQR 5–23) ($P = .003$), compared to those with healed fistulas, respectively. There was no significant difference in the duration of time attending the preexisting service, with patients receiving care at the tertiary center for a similar period (Table 1).

At baseline, 60% ($n = 36/60$) were receiving immunomodulators, 55% ($n = 33/60$) thiopurine, and 5% ($n = 3/60$) methotrexate. Seventy-three percent ($n = 44/60$) were receiving biologic therapies, with the majority on combined immunomodulator and biologic treatment ($n = 31/60$). Median duration of biologic therapy was 5 years (IQR 2–8), 64% of biologic patients ($n = 28/44$) were on escalated dosing, and 9% ($n = 4/44$) were on maximally escalated dosing. This was similar between patients with and without healed fistulas (Table 1).

A higher proportion of patients with active fistulas at baseline underwent surgical intervention in the preceding 12 months compared to those with healed fistulas, 68% ($n = 21/31$) versus 14% ($n = 4/29$) ($P < .001$), respectively (Table 1).

Expectantly, baseline radiologic remission rates were significantly lower in patients with active fistulas compared to those with healed fistulas, 6% ($n = 2/31$) versus 86% ($n = 25/29$) ($P < .001$), respectively (Table 1).

For patients with active fistulas at baseline, 29% ($n = 9/31$) were not receiving biologic therapy at study inclusion, 91% of patients ($n = 20/22$) receiving biologic therapy had the potential for either initial or further dose escalation, and 48% ($n = 15/31$) were infliximab naïve. Thirty-two percent of patients ($n = 10/31$) had not undergone perianal surgical intervention in the preceding 12 months.

3.2. Clinical healing in patients with active fistulas at baseline

In patients with active fistulas at baseline, 71% ($n = 22/31$) achieved clinical healing after a median follow-up of 22 months (IQR 16–25), which was significantly higher than overall clinical healing rates prior to the implementation of the new treatment strategy (71 vs 48%, $P = .039$) (Table 2 and Figure 2). There was no significant difference in the duration of follow-up between patients who achieved and those who failed to achieve clinical healing.

Clinical healing rates of 39% (95% CI, 24–58) and 84% (95% CI, 66–96) at 1 and 2 years, respectively, were estimated using the Kaplan–Meier survival method (Figure 3).

3.3. Radiologic remission and response in patients with active fistulas at baseline

After a median of 16 months (IQR 13–24) between baseline and final MRI, radiologic remission was achieved in 25% ($n = 7/28$) of patients with active fistulas at baseline, which was significantly higher than radiologic remission rates at study inclusion (25 vs 6%, $P = .048$) (Figure 2). Radiologic response was achieved in 68% ($n = 19/31$) (Table 2).

3.4. Predictors of clinical healing in patients with active fistulas at baseline

On univariable analysis, for patients with active fistulas at baseline, negative indicators of achieving clinical healing included increasing body mass index (OR 0.79, 95% CI, 0.65–0.94, $P = .009$), longer prior clinic attendance (OR 0.79, 95% CI, 0.63–0.99, $P = .040$), and longer prior baseline biologic duration (OR 0.71, 95% CI, 0.53–0.94, $P = .016$). Baseline infliximab trough levels of ≤9.3 µg/mL positively predicted clinical healing following implementation of the new treatment strategy, with a correlation coefficient value of 1.0; however, small numbers with counts of zero prevented OR calculation and therefore this was omitted from the multivariable analysis. There were no significant relationships between the individual treatment components of the care model and achieving clinical healing, including the type of biologic therapy prescribed, escalated biologic dosing regimens, and the specific surgical intervention performed.

On multivariable analysis, only increasing body mass index maintained significance as a negative indicator for achieving clinical healing.

3.5. Clinical and radiologic relapse in patients with healed fistulas at baseline

In patients with healed fistulas at baseline, 7% ($n = 2/29$) experienced clinical relapse after a median follow-up of 23 months (IQR 16–24), with estimated relapse rates of 7% (95% CI, 2–26) at 1 and 2 years using the Kaplan–Meier survival method (Figure 3).

