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# Disappointing Durable Remission Rates in Complex Crohn's Disease Fistula

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**Background:** Despite potent drugs and surgical techniques, the treatment of perianal fistulizing Crohn's disease (CD) remains challenging. We assessed treatment strategies for perianal fistulizing CD and their effect on remission, response, and relapse.

**Methods:** Patients with perianal fistulizing CD visiting the Erasmus MC between January 1, 1980 and January 1, 2000 were identified. Demographics, fistula characteristics, and received treatments aimed at the outcome of these strategies were noted.

**Results:** In total, 232 patients were identified (98 male; 42.2%). Median follow-up was 10.0 years (range, 0.5–37.5 yr). Complex fistulas were present in 78.0%. Medical treatment (antibiotics, steroids, immunosuppressants, and anti-tumor necrosis factor) commenced in 79.7% of the patients and in 53.2%, surgery (colectomy, fistulectomy, stoma, and rectum amputation) was performed. Simple fistulas healed more often than complex fistulas (88.2% versus 64.6%;  $P < 0.001$ ). Rectum involvement was not associated with a lower remission rate, and anti-tumor necrosis factor therapy did not increase complete fistula healing rates in simple and complex fistula. Initially, healed fistulas recurred in 26.7% in case of simple fistulas and in 41.9% in case of complex fistulas ( $P = 0.051$ ). Only 37.0% of the complex fistulas were in remission at the end of follow-up compared with 66.7% of the simple fistulas ( $P < 0.001$ ).

**Conclusions:** Only the minority of CD complex perianal fistulas were in remission after conventional treatment strategies after a median follow-up of 10 years. Simple fistulas were more likely to heal than complex fistulas, and less of these healed fistulas relapsed. However, more than 3 quarters of the patients had complex perianal fistulas.

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**Key Words:** complex perianal fistulas, Crohn's disease, healing

The development of perianal fistulas along with rectal pain and continuous drainage is a common complication of Crohn's disease (CD).<sup>1–5</sup> The cumulative incidence of perianal fistulas was estimated at 23% to 26% after 20 years of CD.<sup>6,7</sup> In almost half of the patients, perianal fistulas were diagnosed before or at the time of the diagnosis of CD.<sup>6,7</sup> Patients with active rectal disease have more frequently perianal fistulas compared with patients with isolated ileal disease.<sup>6–12</sup> Furthermore, male gender, age at diagnosis of CD, and smoking are associated with the development of perianal fistulas, although data are conflicting.<sup>6–8,10,12–15</sup>

Although a range of medical and surgical options is available nowadays, the treatment of perianal fistulas remains challenging. Current medical strategies include antibiotics

(ciprofloxacin and metronidazole),<sup>16–18</sup> immunosuppressants, such as azathioprine and 6-mercaptopurine,<sup>19,20</sup> and the anti-tumor necrosis factors (TNFs), such as infliximab, adalimumab, and certolizumab pegol.<sup>21–25</sup> Symptomatic simple fistulas can be treated with a noncutting seton or fistulotomy. Active luminal disease should be treated before surgical treatment.<sup>26</sup> In case of complex fistulas, drainage is achieved by placement of a noncutting seton to reduce the risk of perianal abscess formation preferably in combination with anti-TNF and antibiotics. In the ADAFI trial,<sup>27</sup> patients with perianal fistulas treated with the anti-TNF agent, adalimumab along with ciprofloxacin for 12 weeks, had a significant higher response and remission rate than patients treated with adalimumab alone.

With this study, we aimed to assess in a single center retrospective cohort different treatment strategies for perianal fistulizing CD and the effect of these treatments on the response, remission, and relapse rate.

## MATERIALS AND METHODS

### Patients

Patients treated for perianal fistulizing CD who visited the Erasmus MC University Hospital between January 1, 1980 and the January 1, 2000 were identified through a search in the hospital

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diagnosis system. This search was performed as follows: First, all letters from patients were identified by the term fistulizing disease. Second, letters containing the words CD were obtained, and finally, these letters were combined with the obtained letters from the first search. The patient charts obtained from the latter search were reviewed independently by 2 investigators. Patients with the first diagnosis of perianal fistulizing disease at or after the diagnosis of CD and with a follow-up for at least 6 months were included. Follow-up time was from the onset of fistulizing CD until the date of last follow-up or January 1, 2010.

