

# Postoperative Complications in Pediatric Inflammatory Bowel Disease: A Population-based Study

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**Background:** We describe, in a population-based cohort, the incidence of and factors associated with postoperative complications (POCs) in pediatric-onset inflammatory bowel disease.

**Methods:** Using the pediatric population-based EPIMAD Cohort (1988–2004), among 692 incident inflammatory bowel disease cases, 128 patients with Crohn's disease (CD) and 25 with ulcerative colitis (UC) (22%) had undergone at least 1 major abdominal surgery at a median age of 16 years [interquartile range, Q1–Q3 = 14–17]. Factors associated with POC were assessed using Cox models.

**Results:** After a median postoperative follow-up of 8 years (3–12), 76 (49.7%) patients had experienced at least 1 POC with a total of 113 complications. The frequency of severe POC (grade >2) was similar in CD and UC (28% of all complications versus 27%,  $P = 0.95$ ). A total of 64 early POCs (within 30 d of surgery) were observed in 47 patients (31%), with 33 being infectious and 31 noninfectious, higher in UC than in CD (25% of patients with CD versus 60% of patients with UC,  $P < 0.001$ ). Forty-nine late POCs ( $\geq 30$  d) were observed in 37 patients (24%). The occurrence of late POC was similar in UC and CD. The cumulative probability of POC was 31% (95% confidence interval, 24–39) at 1 month, 46% (38–54) at 1 year, and 48% (41–57) at 5 years. Multivariate analysis found that the UC type was the only factor associated with early POC (hazard ratio = 2.9; 95% confidence interval, 1.6–5.4).

**Conclusions:** One-half of the children with inflammatory bowel disease had experienced at least 1 POC. Only UC relative to CD was significantly associated with an increased risk of early POC.

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Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic diseases for which 8% to 20% of patients are diagnosed under the age of 20 years. Previous studies<sup>1–4</sup> showed that clinical presentation and natural history of pediatric-onset IBD was particular, with more extensive and aggressive disease accompanied by growth failure and malnutrition in approximately 25% of cases.<sup>5</sup> Moreover, epidemiological data indicate that IBD incidence, particularly of CD in this age range, is still rising.<sup>6–8</sup> In our population-based pediatric IBD cohort (EPIMAD Registry), the cumulative probability of intestinal resection in CD and of colectomy in UC 5 years after diagnosis was 34% and 20%, respectively.<sup>1,2</sup>

Surgery may be associated with postoperative complications (POC). In adults, POCs were reported from 11% in a Swedish cohort<sup>9</sup> to 14% in a population-based study from Olmsted County (USA).<sup>10</sup> In another study performed in Olmsted County, about one-third of patients with CD experienced at least 1 early POC (within 30 d after surgery) and one-fourth experienced at least 1 late POC (at least 30 d after surgery).<sup>11</sup> Some data on POC in pediatric IBD are available from tertiary referral centers. However, the prevalence of POC and the underlying associated factors are unknown in population-based pediatric-onset IBD cohorts.

The aims of our study were: (1) to assess the prevalence of POC in children with IBD found in our population-based EPIMAD registry, (2) to assess the prevalence of early complications (within 30 d after surgery) and late complications (at least 30 d after), and (3) to identify underlying factors associated with the risk of POC, including infectious POC.

## PATIENTS AND METHODS

### Patient Population

All patients younger than 17 years at the time of IBD diagnosis were included. They were found in the EPIMAD Registry, had been diagnosed with CD or UC from January 1988 to December 2004, and had undergone their first intestinal resection (including colectomy for UC) before the age of 18.