Table 1. Baseline patient demographics, disease characteristics, radiologic disease activity, and patient-reported outcomes.

	Active	Healed	*P*-value*
N (%)	31 (52)	29 (48)	—
Male, *n* (%)	14 (45)	17 (59)	.297
Age, median years (IQR)	38 (30, 47)	42 (32, 51)	.231
BMI, median unit (IQR)	28 (23, 31)	26 (23, 28)	.569
CD duration, median years (IQR)	9 (4, 20)	15 (9, 24)	.047
PD duration, median years (IQR)	5 (2, 13)	15 (5, 23)	.003
Disease location, *n* (%)			
Ileal	18 (58)	20 (69)	.381
Colonic	27 (87)	26 (90)	.538
Isolated PD	1 (3)	0 (0)	.517
Stricturing, *n* (%)	7 (23)	12 (41)	.118
Anal stenosis, *n* (%)	3 (10)	3 (10)	1.000
EIM, *n* (%)	19 (61)	15 (52)	.455
Smoker, *n* (%)	6 (19)	3 (10)	.474
Prior clinic attendance, median years (IQR)	6 (2, 9)	8 (4, 9)	.264
Biologics, *n* (%)	22 (71)	22 (76)	.668
Infliximab IV	8 (26)	9 (31)	.653
Adalimumab	13 (42)	11 (38)	.752
Ustekinumab	1 (3)	2 (7)	.606
Biologic duration, median years (IQR)	3 (1, 8)	6 (4, 8)	.201
Escalated biologic dosing, *n* (%)	14 (45)	14 (48)	1.000
Maximal biologic dosing, *n* (%)	2 (6)	2 (7)	1.000
Infliximab naïve, *n* (%)	15 (48)	13 (45)	.782
IM, *n* (%)	20 (65)	16 (55)	.460
TDM, median unit (IQR)			
Infliximab trough level	9.1 (5.7, 11.9)	7.1 (5.7, 8.5)	.501
Adalimumab level	7.5 (5.8, 8.9)	12.0 (8.6, 13.5)	.021
6-TGN level	240 (155, 267)	315 (211, 475)	.156
Antibiotics, *n* (%)	8 (26)	1 (3)	.027
Surgery prior 12 months, *n* (%)	21 (68)	4 (14)	<.001
Radiologic remission, *n* (%)	2 (6)	25 (86)	<.001
Radiologic disease activity, median score (IQR)			
VAI	12 (8, 17)	0 (0, 4)	<.001
VAI_{infl}	8 (4, 11)	0 (0, 0)	<.001
MAGNIFI-CD	14 (9, 19)	6 (3, 8)	<.001
FS	2 (1, 3)	6 (5, 6)	<.001
Patient-reported outcomes, *n*	20	18	-
IBDQ-32, median score (IQR)	145 (115, 178)	184 (173, 192)	.005
DASS-D, median score (IQR)	7 (5, 9)	6 (1, 9)	.340
DASS-A, median score (IQR)	4 (3, 7)	2 (1, 4)	.043
DASS-S, median score (IQR)	7 (6, 11)	6 (4, 8)	.239

Abbreviations: BMI, body mass index; CD, Crohn's disease; EIM, extraintestinal manifestations; IM, immunomodulator; IV, intravenous; PD, perianal disease.
*Comparison between baseline clinical disease activity.

Radiologic remission was observed in 80% of patients, which was not significantly different from baseline inclusion (80 vs 86%, $P = .542$).

3.6. Patient-reported outcome measures

Thirty-one patients completed questionnaires at the final follow-up (52% response rate); with 28 patients completing both baseline and final questionnaires. There was no significant difference in response rates between patients with or without clinical fistula healing. There was no significant difference in health-related quality of life nor depression, anxiety, or stress severity following the implementation of the new treatment strategy (Table 2).

