# Natural History of Anal Ulcerations in Pediatric-Onset Crohn's Disease: Long-Term Follow-Up of a Population-Based Study

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INTRODUCTION: **Anal ulcerations are frequently observed in Crohn's disease (CD). However, their natural history remains poorly known, especially in pediatric-onset CD.**

METHODS: **All patients with a diagnosis of CD before the age of 17 years between 1988 and 2011 within the population-based registry EPIMAD were followed retrospectively until 2013. At diagnosis and during follow-up, the clinical and therapeutic features of perianal disease were recorded. An adjusted time-dependent Cox model was used to evaluate the risk of evolution of anal ulcerations toward suppurative lesions.**

RESULTS: **Among the 1,005 included patients (females, 450 [44.8%]; median age at diagnosis 14.4 years [interquartile range 12.0–16.1]), 257 (25.6%) had an anal ulceration at diagnosis. Cumulative incidence of anal ulceration at 5 and 10 years from diagnosis was 38.4% (95% confidence interval [CI] 35.2–41.4) and 44.0% (95% CI 40.5–47.2), respectively. In multivariable analysis, the presence of extraintestinal manifestations (hazard ratio [HR] 1.46, 95% CI 1.19–1.80, $P = 0.0003$) and upper digestive location (HR 1.51, 95% CI 1.23–1.86, $P < 0.0001$) at diagnosis were associated with the occurrence of anal ulceration. Conversely, ileal location (L1) was associated with a lower risk of anal ulceration (L2 vs L1 HR 1.51, 95% CI 1.11–2.06, $P = 0.0087$; L3 vs L1 HR 1.42, 95% CI 1.08–1.85, $P = 0.0116$). The risk of fistulizing perianal CD (pCD) was doubled in patients with a history of anal ulceration (HR 2.00, 95% CI 1.45–2.74, $P < 0.0001$). Among the 352 patients with at least 1 episode of anal ulceration without history of fistulizing pCD, 82 (23.3%) developed fistulizing pCD after a median follow-up of 5.7 years (interquartile range 2.8–10.6). In these patients with anal ulceration, the diagnostic period (pre vs biologic era), exposure to immunosuppressants, and/or anti–tumor necrosis factor did not influence the risk of secondary anoperineal suppuration.**

DISCUSSION: **Anal ulceration is frequent in pediatric-onset CD, with nearly half of patients presenting with at least 1 episode after 10 years of evolution. Fistulizing pCD is twice as frequent in patients with present or past anal ulceration.**

**KEYWORDS:** Crohn's disease; anal ulceration; fistulizing pCD

**SUPPLEMENTARY MATERIAL** accompanies this paper at http://links.lww.com/AJG/C943.

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## INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disease whose natural history is characterized by periods of remission and relapse with a heterogeneous disease course (1,2). Perianal CD (pCD) is a severe phenotype of CD observed in about 40% of patients including fistulizing lesions (fistulas and abscesses) and nonfistulizing lesions (fissures, ulcerations, and strictures) (3–7). Although described in about 5%–40% of patients with CD, the

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natural history of anal ulceration in CD is largely unknown especially in pediatric-onset CD, which is characterized by a more severe disease course resulting in high rate of surgery, disability, as well as specific complications such as growth or pubertal delay (8–10). The prognosis of anal ulceration is uncertain. They seem to heal slowly in about half of the cases within 1 year but may also cause secondary fistulizing lesions in 5%–25% of cases (11,12). To date, no therapeutic strategy, including biologics alone or in combination, has been described as effective on anal ulcers (12).

A better characterization of the epidemiology of anal ulcerations and understanding of the natural history, risk factors, and management is warranted. The limited data available come from small cohorts from referral centers with inherent selection bias, which do not adequately inform population-level estimates. Population-based observational cohort studies evaluate an entire population in a defined geographic area during an extended period. They avoid selection biases associated with referral center cohort studies and are ideal to inform on natural history of disease.

Hence, the aim of this study was to describe the natural history of anal ulceration in pediatric-onset CD using data from a population-based cohort. We also examined risk factors associated with anal ulceration and with the development of fistulizing pCD.