## Data Extraction

Demographic information, date of diagnosis CD, disease localization, time between the diagnosis of CD and the development of perianal fistulas, fistula character, medical and surgical treatment received for perianal fistulas, and subsequently response, remission, and relapse were extracted from all charts.

The diagnosis of CD and the extent of the disease were confirmed, according to the Lennard-Jones<sup>28</sup> criteria. The localization of the disease was classified into 7 groups: upper gastrointestinal tract, small bowel, large bowel, ileocecal, large and small bowel, perianal, and entire gastrointestinal tract. In addition, involvement of the rectum was determined.

The diagnosis of perianal fistulizing disease was based on endoscopic, radiographic, or clinical evidence. Fistula character was classified as “simple” or “complex” following the criteria of Sandborn et al.<sup>29</sup> The medical therapies received as treatment for perianal fistulas were divided in antibiotics, corticosteroids, immunosuppressants, and anti-TNFs. Furthermore, the patient's history of colon resection, fistulectomy, placement of a stoma, and rectum amputation was noted. The response to medical and/or surgical treatment was defined as a decrease of discharge, pain, and bleeding from the fistula tract, and remission was defined as the absence of an external opening without discharge on history and physical examination. Relapse was defined as recurred discharge on history and physical examination with reopening of the previous external opening and/or formation of new perianal fistulas after initial remission. Worsening of the disease after the start of medical and/or surgical treatment with or without an initial response was defined as an increase of discharge, pain, and bleeding from the fistula tract.

## Outcome Assessment

The primary objective was to assess the remission rate of CD perianal fistulas after medical and/or surgical treatment. Secondary parameters included response and relapse.

## Statistical Analysis

The data were presented in percentages, medians, and ranges. The Mann–Whitney U test was used to compare nonparametric data sets, and the Fisher's exact test was used to determine whether a significant association existed between 2 data sets. All statistical analyses were performed using the SPSS statistical package (version 20.0.0; SPSS Inc., Chicago, IL).  $P < 0.05$  was considered statistically significant.

## RESULTS

### Demographics

In the final search, 436 patients who visited the Erasmus MC University Hospital between January 1, 1980 and January 1, 2000 from whom letters contained the terms “fistulizing disease” and “CD” were identified (Table 1, Fig. 2). Of these patients, 204 were excluded because of the following reasons: CD was not confirmed endoscopically, histologically, or radiologically (13.1%); the diagnosis of fistulizing disease was before the diagnosis of CD (10.1%); fistulizing disease was not diagnosed (1.4%); only enterocutaneous or enteroenteric fistulas (6.0%), rectovaginal fistulas (2.8%), or pouch–vaginal fistulas (0.7%) were confirmed; the fistulas were related to a complicated surgery (0.9%); the follow-up period after the diagnosis of perianal fistulas was <6 months (10.1%); and no information on complexity of perianal fistulas was documented (1.8%). A total of 232 patients (98 men [42.2%]) were included for further evaluation.

The median age at diagnosis of CD was 22.8 years (range, 4.0–68.7 yr). CD localization is shown in Table 1. The median age at diagnosis of fistulizing disease was 29.4 years (range, 9.1–77.3 yr). In total, 66 patients (28.4%) developed fistulas within 6

**TABLE 1. Demographic Characteristics of the Perianal Fistulizing CD Cohort**

|  | Perianal Fistulizing CD (n = 232) |
|--|-----------------------------------|
| Male, n (%)  | 98 (42.2)                         |
| CD characteristics   |                                   |
| Age at diagnosis, median (range), yr                                 | 22.8 (4.0–68.7)                   |
| Localization, n (%)  |                                   |
| Upper GI   | 11 (4.7)                          |
| Small bowel  | 16 (6.9)                          |
| Ileocecal  | 35 (15.1)                         |
| Large bowel  | 88 (37.9)                         |
| Small + large bowel  | 67 (28.9)                         |
| Whole GI tract   | 2 (0.9)                           |
| Isolated perianal disease  | 13 (5.6)                          |
| Rectal involvement, n (%)  | 96 (41.4)                         |
| Perianal fistula characteristics                                     |                                   |
| Diagnosis after 1999, n (%)  | 129 (55.6)                        |
| Age at diagnosis, median (range), yr                                 | 29.4 (9.1–77.3)                   |
| Diagnosis within 6 mo after diagnosis of CD, n (%)                   | 66 (28.4)                         |
| Time to diagnosis if >6 mo after diagnosis of CD, median (range), yr | 7.0 (0.7–38.0)                    |
| Follow-up time, median (range), yr                                   | 10.0 (0.5–37.5)                   |
| Complex, n (%)   | 181 (78.0)                        |

GI, gastrointestinal tract.