3.7. Treatment optimization

Following the implementation of the new treatment strategy, all patients with active fistulas at baseline received biologic therapy, with 87% ($n = 27/31$) requiring escalated biologic

Table 2. Clinical, radiologic, and patient-reported outcomes after a minimum of 12-month follow-up post new protocolized treatment strategy, based on patients' baseline clinical disease activity.

	Active	*P*-value*	Healed	*P*-value*
Clinical outcomes, *n*	31	-	29	-
Clinical follow-up, median months (IQR)	22 (16, 25)	-	23 (16, 24)	-
Clinical healing, *n* (%)	22 (71)	.039**	28 (97)	.500
Radiologic outcomes, *n*	28	-	25	-
Radiologic follow-up, median months (IQR)	16 (13, 24)	-	15 (12, 24)	-
Radiologic remission, *n* (%)	7 (25)	.048	20 (80)	.542
Radiologic response, *n* (%)	19 (68)	-	6 (24)	-
Patient-reported outcomes, *n*	16	-	15	-
IBDQ-32, median score (IQR)	156 (124, 175)	.950	179 (158, 199)	.550
DASS-D, median score (IQR)	7 (4, 11)	.899	5 (1, 9)	.612
DASS-A, median score (IQR)	4 (1, 9)	.975	2 (1, 5)	.620
DASS-S, median score (IQR)	9 (6, 13)	.155	5 (4, 8)	.776

*Comparison with paired baseline inclusion rates and scores.
**Comparison with overall baseline cohort, with clinical healing rates reflective of preexisting service prior to implementation of the new protocolized treatment strategy.

dosing and 32% (*n* = 10/31) maximally dosed. Five patients switched from adalimumab to infliximab, 4 switching due to active fistulizing disease despite escalated adalimumab dosing, and 1 due to high anti-adalimumab antibody titers; the latter patient subsequently switched to ustekinumab due to the development of high anti-infliximab antibody titers. At the end of the follow-up, 58% (*n* = 18/31) were on infliximab, 29% (*n* = 9/31) adalimumab, 10% (*n* = 3/31) ustekinumab, and 1 patient on vedolizumab. There was no significant difference in the duration of follow-up between patients on different biologic agents. In those receiving anti-TNF therapy, there was a significant increase in trough infliximab and adalimumab levels, with a median increase of 7.7 µg/mL (IQR 6.1–14.1) (*P* = .025) and 9.6 µg/mL (IQR 4.1–11.3) (*P* = .008), respectively.

For patients with active fistulas at baseline, 61% (*n* = 19/31) underwent perianal surgical intervention including examination under anesthesia. The median number of surgeries was three (IQR 2–4), 45% (*n* = 14/31) had surgical conditioning, 29% (*n* = 9/31) had closure or ablative techniques performed, and 29% (*n* = 9/31) had seton removal only. The closure and ablative techniques performed included suture closure of the internal opening (*n* = 2), fistulotomy or fistulectomy (*n* = 3), autologous fat graft injection (*n* = 1), mucosal advancement flap (*n* = 3), and laser closure (*n* = 3). Of the 12 patients not undergoing surgical intervention, 75% (*n* = 9/12) achieved clinical healing following medical treatment optimization alone, 17% (*n* = 2/12) had surgery recommended but did not proceed, and 1 patient had long-term seton placement deemed the most appropriate definitive surgical management.

For patients with healed fistulas at baseline, 7% (*n* = 2/29) commenced biologic therapy for active luminal Crohn's disease, 17% (*n* = 5/29) required biologic dose escalation, and 1 patient switched from infliximab to ustekinumab due to a central demyelinating lesion. Of the 5 patients requiring biologic dose escalation, the majority (*n* = 4/5) did so proactively for low drug levels detected on routine testing as part of the new treatment strategy; with only 1 patient requiring dose escalation for active luminal Crohn's disease. Three patients underwent a single perianal surgical intervention, with no patients undergoing closure or ablative techniques. Of these 3 patients, 2 had perianal disease relapse and 1 had an examination under anesthesia to explore symptoms with no active disease identified.