The EPIMAD Registry is a prospective population-based study recording all the incident cases of IBD from 1988 to the present in northern France. This study area includes 5,790,526 inhabitants, which represents 9.3% of the French population and is divided into 4 regions. The population below 17 years was as follows: Nord: 593,837, Pas de Calais: 332,228, Somme: 115,969, and Seine-Maritime: 270,107 with a total of 1,312,141 children. The EPIMAD Registry has previously been described.<sup>6–8</sup> Data for all patients diagnosed with IBD from January 1, 1988, to December 31, 2004, were collected from all adult ( $n = 250$ ) and pediatric ( $n = 12$ ) gastroenterologists practicing in the private and public sectors. Only residents of the studied areas at the time of diagnosis were included. Each gastroenterologist reported all patients being consulted for the first time with clinical symptoms compatible with IBD. The gastroenterologist was contacted by phone at least 3 times per year by an investigator. This investigator visited the gastroenterologist's office and collected data from medical charts on a standardized questionnaire for each new case. Main data collected included age, sex, year of diagnosis, interval between onset of symptoms and diagnosis, and clinical, radiological, endoscopic, and histological findings at the time of diagnosis. The final diagnosis of IBD was established by 2 expert gastroenterologists and was recorded as definitive, probable, or possible according to previously published criteria.<sup>12</sup> Only definitive and probable cases were considered for further analysis.

### Additional Data Collection for This Study

Data were extracted from medical charts of adult and pediatric gastroenterologists and were collected in standardized questionnaires specifically designed for the study. All records were reviewed for accuracy and completeness and approved by the principal investigator (E.P.). Sociodemographic characteristics were collected at diagnosis and at the time of the first intestinal resection: age, sex, smoking status, weight, and height. The digestive location and behavior was defined according to the Montreal Classification.<sup>13</sup> For CD, stricturing (B2) and penetrating (B3) behaviors were pooled and defined as “complicated behavior.” At the time of the first intestinal resection, anoperineal

lesions included abscesses and fistulae, and extraintestinal manifestations were defined as joint, skin, ocular, and hepatobiliary manifestations.

Only intestinal resections were considered as ileocecectomy, right ileocelectomy (both pooled together), partial or total colectomy (ileorectal anastomosis and ileoanal anastomosis), and small bowel resection. Appendectomy, stricturoplasty, and perianal surgery were excluded from analysis. The presence of ileostomy was collected as data.

Exposure to treatments within the 3 months before the first intestinal resection was specified in detail: systemic steroids (SS), immunosuppressants including azathioprine, methotrexate, 6-mercaptopurine, cyclosporine, antitumor necrosis factor alpha (anti-TNF- $\alpha$ ) therapy such as infliximab and adalimumab, and artificial nutrition (enteral or parenteral nutrition). At the time of the first intestinal resection, antibiotic therapy, antibiotic prophylaxis, and thromboembolic prophylaxis data were collected. Laboratory data were also recorded including albumin, hemoglobin, and C-reactive protein levels. Follow-up duration was defined as the time between the first surgical intestinal resection and the last follow-up visit.

### Classification of Complications

Complications were pooled in 4 groups. The first group, “extra-abdominal and infectious complications,” included urinary tract infection, pneumonia, *Clostridium difficile* infection, *Candida* infection, septicemia, and other infectious syndromes. The second group, “abdominal infectious complications,” included wound infection, peritonitis, intraabdominal abscess, and anastomotic fistula. The third group, “mechanical complications,” included ileus, digestive hemorrhage, hernia, and ileal pouch dysfunction and obstruction. The fourth group, “other complications,” included thromboembolic complications, healing problems, anemia, and hematoma.

The complications were classified into 4 severity grades according to Dindo et al.<sup>14</sup> Grade 1: complications requiring a symptomatic medical treatment such as antiemetics; grade 2: complications requiring intravenous access for parenteral nutrition, antibiotic therapy or transfusion; grade 3: complications requiring radiological, surgical, or endoscopic treatment with or without general anesthesia; grade 4: life-threatening complications with single- or multi-organ failure requiring intensive care; grade 5: death of the patient. Severe POC was defined as POC with a grade  $>2$ . Complications were also divided into “early complications” when they occurred within 30 days after surgery, and “late complications” when they occurred after the 30th postoperative day.