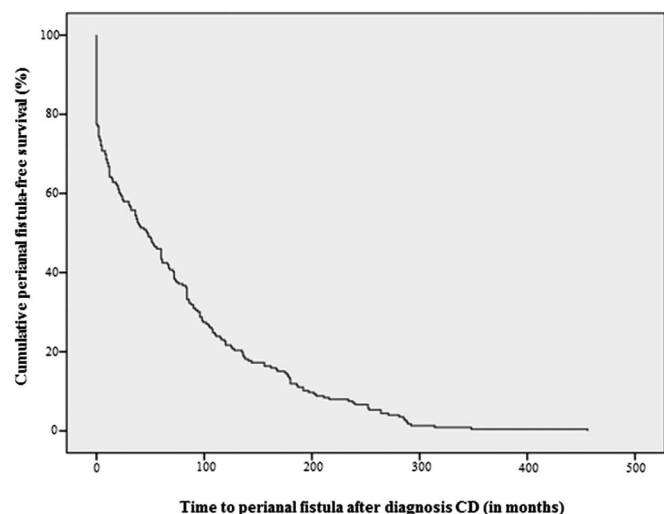


FIGURE 1. Cumulative perianal fistula-free survival after diagnosis of CD.

months after the onset of CD and in 78.9%, perianal fistulas developed within 10 years after the diagnosis of CD with a median duration of 7.0 years (range, 0.7–38.0 yr) (Fig. 1). Median follow-up time from fistula diagnosis was 10.0 years (range, 0.5–37.5 yr). Patients with a complex fistula (78.0%) did not significantly differ from patients with a simple fistula (22.0%) about sex, age at diagnosis of (fistulizing) CD, time of diagnosis (before or after 1999), and rectal involvement.

### Medical Treatment

In this cohort, 185 patients (79.7%) received any drugs (antibiotics, steroids, immunosuppressants, and anti-TNFs) (Tables 2 and 3). Of the patients with simple fistulas (51), 41.2% underwent no treatment<sup>6</sup> or solely surgery.<sup>15</sup> In 15 patients (29.4%), the treatment included drugs solely (Table 2), and in

the remaining 15 patients, (29.4%) the treatment involved both drugs and surgery. Of the 30 patients (58.8%) with a simple fistula who received drugs, only 1 type of drug was prescribed in 12 patients (40.0%) (Table 3).

In 26 patients (14.4%) suffering from a complex fistula, the treatment involved solely surgery (11.6%) or no treatment (2.8%). In 82 patients (45.3%), the treatment included solely drugs (Table 2). Combination strategy including drugs and surgery was given in 73 patients (40.3%). Of the 155 patients (85.6%) with a complex fistula who received drugs, only 1 type of drug was prescribed in 42 patients (27.1%) (Table 3).

In patients with simple fistulas, significantly more often no drugs were prescribed (41.2%) compared with patients with complex fistulas (14.4%) ( $P < 0.001$ ). When drugs were the only treatment administered, significantly more antibiotics were prescribed in case of complex fistulas ( $P = 0.047$ ) and significantly more steroids in case of simple fistulas ( $P = 0.027$ ) (Table 2). Of all patients who received drugs with or without additional surgery (79.7%), 54 patients (29.2%) received only 1 type of drug (Table 3). The number of patients receiving antibiotic therapy combined with one or more of the other drugs was significantly higher when a complex fistula was diagnosed compared with patients with a simple fistula (65.5% versus 27.8%;  $P = 0.004$ ). Vice versa, steroids combined with one or more drugs and maintenance anti-TNFs in combination with one or more drugs were used more often by patients with the diagnosis of simple fistula compared with patients with a complex fistula ( $P < 0.001$  and  $P = 0.042$ , respectively) (Table 3).