## METHODS

### Study population

All patients from the prospective EPIMAD registry with a diagnosis of CD between 1988 and 2011 younger than 17 years at diagnosis were included. The EPIMAD registry covers a large area of Northern France with almost 6 million inhabitants representing 9.3% of the entire French population. The methodology of the EPIMAD registry has been previously described in detail (13). Briefly, all patients consulting for the first time for symptoms compatible with inflammatory bowel disease (IBD) were reported since 1988 by adult (n = 250) and pediatric (n = 12) gastroenterologists, regardless of their type of practice (hospital [n = 94] or private [n = 168]). Only patients who were residents in Northern France at the time of diagnosis were included. Interviewing practitioners collected data for each new case from medical records using a standardized questionnaire including age, sex, year of diagnosis, clinical, radiological, endoscopic, and histologic findings at the time of diagnosis. A final diagnosis of CD, ulcerative colitis, or IBD—unclassified was made by 2 expert gastroenterologists according to previously defined criteria.

### Study design and data collection

This study was part of the INSPIRED (impact of therapeutic strategies on the natural history of pediatric IBD) project whose methodology has already been presented in detail (14). Briefly, additional data were collected from the charts by trained research assistants, and each file was further audited by 2 independent expert gastroenterologists. Baseline characteristics collected were type of IBD, age at diagnosis, sex, IBD phenotype according to Paris classification (15,16), smoking status at baseline, and extraintestinal manifestations. At each visit, anoperineal involvement was detailed according to the existence of a fistula, abscess, anal ulcerations including fissures and ulcers, skin tags, or anal stenosis. During follow-up, endoscopic and radiological evaluation were collected, and disease location and behavior were classified at each visit. Dates of initiation and withdrawal, and dosage and reason for withdrawal of the following medications were recorded for each patient: oral and topical 5-aminosalicylic acid, oral and topical corticosteroids, immunosuppressants (IS) (azathioprine, 6-mercaptopurine, and methotrexate), anti–tumor necrosis factor (TNF) agents (infliximab, adalimumab, golimumab, and certolizumab), and antibiotics. Combination therapy was restricted to patients exposed to IS within the 30 days after anti-TNF initiation. Patients were followed from diagnosis to December 31, 2013, date of loss to follow-up, or date of death.

### Definitions and outcomes

Fissure or superficial ulceration (U1 according to Cardiff classification) and cavitating ulcers (U2) were grouped under the general term anal ulcerations. Anal fistulas and abscesses were grouped under the term fistulizing pCD. Only the first episodes of anoperineal ulcerations and fistulizing pCD were considered.

### Statistical analyses

The study population was described using numbers and percentages for qualitative characteristics and using medians and interquartile ranges (IQRs) for quantitative characteristics. Cumulative probabilities of anal ulceration occurrence were described and estimated using survival curves (Kaplan-Meier curves). The risk factors for anal ulceration were first studied using univariable models (log-rank test). In a second step, a Cox model (multivariable model) was used, including variables related to the occurrence of anal ulceration with a statistical significance level $<0.15$ in the univariable models. A top-down stepwise method was then used to retain in the final model only the variables significantly related to the occurrence of anal ulceration ($P < 0.05$).

To estimate and compare the incidence of fistulizing pCD in patients with and without previous anal ulceration, a time-dependent survival model was used. The principle is as follows: A patient with anal ulceration at diagnosis is considered to be in the "anal ulceration" group, a patient who never had anal ulceration during the course of his or her illness is considered to be in the "no anal ulceration" group, and a patient who had anal ulceration during his or her follow-up is considered to be in the "no anal ulceration" group until the ulceration occurs, and then in the "anal ulceration" group from the onset of the ulceration. The risk of fistulizing pCD according to "anal ulceration" status was studied univariately (univariable Cox model) and then, after taking into account potential factors for the occurrence of fistulizing pCD, in a multivariable Cox model. The adjustment factors were the following characteristics, collected at diagnosis: sex, age, rectal involvement, location, phenotype, extraintestinal manifestations (EIMs), Harvey-Bradshaw score, and smoking status.