Of the 2 patients with healed fistulas at baseline who experienced perianal disease relapse, 1 was recommended to commence biologic therapy but did not proceed due to patient preference and instead had placement of a long-term seton. The other recaptured clinical healing following surgical optimization and continuation of biologic therapy.

4. Discussion

Implementing a new protocolized multidisciplinary treatment strategy, with structured reviews and proactive optimization of medical and surgical care, achieved high clinical healing rates of Crohn's perianal fistulas. Fistula healing was significantly greater than baseline healing rates and above that published with either medical or surgical treatments alone.[3–5] Furthermore, most patients in this study had sustained fistula healing and, in the minority who relapsed, healing could be reestablished through early treatment optimization.

Using this new treatment strategy, patients had significant improvement in radiologic disease activity, highlighting the deeper state of disease control achievable. This represents a more objective assessment of disease activity, portending greater sensitivity and specificity over other evaluation modalities.[17,18] However, despite incorporating validated scoring indices, there is a lack of consensus definitions for radiologic remission and response in Crohn's perianal fistulas[7,11–13]; with the current utility of scoring indices residing in the change of scores over serial imaging. Additionally, due to a lack of fine granularity, these indices often fail to convey partial improvement. This was partly addressed by incorporating the FS, which quantifies the degree of fibrosis of the fistula tract (0%–100%) using a hierarchical scale and accurately predicts long-term clinical closure.[14]

We found that most patients with clinically active disease at baseline had the potential for optimization of medical and/or surgical care. From a medical care perspective, the new treatment strategy resulted in biologic dose escalation

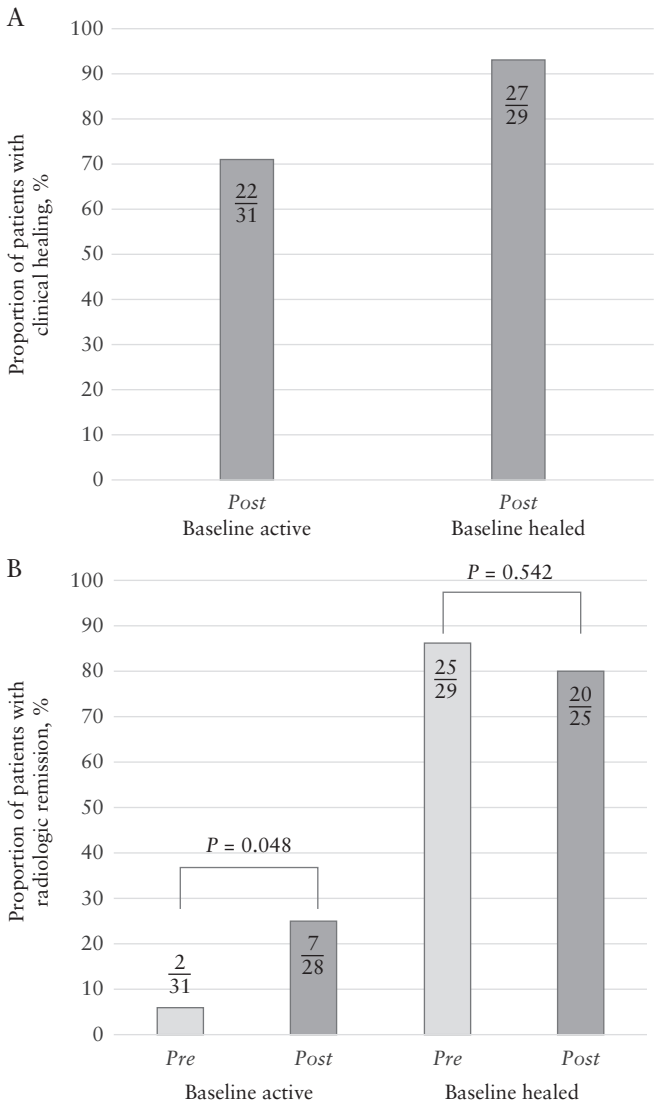

Figure 2. Proportion of patients achieving (A) clinical healing and (B) radiologic remission post implementation of the new protocolized treatment strategy compared to baseline inclusion rates pre-implementation, based on patients' baseline clinical disease activity.