Overall, the most often prescribed drugs in both simple and complex fistula were immunosuppressants (82.2%). If immunosuppressants were prescribed, steroids were part of the treatment in simple fistulas in 13 patients (56.5%). In complex fistulas, induction with anti-TNF was most often given concomitant with

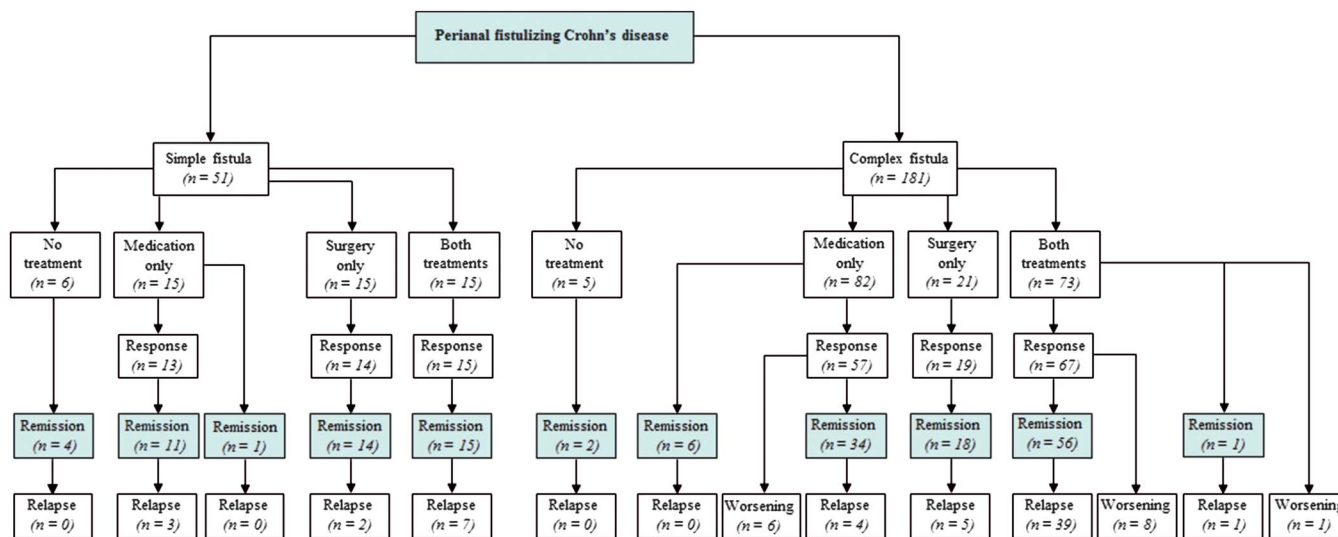


FIGURE 2. Flowchart showing the natural history of the patients with perianal fistulizing CD.

**TABLE 2.** Drugs Prescribed in Patients Who Received Solely Drugs, Divided as Simple and Complex Fistulas

|                               | Total,<br>n (%) | Simple,<br>n (%) | Complex,<br>n (%) | <i>P</i> |
|-------------------------------|-----------------|------------------|-------------------|----------|
|                               | n = 97          | n = 15           | n = 82            |          |
| Drugs only                    |                 |                  |                   |          |
| Antibiotics                   | 51 (52.6)       | 4 (26.7)         | 47 (57.3)         | 0.047    |
| Steroids                      | 27 (27.8)       | 8 (53.3)         | 19 (23.2)         | 0.027    |
| Immunosuppressants            | 82 (84.5)       | 13 (86.7)        | 69 (84.1)         | 1.000    |
| Induction with anti-TNFs      | 55 (56.7)       | 9 (60.0)         | 46 (56.1)         | 1.000    |
| Maintenance therapy anti-TNFs | 36 (37.1)       | 8 (53.3)         | 28 (34.1)         | 0.244    |

immunosuppressants (52.7%). In 13 (43.3%) of patients with simple fistulas and in 51 of patients with complex fistulas (32.9%), anti-TNF maintenance therapy was prescribed. Almost all of these patients received concomitant immunosuppressant drugs (92.3% versus 88.2%).

**Surgery**

In total, 124 patients (53.4%) underwent surgery for their fistulizing disease (Table 4). In patients with a simple fistula, significantly more fistulectomies were performed than in patients with a complex fistula (73.3% versus 42.6%; *P* = 0.006). Of patients with a complex fistula, 60 (63.8%) underwent a fecal diversion compared with 8 (26.7%) in patients with simple fistulas (*P* = 0.001). In addition, significantly more patients with a complex fistula underwent rectum amputation (25.5% versus 6.7%; *P* = 0.037). Surgery was combined with medical treatment in 15 patients (29.4%) with a simple fistula and in 73 patients (40.3%) diagnosed with a complex fistula (*P* = 0.192).