Finally, the study of risk factors for the occurrence of fistulizing pCD after anal ulceration was performed in patients with ulceration at diagnosis or during follow-up, excluding those with fistulizing pCD concomitant or before ulceration. A multivariable Cox model was built, including variables related to the occurrence of fistulizing pCD with a statistical significance level $< 0.15$ in the univariable models. A top-down stepwise method was then used to retain in the final model only the variables significantly related to the occurrence of fistulizing pCD ($P < 0.05$). The proportional hazards assumption was checked for all final Cox regression models. Statistical analyses were performed with the R software (17,18).

This study was approved by the Comité de Protection des Personnes (CPP) of Amiens (CNIL 915476, CPP TB/LR/2014-25, CCTIRS 14-519, September 4, 2014).

**Table 1. Baseline characteristics of patients (n = 1,005)**

| Characteristics | N (%) |
|---|---|
| Female sex | 450 (44.8) |
| Age ≥10 yr | 885 (88.1) |
| Age, yr, median (IQR) | 14.4 (12.0–16.1) |
| Location (unknown, n = 12) | |
| L1, ileal | 213 (21.4) |
| L2, colonic | 234 (23.6) |
| L3, ileocolonic | 546 (55.0) |
| Upper gastrointestinal tract involvement | 296 (29.5) |
| Rectal involvement | 395 (39.3) |
| Behavior (unknown, n = 3) | |
| B1, inflammatory | 825 (82.3) |
| B2, stricturing | 145 (14.5) |
| B3, penetrating | 32 (3.2) |
| Extraintestinal manifestations (unknown, n = 25) | |
| Present | 226 (23.1) |
| Axial arthritis | 17 (1.7) |
| Peripheral arthritis | 88 (9.0) |
| Ocular involvement | 14 (1.4) |
| Erythema nodosum | 51 (5.2) |
| Pyoderma gangrenosum | 2 (0.2) |
| Aphtosis | 113 (11.5) |
| Primitive sclerosing cholangitis | 5 (0.5) |
| Not present | 754 (76.9) |
| Smoking (unknown, n = 190) | |
| Active | 92 (9.2) |
| No | 718 (71.4) |
| Past | 5 (0.5) |
| pCD (unknown, n = 20) | |
| Present | 308 (31.3) |
| Ulceration | 257 (26.1) |
| Concomitant with fistulizing pCD | 20 (2.0) |
| Concomitant with skin tag | 9 (0.9) |
| Fistulizing pCD | 63 (6.4) |
| Abscess | 36 (3.7) |
| Fistula | 52 (5.3) |
| Anal stenosis | 1 (0.1) |
| Skin tag | 22 (2.2) |
| Others | 9 (0.9) |
| Not present | 677 (68.7) |

IQR, interquartile range; pCD, perianal Crohn's disease.

## RESULTS

### Clinical characteristics at diagnosis

Between 1988 and 2011, 1,005 patients with a diagnosis of CD younger than 17 years of age were enrolled in the EPIMAD registry. Demographic and clinical characteristics at diagnosis are depicted in Table 1. Almost half of patients were female (n = 450, 44.8%). Median age at diagnosis and median duration of follow-up were, respectively, 14.4 years (IQR 12.0–16.1) and 8.8 years (4.6–14.2) (6,271 person-years). Most patients had ileocolonic location (L3, n = 546 [55.0%]) and inflammatory behavior (B1, 825 [82.3%]). Rectal involvement was observed in 395 (39.2%) patients. pCD was observed in 308 (31.3%) patients at diagnosis including 257 (26.1%) patients with anal ulcerations and 63 (6.4%) with fistulizing pCD. Among them, 20 (2%) patients had both ulcerations and fistulizing pCD at diagnosis, representing 7.8% of patients with anal ulcerations. Skin tags were observed in 22 (2.2%) patients at diagnosis including 9 (0.9%) in association with anal ulcerations. Only 1 patient had anal stricture at diagnosis.