and commencement of intravenous infliximab in more than half of patients who were infliximab naïve. In the absence of head-to-head comparative studies, the justification for anti-TNF therapies, specifically infliximab, as first-line medical treatment comes from large registration trials and real-world experience studies suggesting superior sustained fistula healing rates compared to other available medical treatments.[6,19–21] This treatment change aligns with infliximab having the highest quality efficacy data, with high post-induction clinical response rates and sustained clinical healing rates of 36% in randomized controlled trials.[3,4] Using this treatment strategy, there was an expectant increase in the proportion of patients prescribed infliximab compared to baseline, 58% compared to 26%, respectively. Of the 18 patients on infliximab at the end of follow-up, 67% achieved clinical healing. Consistent with our findings, greater clinical success with infliximab has been observed in real-world experience at tertiary centers, with up to 54% achieving clinical fistula healing[6,22]; likely reflecting changes in dosing, with more than 60% on escalated dosing regimens.[6]

The efficacy and value of switching within anti-TNF class in patients with Crohn's perianal fistulas failing initially prescribed agents have not been previously evaluated. Given existing evidence suggesting the superiority of infliximab compared to adalimumab in real-world experience,[6,21] with limited medical treatment options, a trial of infliximab in patients with an inadequate clinical response to optimized adalimumab therapy was recommended. Interestingly, this approach showed that at least half of patients who transitioned from adalimumab to infliximab for pharmacodynamic failure achieved clinical healing of their perianal fistulas. The reverse of switching from infliximab to adalimumab was not explored. Similarly, in a small retrospective study evaluating the benefits of switching within anti-TNF class in patients with active luminal Crohn's disease,[23] 55% of patients who switched from adalimumab to infliximab achieved remission. Although small numbers, this suggests a potential benefit in trialing a switch within a class for patients with clinically active Crohn's perianal fistulas, at least from adalimumab to infliximab, and challenges traditional treatment dogmas of futility in switching within class after pharmacodynamic anti-TNF failure.[24,25]

The new treatment strategy incorporated biologic dose escalation, with an expectant increase in anti-TNF drug levels. Furthermore, low infliximab levels of ≤9.3 µg/mL in patients with clinically active disease at baseline were predictive of those who would achieve clinical healing following treatment optimization and biologic dose escalation. This is congruent with increasing evidence that suggests higher anti-TNF drug levels correlate with improved rates of clinical and radiologic fistula healing in retrospective and post-hoc analyses.[6,7,18] These studies all showed incremental gains with higher drug levels, a pertinent point indicating that a subset of patients will benefit from achieving drug levels above published target thresholds.[6,7,26]

For patients with Crohn's perianal fistulas failing anti-TNF therapy, ustekinumab appears to hold greater efficacy compared to other biologics,[19,20] representing the rationale for placing ustekinumab as second-line medical treatment in the new treatment strategy. Of the few patients with clinically active disease initiating ustekinumab for anti-TNF refractory disease or due to contraindications to anti-TNF therapy, all patients achieved clinical healing with either stability or improvement on radiologic disease activity. This aligns with findings by GETAID Study Group,[19] whereby 39% of patients with clinically active Crohn's perianal fistulas experienced treatment success following ustekinumab initiation, in a predominantly anti-TNF refractory cohort.

The role of vedolizumab is less clear, with variable rates of fistula healing published. In our cohort, only 1 patient was commenced on vedolizumab at maximally escalated dosing due to comorbidities precluding anti-TNF and ustekinumab therapies. Although the patient achieved clinical healing with a reduction in radiologic activity, meaningful conclusions or recommendations regarding vedolizumab cannot be made. Therefore, justification for its use as a third-line medical treatment comes from existing literature. In a large multicenter retrospective cohort by the GETAID Study Group,[20] only 23% achieved treatment success in a predominantly anti-TNF refractory cohort.