**Overall Effect of Treatment Strategies**

The overall response to treatment rate was 83.7% (Fig. 2). There was no significant difference between simple fistulas (93.3%) and complex fistulas (81.3%) (*P* = 0.068) regarding the response rate. The overall remission rate was significantly higher in patients with simple fistulas (88.2%) compared with complex fistulas (64.6%) (*P* < 0.001), with a total overall remission rate of 69.8%. Fistula remission was achieved after a median duration of 27.0 months (range, 0–303.0 mo): in case of simple fistulas, the median duration was 34.0 months (range, 0–187.0 mo) and after 27.0 months (range, 0–303.0 mo) in complex fistulas (*P* = 0.785). Initially healed fistulas recurred in 37.7%. Simple fistulas relapsed less often compared with complex fistulas (26.7% versus 41.9%; *P* = 0.051). Only 37.0% of the complex fistulas were in remission at the end of follow-up compared with 66.7% of the simple fistulas (*P* < 0.001).

**TABLE 3.** Drugs Prescribed for Simple and Complex Fistulas

|                               | Total,<br>n (%) | Simple,<br>n (%) | Complex,<br>n (%) | <i>P</i> |
|-------------------------------|-----------------|------------------|-------------------|----------|
|                               | n = 54          | n = 12           | n = 42            |          |
| One Type of Drug              |                 |                  |                   |          |
| Antibiotics                   | 8 (14.8)        | 2 (16.7)         | 6 (14.3)          | 1.000    |
| Steroids                      | 9 (16.7)        | 3 (25.0)         | 6 (14.3)          | 0.399    |
| Immunosuppressants            | 34 (63.0)       | 7 (58.3)         | 27 (64.3)         | 0.744    |
| Induction with anti-TNFs      | 3 (5.5)         | 0 (0.0)          | 3 (7.1)           | 1.000    |
| Maintenance therapy anti-TNFs | 0 (0.0)         | 0 (0.0)          | 0 (0.0)           | NA       |
| More than 2 Types of Drugs    | n = 131         | n = 18           | n = 113           | <i>P</i> |
| Antibiotics                   | 79 (60.3)       | 5 (27.8)         | 74 (65.5)         | 0.004    |
| Steroids                      | 54 (41.2)       | 15 (83.3)        | 39 (34.5)         | <0.001   |
| Immunosuppressants            | 118 (90.1)      | 16 (88.9)        | 102 (90.3)        | 1.000    |
| Induction with anti-TNFs      | 90 (68.7)       | 14 (77.8)        | 76 (67.3)         | 0.427    |
| Maintenance therapy anti-TNFs | 64 (48.9)       | 13 (72.2)        | 51 (45.1)         | 0.042    |
| Total                         | n = 185         | n = 30           | n = 155           | <i>P</i> |
| Antibiotics                   | 87 (47.0)       | 7 (23.3)         | 80 (51.6)         | 0.005    |
| Steroids                      | 63 (34.1)       | 18 (60.0)        | 45 (29.0)         | 0.002    |
| Immunosuppressants            | 152 (82.2)      | 23 (76.7)        | 129 (83.2)        | 0.435    |
| Induction with anti-TNFs      | 93 (50.3)       | 14 (46.7)        | 79 (51.0)         | 0.694    |
| Maintenance therapy anti-TNFs | 64 (34.6)       | 13 (43.3)        | 51 (32.9)         | 0.298    |

Overview of all patients who received drugs (n = 185) with or without additional surgery divided in patients who received one type of drug (n = 54) and patients who received 2 or more types of drugs (n = 131).

**Response, Remission, and Relapse Rates Per Treatment Strategy**

**No Treatment**

In 6 patients (11.8%) with a simple fistula and 5 (2.8%) patients with a complex fistula, no treatment was given (Fig. 2). In 4 of these patients with simple fistulas (66.7%) and 2 patients with complex fistulas (40.0%), durable remission was achieved. The time to remission was comparable between patients with a simple fistula (40.0 mo [range, 12.0–187.0 mo] versus 37.5 mo [range, 3.0–72.0 mo]; *P* = 1.000).