### Risk of anal ulceration

After a median follow-up of 8.8 years (IQR 4.6–14.2) and 6,271 person-years, 421 (41.9%) patients had at least 1 episode of anal ulceration. One hundred sixty-four (16.3%) patients developed anal ulceration after CD diagnosis. The cumulative probabilities of having 1 or more anal ulcerations at 5 and 10 years after diagnosis were 38.4% (95% confidence interval [CI] 35.2–41.4) and 44.0% (95% CI 40.5–47.2), respectively (Figure 1).

Among the 421 patients who suffered from an anal ulceration, 6 needed a stoma in the following year. The risk of stoma was, respectively, 1.4% (95% CI 0.3–2.6) and 1.9% (95% CI 0.6–3.2) 1 and 2 years after anal ulceration.

### Factors associated with anal ulceration occurrence

In multivariable analysis, factors at diagnosis associated with anal ulceration occurrence at diagnosis or during follow-up were the presence of EIMs (hazard ratio [HR] 1.39, 95% CI 1.12–1.73; $P = 0.0028$), upper gastrointestinal tract involvement (HR 1.52, 95% CI 1.23–1.86; $P < 0.0001$), active smoking (HR 0.68, 95% CI 0.46–1.00; $P = 0.0485$), and ileocolonic/colonic location (L2 vs L1, HR 1.49, 95% CI 1.10–2.03, $P = 0.0107$; L3 vs L1, HR 1.41, 95% CI 1.07–1.84, $P = 0.0131$) (Figure 2 and Table 2).

### Risk of fistulizing pCD according to anal ulceration

In time-dependent analysis, the risk of fistulizing pCD was doubled when patients had a history of anal ulceration (HR 2.02, 95% CI 1.49–2.73; $P < 0.0001$). Similar results were observed after adjustment for patient characteristics at disease diagnosis including sex, age, presence of EIMs, rectal involvement, disease location and phenotype, Harvey-Bradshaw score, and smoking status (HR 2.00, 95% CI 1.45–2.74; $P < 0.0001$).

### Risk of secondary fistulizing pCD and associated risk factors in patients with anal ulceration

Among the 421 patients who suffered from anal ulceration, 352 (83.6%) patients had no history of fistulizing pCD. Among them, 82 (23.3%) patients developed fistulizing pCD. The risk of developing fistulizing pCD was, respectively, of 17.4% (95% CI 13.0–21.6) and 27.7% (95% CI 21.8–33.2) 5 and 10 years after anal ulceration.

In the year after the diagnosis of anal ulceration, 228 patients were exposed to corticosteroid therapy, 108 to antibiotic therapy, 167 to IS, 59 to anti-TNF, and 29 to the combination of IS and anti-TNF. No patient was treated with anti-TNF before anal ulceration diagnosis. Treatments used after the diagnosis of secondary fistulizing pCD were not considered.

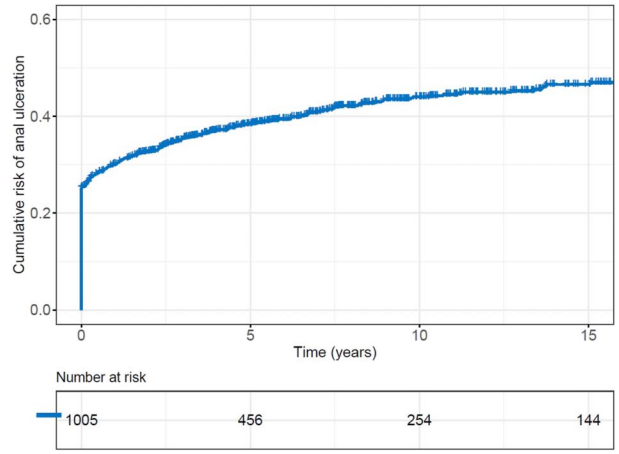


**Figure 1.** Cumulative risk of anal ulceration in patients with pediatric-onset Crohn's disease.

In multivariable analysis, factors associated with the occurrence of fistulizing pCD after anal ulceration were inflammatory skin tags (HR 2.17, 95% CI 1.04–4.51, $P = 0.037$) and the use of antibiotic therapy within 1 year of the diagnosis of ulceration but before the diagnosis of fistulizing pCD (HR 1.58, 95% CI 1.01–2.48, $P = 0.046$). Exposure to corticosteroid therapy, IS, and/or anti-TNF did not influence the risk of fistulizing pCD (Table 3). Also, the diagnostic period (pre vs biologic era) did not influence the risk of fistulizing pCD ($P = 0.98$) (see Supplementary Figure 1, Supplementary Digital Content 1, http://links.lww.com/AJG/C943).