### Statistical Analysis

Quantitative variables were expressed as median and interquartile ranges [Q1-Q3]. Qualitative variables were expressed as frequency and percentage. The comparison of quantitative variables was performed using the Mann-Whitney test. For qualitative variables, we used chi-square or Fisher's exact test. The cumulative incidence curve of POC in this pediatric cohort was

calculated using the Kaplan–Meier method. The start date is the date of the first intestinal resection. The time to event was defined as the time between the first intestinal resection and the first POC. For patients who did not have POC, this observation was not taken into account at the date of the last follow-up visit. The identification of factors associated with the occurrence of POC (as well as early, late, and infectious POC) was performed by bivariate Cox proportional hazards models. Parameters with a  $P < 0.2$  in bivariate analyses were introduced into a Cox proportional hazards multivariable regression with stepwise selection. Results are expressed as hazard ratio (HR) with 95% confidence intervals. Data were analyzed with SAS software V.9.3 (SAS, Chicago, IL). A  $P \leq 0.05$  was considered statistically significant.

## RESULTS

### Sociodemographic, Clinical, and Therapy Characteristics at the Time of the First Intestinal Resection

Between January 1988 and December 2004, 692 patients (532 CD and 160 UC) below 17 years of age at diagnosis were enrolled in the registry at a median age of 13 years [11–15]. Among them, 153 (22%) had undergone intestinal resection before the age of 18 years (128 CD and 25 UC) at a median age of 16 years [14–17], similar to CD and UC ( $P = 0.09$ ). Median time between IBD diagnosis and a first intestinal resection was 18 months [7–42]. Main demographic and clinical

characteristics at the time of a first intestinal resection are given in detail in Table 1. In CD, the most frequent location was ileocolonic (L3) (62%), and 89% of patients had a complicated behavior. In UC, 83% of patients had extensive colonic disease (E3). Data on treatment received within the 3 months before the first intestinal resection showed that more than one-half of the patients ( $n = 86$ ; 57%) had been exposed to SS therapy, approximately one-third to IS ( $n = 54$ ; 36%) and only 5 children (3%) to anti-TNF- $\alpha$  therapy. All patients received preoperative antibiotic prophylaxis and 64% postoperative prophylaxis for thromboembolic complications.

### Description of the First Intestinal Resection

In CD, ileocectomy/right ileocectomy was performed in 76% ( $n = 97$ ) of patients. In UC, 88% ( $n = 22$ ) of patients underwent subtotal colectomy with ileorectal anastomosis and 12% ( $n = 3$ ) coloproctectomy with ileoanal anastomosis.

At the time of the first intestinal resection, laboratory data were available for 104 patients; 71% had anemia, 41% C-reactive protein  $>10$  mg/L, and 14% hypoproteinemia.

### Postoperative Complications

The median total duration of follow-up was 10 years [6–14]. After a median postoperative follow-up of 8 years [3–12], among the 153 patients with pediatric-onset IBD who had undergone at least 1 major abdominal surgery, 76 (49.7%) had experienced at least 1 POC with a total of 113 complications; 51 patients had 1 POC and 25 more than 1. Overall, the frequency of patients

**TABLE 1.** Sociodemographic and Clinical Characteristics at the Time of the Patient's First Intestinal Resection in the Pediatric-onset IBD Cohort ( $n = 153$ )