**Drugs Only**

The overall response in this group was 72.2%, with no difference between simple and complex fistulas (*P* = 0.222) (Fig. 2). The remission rate after an initial response to the medication was 64.3% without a significant difference between simple and complex fistulas (*P* = 0.121). Immunosuppressants, anti-TNF therapy, or the

**TABLE 4.** Surgery for Simple and Complex Fistulas Divided Per Type of Surgery

|                            | Total,<br>n (%) | Simple,<br>n (%) | Complex,<br>n (%) | <i>P</i> |
|----------------------------|-----------------|------------------|-------------------|----------|
|                            | n = 124         | n = 30           | n = 94            |          |
| Colectomy                  | 63 (50.8)       | 11 (36.7)        | 52 (55.3)         | 0.094    |
| Fistulectomy               | 62 (50.0)       | 22 (73.3)        | 40 (42.6)         | 0.006    |
| Fecal diversion<br>(stoma) | 68 (54.8)       | 8 (26.7)         | 60 (63.6)         | 0.001    |
| Rectum amputation          | 26 (21.0)       | 2 (6.7)          | 24 (25.5)         | 0.037    |

combination of both somewhere in the disease course of patients with simple fistula did not improve remission rates compared with patients who did not receive one of these drugs or the combination of the both ( $P = 1.000$ ,  $P = 0.525$ , and  $P = 0.569$ , respectively). Similar results were seen for patients with complex perianal fistulas treated with immunosuppressants ( $P = 0.379$ ), anti-TNF ( $P = 0.119$ ), and the combination of the both ( $P = 0.121$ ). Overall, fistula remission was achieved after a median duration of 43.0 months (range, 5.0–101.0 mo) in simple fistulas and after 23.5 months (range, 3.0–203.0 mo) in complex fistulas ( $P = 0.254$ ). The recurrence rate after an initial response and remission in simple fistulas was 27.3% and 11.8% in complex fistulas ( $P = 0.337$ ) with an overall relapse rate of 15.6%.

### Surgery Only

Fistulas that were treated with surgery only had an overall response rate of 91.7% (Fig. 2). Overall remission after an initial response was 97.0%. Median time to remission was 13.0 months (range, 0.0–137.0 mo) in case of simple fistulas and 24.5 months (range, 1.0–264.0 mo) in case of complex fistulas ( $P = 0.589$ ). No significant difference was found in relapse rate between simple (14.3%) and complex (27.8%) fistulas ( $P = 0.426$ ) with an overall recurrence of 21.9%.

### Drugs and Surgery Combined

In 29.4% of the simple fistulas and 40.3% of the complex fistulas, a multimodal treatment with medication and surgery was necessary (Fig. 2). The overall response rate was 93.2% with no difference between simple and complex fistulas ( $P = 0.584$ ). The overall remission rate after an initial response was 86.6%. Fistulas went more often in remission in case of a simple fistula (100.0%) compared with complex fistulas (83.6%) ( $P = 0.202$ ) after a median duration of 48.0 months (range, 0.0–136.0 mo) versus 34.0 months (range, 0.0–303.0 mo) ( $P = 0.854$ ). When remission was achieved after initial response, the overall recurrence rate was 64.8%.

### Remission Rates Per CD Localization

All patients with CD localized only perianal or in the whole gastrointestinal tract had a complex fistula. These complex fistulas

healed in 69.2% when isolated perianal disease was present and in all patients with involvement of the entire gastrointestinal tract. Simple fistulas healed significantly more often when luminal CD was present in both small intestine and colon compared with complex fistulas (95.2% versus 62.2%;  $P = 0.006$ ). When luminal CD was localized in the large bowel or ileocecal, no significant difference in fistula closure was found between simple and complex fistulas ( $P = 0.130$  and  $P = 0.121$ ). Involvement of the rectum was not associated with a lower remission rate in both simple and complex fistulas ( $P = 0.321$  and  $P = 0.255$ ).