## DISCUSSION

This study evaluated the risk of anal ulcerations and their natural history in a 2-decade population-based study including 1,000 patients with pediatric-onset CD with a median follow-up of more than 8 years representing a total follow-up of 6,271 patient-years. To the best of our knowledge, this is the largest study concerning anal ulcerations in IBD published yet. We observed that nearly 1 in 2 patients developed anal ulceration during the first 10 years from diagnosis. EIMs, upper digestive location, and colonic/ileocolonic location (vs ileal location) at diagnosis were associated with the occurrence of anal ulceration. The risk of fistulizing pCD was doubled in patients with a history of anal ulceration.

Most of the literature reduces anoperineal involvement to suppurative lesions. Very few studies in CD as reported the risk of anal ulcerations of anal ulceration in CD. Population-based study from administrative data set reported an overall prevalence of chronic anal fissure of 4% in patients with CD (19). The sources of the data can explain an underestimation of the risk. In our study, patients were included prospectively and consecutively in a population-based registry, and highly detailed data were retrieved from patient records by experts rather than from administrative databases. Similar risk was observed by Bouguen et al (20) who reported the natural history of anal ulceration in a referral center cohort of 99 patients at the biologic era. However, in another French population-based study including 331 adult patients with CD diagnostic between 1994 and 1997, 23% of them experienced anal ulceration (21). Finally, a US population-based study, including a total of 310 adult and pediatric patients with CD, reported a cumulative incidence rate of anal ulceration at 10 years of 17% (3).

Finally, a more aggressive disease course is observed in pediatric-onset CD with anal ulceration, as for luminal disease. We observed that anal ulcerations represent frequently an inaugural element in the proctological history of patients. Ulcerations seem much more frequent at diagnosis than fistulizing pCD, which appear secondarily. These results advocate for systematic anal examination at both diagnosis and follow-up visit as both MRI and colonoscopy underestimated the presence of ulceration.

We identified EIMs, upper gastrointestinal tract involvement, and ileocolonic/colonic location (vs ileal location) as associated with an increased risk of anal ulceration. Disease location is an important predictor of fistulizing pCD. Fistulizing pCD is more common when colonic disease is present. Similar results were