Characteristics	Total Population ( $n = 153$ ) <sup>a</sup>	CD ( $n = 128$ )	UC ( $n = 25$ )
Male gender	$n = 82$ (54%)	$n = 72$ (56%)	$n = 10$ (40%)
Median age at IBD diagnosis, yr [IQR]	13.5 [11.4–15.3]	13.5 [11.5–15.3]	13.5 [11.2–15.0]
Active smokers at first digestive resection (%)	$n = 13$ (9%)	$n = 12$ (10%)	$n = 1$ (4%)
Median age at first digestive resection, yr [IQR]	15.8 [14.3–17.0]	15.8 [14.5–17.1]	15.1 [14.0–16.4]
Digestive location at first digestive resection (%) <sup>a</sup>		L1, $n = 39$ (31%) L2, $n = 9$ (7%) L3, $n = 77$ (62%) L4, $n = 18$ (14%)	E2, $n = 4$ (17%) E3, $n = 20$ (83%)
Behavior at first digestive resection (%) <sup>a</sup>		B1, $n = 14$ (11%) B2, $n = 73$ (58%) B3, $n = 39$ (31%)	
Perianal disease at first digestive resection (%)		$n = 5$ (4%)	
Extraintestinal manifestations at first digestive resection (%)	$n = 13$ (9%)	$n = 12$ (11%)	$n = 1$ (4%)
Median time between IBD diagnosis and first digestive resection, mo [IQR]	18 [7–42]	19 [7–44]	15 [5–33]
Median postoperative follow-up, yr [IQR]	8 [3–12]	8 [3–12]	7 [4–9]

Diagnoses from 1988 to 2004 were recorded in the EPIMAD population-based registry and those who had undergone their first digestive resection before the age of 18 were selected.

<sup>a</sup>According to the Montreal classification.

with at least 1 POC was significantly higher in UC than in CD (45% of patients with CD versus 72% of patients with UC experienced at least 1 POC,  $P = 0.01$ ). The cumulative probability of any POC was 31% (95% confidence interval, 24–39) at 1 month, 46% (38–54) at 1 year, and 48% (41–57) at 5 years (Fig. 1). Median time before POC was 21 days [7–111] without any difference between CD and UC (23 days [8–134] versus 18 [7–80];  $P = 0.33$ ). The distribution of the POC severity grade was as follows: grade 1, 38% ( $n = 42$ ); grade 2, 35% ( $n = 39$ ); grade 3, 28% ( $n = 31$ ); and grade 4, 0% ( $n = 0$ ). The frequency of severe POC (grade >2) was similar in CD and UC (28% versus 27%;  $P = 0.95$ ).

### Early POCs

A total of 64 early POCs were observed in 47 patients (31%) including 33 infectious and 31 noninfectious POCs. Overall, the frequency of patients with at least 1 early POC was significantly higher in UC than in CD (25% of patients with CD versus 60% of patients with UC experienced at least 1 early POC,  $P < 0.001$ ). Early complications are detailed in Table 2. The median time before early POC was 8 days [5–12] without any difference between CD and UC (CD, 8 days [4–11] versus UC 7 days [5–18];  $P = 0.52$ ). More than half ( $n = 36$ ; 56%) of early POCs were of grade 2 severity, 21 (34%) were grade 1, and 6 (10%) were grade 3 with no difference between CD and UC ( $P = 0.23$ ). Among these early POC, 33 were infectious including 9 abdominal infectious complications and 24 extraabdominal infectious complications.

### Late POCs

A total of 49 late POCs were observed in 37 patients (24%) including 6 infectious and 43 noninfectious complications. Overall, the frequency of patients with at least 1 late POC was similar

in UC and CD (23% of patients with CD versus 28% of patients with UC experienced at least 1 early POC,  $P = 0.63$ ). Late complications are given in detail in Table 3. Median time before late POC was 5.6 months [2.5–28.2], without any significant difference between CD and UC (5.3 [2.1–28.2] versus 5.6 [3.0–33.8],  $P = 0.76$ ). The frequency of severe late complications was similar between complications of grade  $\leq 2$  (49%) and grade >2 (51%) with no difference between CD and UC ( $P = 0.89$ ). Most late complications were mechanical abdominal complications ( $n = 26$ ; 53%). There were also 2 late thromboembolic complications among patients with UC.

### Factors Associated with POCs

#### Factors Associated with All POCs

UC (UC versus CD, HR = 2.2; 95% confidence interval [CI], 1.3–3.8) and the type of intestinal resection (subtotal or total colectomy versus other type of surgery; HR = 1.7; 95% CI, 1.0–2.9) were significantly associated with the risk for POC in bivariate analysis. In multivariate analysis, the only factor significantly associated with POC was UC (UC versus CD, HR = 2.2; 95% CI, 1.3–3.8) (Table 4).