From a surgical care perspective, more than half of patients with clinically active disease underwent at least 1 surgical intervention; the majority undergoing surgical conditioning of

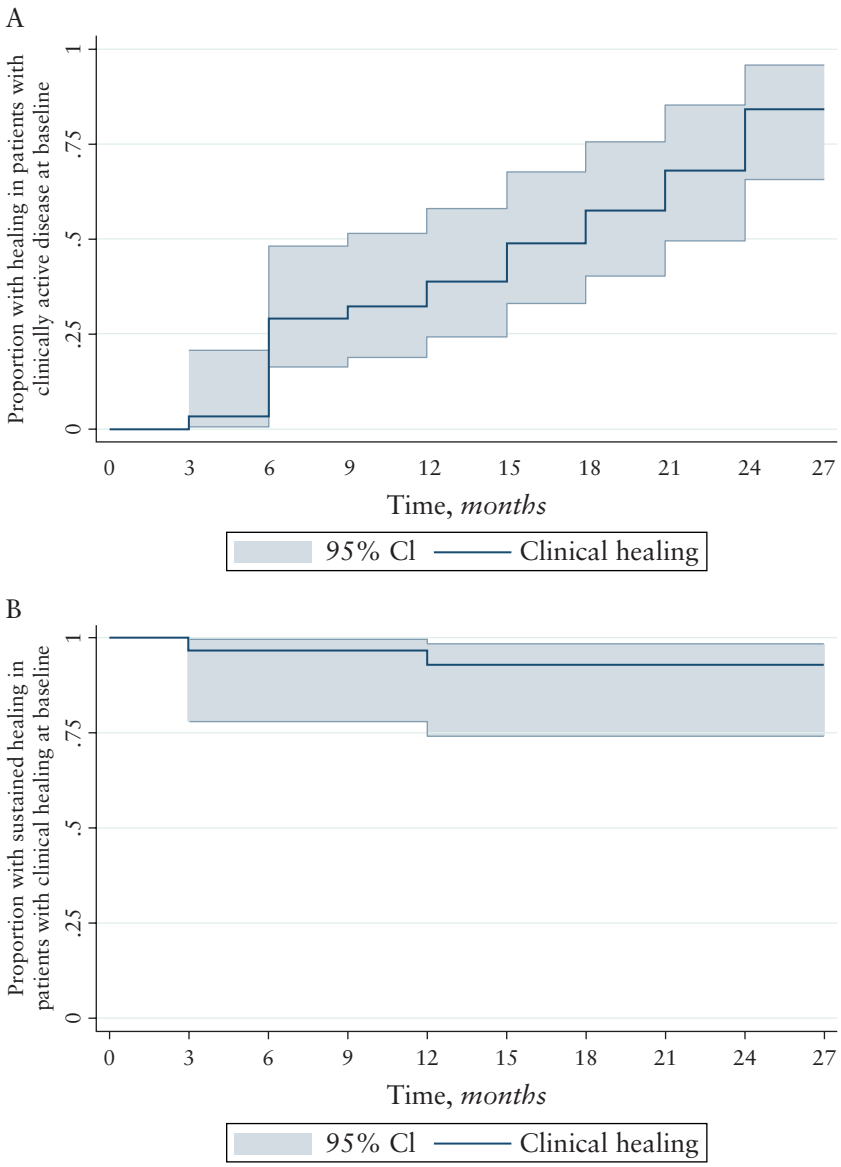

Figure 3. Time to (A) clinical healing (n = 31) and (B) clinical relapse (n = 29) for patients with clinically active and healed fistulas at baseline, respectively. Estimates calculated using the Kaplan–Meier survival method.