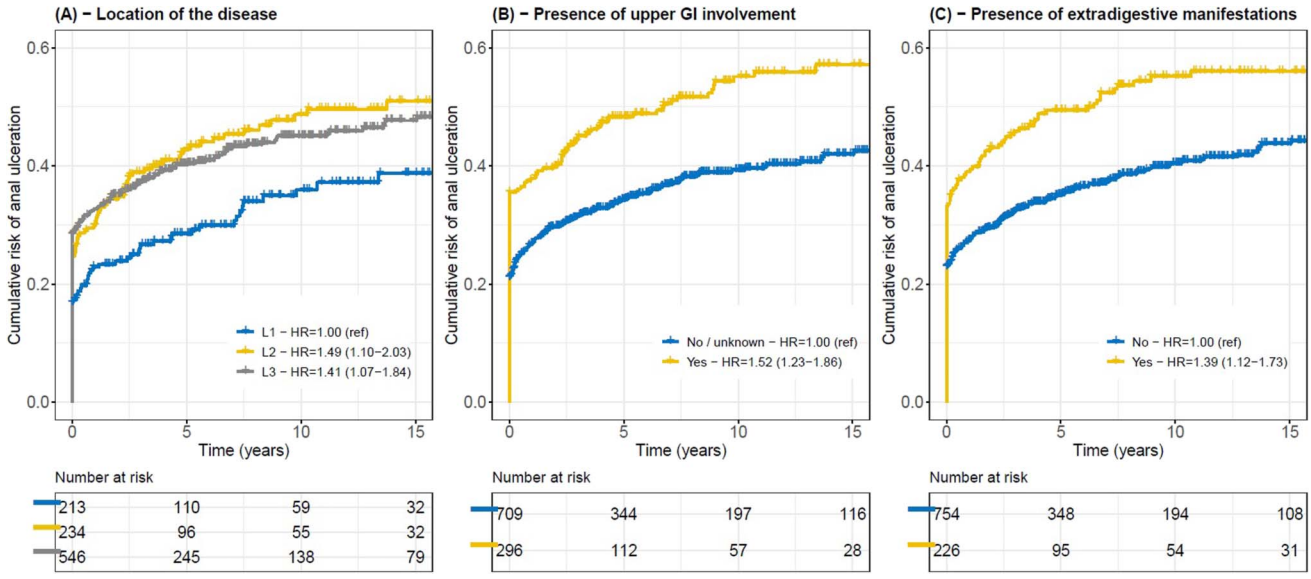


**Figure 2.** Cumulative incidence of anal ulceration according to the location of the disease (**a**), presence of upper gastrointestinal involvement (**b**), and presence of extradigestive manifestations (**c**). GI, gastrointestinal; HR, hazard ratio.

**Table 2. Risk factors associated with the occurrence of anal ulceration during follow-up; univariable and multivariable analyses (n = 1,005, 6,271 person-years)**

| Characteristics | No. of occurrences | Person-years | Log-rank test (*P* value) | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| | | | | HR | 95% CI | *P* value |
| Sex | | | 0.73 | | | |
| Male | 233 | 3,308 | | | | |
| Female | 188 | 2,962 | | | | |
| Age | | | **0.0033** | | | NS |
| <10 yr old | 65 | 609 | | | | |
| ≥10 yr old | 356 | 5,662 | | | | |
| Behavior | | | **0.0048** | | | NS |
| B1, inflammatory | 362 | | | | | |
| B2, stricturing | 49 | | | | | |
| B3, penetrating | 9 | | | | | |
| Location | | | **0.0025** | | | **0.0172** |
| L1, ileal | 69 | 1,460 | | 1.00 | — | — |
| L2, colonic | 107 | 1,392 | | 1.49 | 1.10–2.03 | |
| L3, ileocolonic | 240 | 3,361 | | 1.41 | 1.07–1.84 | |
| Upper gastrointestinal tract involvement | | | **<0.0001** | | | **<0.0001** |
| Not present/unknown | 267 | 4,752 | | 1.00 | — | |
| Present | 154 | 1,519 | | 1.52 | 1.23–1.86 | |
| Rectal involvement | | | 0.0680 | | | NS |
| Not present | 243 | 4,068 | | | | |
| Present | 178 | 2,203 | | | | |
| Extraintestinal manifestations | | | **<0.0001** | | | **0.0028** |
| Not present | 271 | 4,593 | | 1.00 | — | |
| Present | 140 | 1,501 | | 1.39 | 1.12–1.73 | |
| Smoking | | | **0.0125** | | | **0.0403** |
| No/past/unknown | 393 | 5,570 | | 1.00 | — | |
| Active | 28 | 701 | | 0.68 | 0.46–1.00 | |

CI, confidence interval; HR, hazard ratio; NS, nonsignificant ($P > 0.05$).
Bold entries are for significative results.

reported for anal ulceration in adult population (21). These results should encourage practitioners to efficiently treat patients presenting with rectal involvement to avoid the onset of both ulcerating and fistulizing perianal disease. The association between EIMs and anal ulceration has only been reported once in adults CD (21). A direct link between these 2 entities seems difficult to identify. However, EIMs, as upper gastrointestinal involvement, are clearly identified as risk factors for disabling disease in CD.