#### Factors Associated with Early POCs

UC (UC versus CD, HR = 2.9; 95% CI, 1.6–5.4), type of intestinal resection (subtotal or total colectomy versus other type of surgery; HR = 2.5; 95% CI, 1.4–4.6), and SS therapy during the 3 months before surgery (HR = 2.0; 95% CI, 1.1–3.9) were significantly associated with the risk for early POC in bivariate analysis. In multivariate analysis, the only factor significantly associated with early POC was UC (UC versus CD, HR = 2.9; 95% CI, 1.6–5.4).

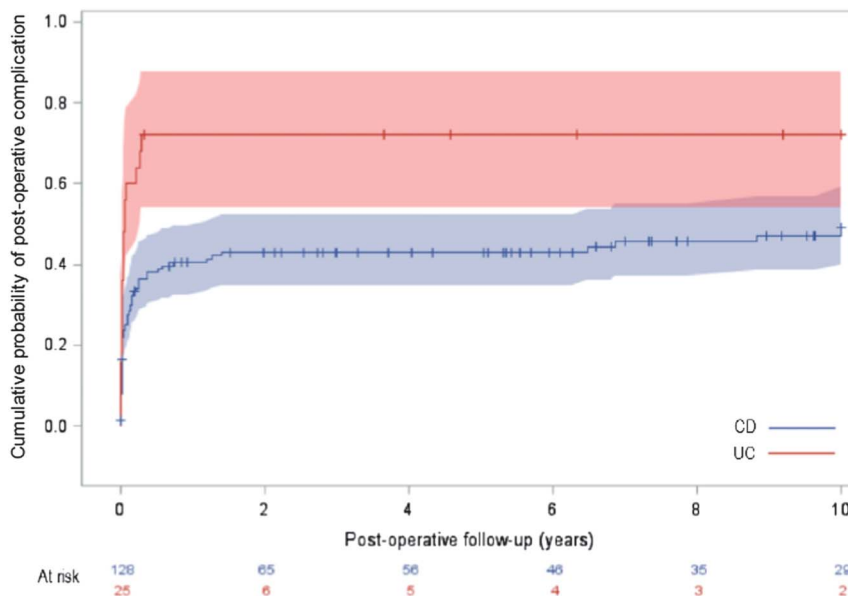


FIGURE 1. Cumulative probability of late POCs in the pediatric-onset IBD cohort ( $n = 153$ ). Diagnoses from 1988 to 2004 were recorded in the EPIMAD population-based registry and those who had undergone their first digestive resection before the age of 18 were selected.



**TABLE 2.** Description of Early POCs in the Pediatric-onset IBD Cohort (n = 153)

Type of Early POCs (n = 64)	CD (n = 42)	UC (n = 22)
Infectious early POC (n = 33)		
Wound abscess	n = 5 (12%)	—
Intraabdominal abscess	n = 3 (7%)	n = 1 (5%)
Septicemia	n = 2 (5%)	n = 1 (5%)
Urinary tract infections	n = 1 (2%)	n = 3 (14%)
<i>Candida</i> infections	n = 3 (7%)	n = 1 (5%)
Other infections	n = 8 (19%)	n = 3 (14%)
Anastomotic leakage	1 (2%)	—
Anastomotic fistulae	1 (2%)	—
Noninfectious (n = 31)		
Anemia	n = 4 (10%)	n = 6 (27%)
Defect of healing	n = 4 (10%)	n = 3 (14%)
Ileus	n = 6 (14%)	—
Bleeding	—	n = 3 (14%)
Others (pain, drug complications, VTE)	n = 4 (16%)	n = 1 (5%)

Diagnoses from 1988 to 2004 were recorded in the EPIMAD population-based registry and those who had undergone their first digestive resection before the age of 18 were selected. VTE, venous thromboembolism.