the fistula tract and seton insertion. After initial surgical and medical optimization, almost a third subsequently underwent a definitive surgical closure or ablative technique. Given the observed local preference by colorectal surgeons in Australia and New Zealand is for long-term seton placement or seton removal only,[27] this highlights a greater uptake of definitive surgical closure and ablative techniques using this new treatment strategy. Furthermore, this shift from seton management alone aligns with increasing evidence suggesting the superiority of surgical closure and ablative techniques compared to seton removal only in those with amenable disease.[9] Despite this, there was no significant association between clinical healing and definitive surgical closure or ablative techniques observed in our cohort. Interpretation of this is limited by small numbers of patients undergoing each surgical technique. Multiple confounders likely influenced these observed low events,[27] including surgeon preference, surgeon experience, access to specialty equipment, and feasibility of surgery; with patients' disease characteristics and fistula anatomical complexity paramount in determining whether a surgical technique is possible. The impact of some of these factors was addressed through discussion of patients at multidisciplinary meetings and the ability to have different colorectal surgeons involved based on experience with particular definitive surgical techniques.

In the exploration of predictors for clinical healing, increasing body mass index was a negative indicator for achieving this target. This is consistent with findings in luminal Crohn's disease, whereby obesity negatively impacts treatment success.[28] However, there is contradictory evidence regarding this association with perianal fistulizing disease.[29] This potentially relates to body mass index's inability to adequately assess body adipose tissue composition; relevant as visceral adipose tissue is thought to be proinflammatory, with greater density of visceral fat associated with more severe radiologic disease activity of Crohn's perianal fistulas.[30]

We were unable to show a significant association between the individual treatment components of the care model and

achieving fistula healing. Of note, there were no changes in access to available therapies during the establishment of the new treatment strategy. The implemented treatment strategy proactively optimized care delivery, challenging patients' existing treatment and advocating for escalation of medical therapies and a shift in surgical interventions toward procedures conducive to fistula healing. The observed changes in medical and surgical care therefore reflect the ability of a protocolised treatment strategy to improve care delivery and patient outcomes.

Given low questionnaire response rates and lack of significance, limited conclusions can be drawn regarding any influence the new treatment strategy had on health-related quality of life or mental health. However, there was a significant difference at baseline between patients with healed and active fistulas, exemplifying the importance of disease activity on patient experience and echoing consensus opinions for the inclusion of patient-reported outcome measures when assessing treatment success.[31] This lack of significance is also potentially impacted by the questionnaire used to measure health-related quality of life in our cohort, with the IBDQ-32 not specifically designed for patients with Crohn's perianal fistulas.[13] Subsequent health-related quality-of-life assessment tools specific for Crohn's perianal fistulas have been developed, with the Crohn's Anal Fistula Quality of Life scale anticipated to show a greater association with clinical disease activity and response following treatment intervention.[32]

Limitations of this study include the lack of a control group, single-center cohort, and disease and treatment heterogeneity. Due to the study design, causality cannot be inferred, with only associations able to be identified, and findings cannot be generalized to all centers. Prospective collection of data mitigated risk of recall bias. Assessment bias of clinical healing was mitigated by the inclusion of radiologic outcomes. Lastly, limited long-term follow-up potentially underestimates rates of radiologic remission, which lags clinical healing by at least 12 months.[22]

A new protocolized multidisciplinary treatment strategy, proactively optimizing medical and surgical care delivery, demonstrated high clinical healing rates and improved radiologic disease activity in adults with Crohn's perianal fistulas. Controlled-matched studies across multiple centers are needed to validate the protocolized treatment strategy.

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Author Contributions

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Data Availability

Data, analytic methods, and study material were made available to all study authors. Data, analytic methods, and study materials are not intended to be made available to other researchers outside of the study; the exception, if requested for the purpose of publication review.

Data Transparency Statement

Individual participant data will not be shared.

Publication

The manuscript, including related data, figures and tables has not been previously published and the manuscript is not under consideration elsewhere.

Conferences

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