The negative association between smoking and the risk of ulceration is more difficult to interpret. Smoking is a known risk factor for CD and more severe disease course, but does not seem to increase the risk of perianal fistulizing complications. This negative association may also be explained by methodological issues. The correct identification of the smoking variable is often difficult in this type of study. This is probably even more true in the pediatric population. The number of smokers is relatively low, and the number of missing data is important.

Anal ulcerations are a worrying process. Our study supports the general idea that anal ulceration is a first step to a process, leading to fistulizing lesion. However, there was until then little evidence to support this hypothesis. Fleshner et al (11) studied 56 patients with anal ulcerations in the 90s and showed that fissures could progress to fistula or abscesses in up to 26%. We observed that anal ulcerations doubled the risk of fistulizing pCD. This relationship was found in the same proportion in another French adult population–based (21).

We identified as risk factors for the occurrence of fistulizing pCD after anal ulceration, inflammatory skin tags, and the use of antibiotic therapy within 1 year of the diagnosis of ulceration. This relation may be explained by a sometimes-difficult diagnosis of fistulizing pCD, leading to an underestimated rate of abscesses and fistulas, whereas the perineum is already globally inflammatory and suppurative. Skin tags may also be interpreted as a surrogate marker of pCD severity.

Exposure to corticosteroid therapy, IS, and/or anti-TNF did not influence the risk of fistulizing pCD. Moreover, the diagnostic period (pre vs biologic era) did not influence the risk of secondary

**Table 3. Associations of the characteristics at diagnosis with the occurrence of secondary fistulizing pCD; univariable and multivariable analysis (n = 352, 2,922 person-years)**

| Characteristics | No. of occurrences | Person-years | Log-rank test (*P* value) | Multivariable analysis HR | 95% CI | *P* value |
|---|---|---|---|---|---|---|
| Sex | | | 0.15 | | | |
| Male | 46 | 1,413 | | | | |
| Female | 36 | 1,509 | | | | |
| Age at CD diagnosis | | | 0.46 | | | |
| <10 yr old | 15 | 443 | | | | |
| ≥10 yr old | 67 | 2,479 | | | | |
| Location | | | 0.14 | | | NS |
| L1, ileal | 11 | 387 | | | | |
| L2, colonic | 21 | 573 | | | | |
| L3, ileocolonic | 33 | 1,354 | | | | |
| Upper gastrointestinal tract involvement | | | 0.75 | | | |
| Not present | 61 | 2,135 | | | | |
| Present | 21 | 787 | | | | |
| Rectal involvement | | | 0.42 | | | |
| Not present | 52 | 1,983 | | | | |
| Present | 30 | 939 | | | | |
| Behavior | | | 0.13 | | | NS |
| B1, inflammatory | 53 | 1,811 | | | | |
| B2, stricturing | 15 | 463 | | | | |
| B3, penetrating | 0 | 67 | | | | |
| Extraintestinal manifestations | | | 0.37 | | | |
| Not present | 62 | 2,074 | | | | |
| Present | 20 | 849 | | | | |
| Morphological activity | | | 0.27 | | | |
| Active | 67 | 2,345 | | | | |
| Non-active | 1 | 105 | | | | |
| Harvey-Bradshaw score | | | 0.19 | | | |
| Inactive (<4) | 7 | 381 | | | | |
| Active (4–12) | 65 | 2,245 | | | | |
| Severe (>12) | 10 | 297 | | | | |
| Associated skin tag | | | **0.0173** | | | **0.0342** |
| Not present | 74 | 2,800 | | 1.00 | — | |
| Present | 8 | 123 | | 2.21 | 1.06–4.60 | |
| Smoking | | | 0.23 | | | |
| No/past/unknown | 78 | 2,665 | | | | |
| Active | 4 | 258 | | | | |
| Use in the following year | | | | | | |
| Corticosteroids | | | 0.40 | | | |
| No | 25 | 980 | | | | |
| Yes | 57 | 1,942 | | | | |
| Antibiotic therapy | | | **0.0466** | | | **0.0490** |
| No | 49 | 2,049 | | 1.00 | — | |