## DISCUSSION

In this large retrospective cohort of patients with CD suffering from perianal fistula, we assessed the effect of different treatment strategies including surgery on the healing of these fistulas. Because of the long-term median follow-up of 10 years, we were able not only to investigate the time to first remission, but also the rate of relapse after a first remission. Remission rate of the first episode of perianal fistulas of the 232 patients was 69.8%. Overall simple fistulas were more likely to heal than complex fistulas (88.2% versus 64.6%;  $P < 0.001$ ) without a significant difference in median duration to first fistula healing. These rates are comparable with previous studies reporting remission rates of 66% to 68% with also a higher healing rate of simple fistulas compared with complex fistulas. In addition, no significant difference in time to fistula remission between simple and complex fistulas was observed.<sup>7,9</sup> The overall recurrence after initial healing, including the whole range of applied strategies, was a disappointing 37.7%. Only 37.0% of the complex fistulas were in remission at the end of follow-up compared with 66.7% of the simple fistulas ( $P < 0.001$ ). In several population-based cohorts,<sup>6,7,9</sup> the overall recurrence rate of fistulas was about one-third. A prospective study in patients with solely perianal fistulas observed a recurrence rate of 44.4%,<sup>30</sup> which was higher than the 37.7% in our cohort.

Active rectal disease is indicated as a risk factor for perianal fistula; in our cohort, only the minority of the patients had active rectal disease. Involvement of the rectum was not associated with a lower remission rate in both simple and complex fistulas ( $P = 0.321$  versus  $P = 0.255$ ). However, our cohort included more patients than previous studies.<sup>6,7,12</sup> Furthermore, in patients with active rectal disease, the risk for developing perianal fistulas compared with patients with sole involvement of the small intestine was reported to be higher. Only a small proportion of our cohort had luminal disease present in solely the small intestine (6.9%) or only ileocecal involvement (15.1%). Most patients had involvement of the colon (37.9%) or colon and small intestine (28.9%), which is in agreement with the literature that 5.6% of our patients presented with isolated perianal disease and most of our patients had colonic involvement or small intestine plus colonic disease.<sup>6,10,11</sup>

We showed that 2.6% of the perianal fistulas healed without any form of treatment that is even less than the already very low

spontaneous healing rates of 6% to 13% known from 3 placebo-controlled studies.<sup>21,31,32</sup> Healing rates after treatment with drugs only vary between 9% and 78%<sup>7,9</sup>; however, the lowest reported healing rates did not include anti-TNF therapy, and the number of patients in these studies treated solely with drugs was low. In a recent published meta-analysis including 453 patients with active perianal fistulizing CD, complete closure of the fistula was observed in only 32.8% of the patients after anti-TNF therapy alone.<sup>25</sup> Combining different medical treatments resulted in our cohort in twice as higher closure rates (64.3%), suggesting that solely anti-TNF therapy is not the optimal treatment for perianal fistulizing CD. Surgery only did lead to a remission rate of 3 quarters; however, the number of patients treated with surgery only was small (15.5%).

Infliximab was available in our hospital from 1999, and 57.7% of the patients treated solely with drugs received at least 1 gift of anti-TNF, however, not leading to higher remission rates of perianal fistulas compared with patients who did not receive infliximab ( $P = 1.000$ ). Our negative infliximab results may be influenced by the time to treatment. Furthermore, the addition of ciprofloxacin to anti-TNF significantly increased the rate of healed fistulas in the ADAFI trial.<sup>27</sup> If this strategy fails to heal the fistula, options are scarce. Therefore, it is desirable to start treatment as soon as possible after ruling out the presence of abscesses and preferably placement of noncutting setons to reduce the risk of new perianal abscess formation.

Recently, Sandborn et al<sup>33</sup> reported the results of the first induction and maintenance trials of vedolizumab, an  $\alpha 4\beta 7$ -integrin antibody. Although the number of patients with fistulas in this trial was quite low, vedolizumab every 8 weeks resulted in a significant higher closure rate compared with placebo ( $P = 0.03$ ).<sup>33</sup> A new promising approach in perianal fistula in CD is cellular therapy with mesenchymal stromal cells. In the past years, several reports on clinical trials using mesenchymal stromal cells as a treatment for perianal fistulizing CD have demonstrated that the local administration of mesenchymal stromal cells is safe and feasible, and some of these studies have suggested a potential therapeutic effect.<sup>34–37</sup>

In conclusion, we demonstrated in this large cohort of 232 patients with fistulizing CD that only one third of the patients with complex perianal fistulas achieved a durable remission after conventional treatment strategies. Simple fistulas were more likely to heal than complex fistulas, and less of these healed fistulas relapsed. However, more than 3 quarters of the patients had complex perianal fistulas. Rectum involvement and anti-TNF therapy was not associated with lower remission rates.

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