**Table 3.** (*continued*)

| Characteristics | No. of occurrences | Person-years | Log-rank test (*P* value) | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| | | | | HR | 95% CI | *P* value |
| Yes | 33 | 874 | | 1.55 | 1.00–2.42 | |
| Immunosuppresant | | | 0.71 | | | |
| No | 47 | 1,767 | | | | |
| Yes | 35 | 1,156 | | | | |
| Anti-TNF | | | 0.71 | | | |
| No | 71 | 2,591 | | | | |
| Yes | 11 | 331 | | | | |
| Combination therapy | | | 0.74 | | | |
| No | 77 | 2,781 | | | | |
| Yes | 5 | 141 | | | | |

CI, confidence interval; HR, hazard ratio; NS, nonsignificant ($P > 0.05$); pCD, perianal Crohn's disease; TNF, tumor necrosis factor.
Bold entries are for significative results.

fistulizing pCD. Although anti-TNF agents are associated with long-term outcome improvement in luminal CD, they do not seem to improve anal ulceration history. Similar results were observed in adults (12). A suboptimal use of these molecules during the study period, late, and rarely in combination therapy could explain these results, which must in all cases be confirmed by prospective studies.

Our work had some limitations. If data were collected retrospectively, they were, however, recorded at each visit of the patient from diagnosis to maximal follow-up and reviewed by 2 expert gastroenterologists. Level of detail of the data does not allow for soptimal characterization of pCD, especially according to the Ulceration, Fistula/abscess, and Stricture classification (22), and we do not have systematic mention about healing.

The major strengths of our study are the use of a large unselected cohort of pediatric patients with CD included prospectively and consecutively in a population-based registry and highly detailed data (except Ulceration, Fistula/abscess, and Stricture classification) retrieved from patient records by experts rather than from administrative databases. In addition, this constitutes the longest follow-up of a cohort of unselected pediatric patients with CD. This study provides reliable data on the natural history of anal ulceration in CD impacting real-life practice. Finally, it targets a frequent clinical sign that is still insufficiently taken into consideration in health care practice and in the literature.

Anal ulceration is a frequent manifestation in pediatric-onset CD because almost half of the patients have presented at least 1 episode after 10 years of evolution. EIMs, upper digestive location, and colonic disease at diagnosis were associated with the occurrence of anal ulceration. Anal ulceration is a risk factor for fistulizing pCD, doubling the risk of suppuration. New studies are needed to better understand the impact of biologics on these lesions.

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## CONFLICTS OF INTEREST

**Guarantor of the article:** Perrine Mortreux, MD.

**Specific author contributions:** P.M.: conceptualization; methodology; writing—original draft; and writing—review and editing. A.L.: formal analysis; methodology; software; validation; visualization; and writing—review and editing. C.D.: data curation; writing—review and editing. D.L.: data curation; investigation; validation; and writing—review and editing. V.B., C.S., N.G., and P.W.: data curation; writing—review & editing. C.G.-R.: data curation; funding acquisition; investigation; and writing—review and editing. G.S.: data curation; writing—review & editing. M.F.: conceptualization; data curation; funding acquisition; investigation; validation; and writing—review and editing. D.T.: data curation; writing—review and editing. L.S.: conceptualization; validation; and writing—review and editing. H.S.: formal analysis; methodology; software; validation; visualization; and writing—review and editing. All the authors approved the final version of the manuscript.

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**Data transparency statement:** Data sharing requests will be considered by the INSPIRED study group on written request to helene.sarter@chru-lille.fr. Deidentified participant data and data dictionary will be available, after approval of a written proposal and a signed data access agreement.

## Study Highlights

### WHAT IS KNOWN

- ✓ Anal ulcerations are frequently observed in pediatric-onset Crohn's Disease.
- ✓ Perianal CD is characterized by a more severe disease course resulting in growth or pubertal delay.

### WHAT IS NEW

- ✓ Extraintestinal manifestations, upper gastrointestinal tract involvement, and colonic disease at diagnosis were associated with anal ulcerations.
- ✓ Anal ulceration is a risk factor for fistulizing perianal CD.

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