**Factors Associated with Late POCs**

In bivariate and multivariate analyses, no factor was associated with late POC.

**Factors Associated with Infectious POCs**

In bivariate and multivariate analyses, only UC (UC versus CD, HR = 2.2; 95% CI, 1.0–4.9) was significantly associated with the occurrence of infectious POC.

**TABLE 3.** Description of Late POCs in the Pediatric-onset IBD Cohort (n = 153)

Type of Late POCs (n = 49)	CD (n = 38)	UC (n = 11)
Infectious late POC (n = 6)		
Intraabdominal abscess	n = 1 (3%)	n = 1 (9%)
Anastomotic dehiscence	n = 1 (3%)	—
Other infections	n = 2 (5%)	n = 1 (9%)
Noninfectious late POC (n = 43)		
Obstruction	n = 21 (55%)	n = 5 (45%)
Delayed healing	n = 10 (26%)	n = 2 (18%)
Hernia	n = 2 (5%)	—
Thromboembolic complications	—	n = 2 (18%)
Pain	n = 1 (3%)	—

Diagnoses from 1988 to 2004 were recorded in the EPIMAD population-based registry and those who had undergone their first digestive resection before the age of 18 were selected.

**TABLE 4.** Bivariate and Multivariate Analyses of Factors Associated With POCs in the Total Population (n = 153)

Variables	Bivariate Analysis			Multivariate Analysis		
	HR	95% IC	P	HR	95% IC	P
Male gender	1.2	0.8–1.9	0.41			
Age <14 yr at diagnosis	1.4	0.9–2.2	0.17			
Age at the time of first surgery	1.0	0.9–1.0	0.15			
Time diagnosis to surgery	1.0	0.9–1.1	0.70			
UC	2.2	1.3–3.8	<10 <sup>-2</sup>	2.2	1.3–3.8	<10 <sup>-2</sup>
Extraintestinal manifestations	0.8	0.3–1.7	0.51			
Smoking	1.4	0.8–3.0	0.36			
Corticosteroids	1.2	0.8–1.9	0.48			
Immunosuppressants	1.3	0.8–2.0	0.34			
Artificial nutrition	1.6	1.0–2.5	0.06			
Type of surgery						
Total or subtotal colectomy	2.5	1.4–4.6	0.03			
Definitive stomae	1.2	0.7–2.0	0.46			

**DISCUSSION**

In this population-based cohort of patients with pediatric-onset IBD, 153 children required an initial intestinal resection before the age of 18 years and were followed up for 8 years. Half of them (n = 76; 50%) presented a total of 113 POCs including 51 patients with only 1 POC and 25 with more than 1 POC. Sixty-four early POCs occurred in 47 patients (31%), whereas 37 patients (24%) presented 49 late POC. The cumulative probability of any POC was 31% (95% CI, 24–39) at 1 month, 46% (38–54) at 1 year, and 48% (41–57) at 5 years. The frequency of severe complications (grade >2) was similar in CD and UC. In bivariate analysis, colectomy and UC type were associated with all POCs, SS therapy during the 3 months before surgery, and UC type with early POC. In multivariate analysis, only the UC type remained associated with early POC with a 3-fold higher risk than the CD type. No factor was associated with late POC. These results suggest that surgery presents more risk of POC in patients with UC, probably because surgery is often required in UC for severe acute UC.

Currently, few data are available on POC in pediatric-onset IBD. Our results are similar to those reported by Peyrin-Biroulet et al<sup>11</sup> in an adult CD cohort. He reported, in a population-based cohort of 152 patients in Olmsted County, USA, a cumulative probability of POC of 45% at 5 years and 57.6% at 20 years. In this adult IBD cohort, one-third of patients with CD experienced at least 1 early POC and one-fourth at least 1 late POC. Relative to

the colonic extent, the patients with ileal or ileocolonic diseases were significantly less likely to experience POC.

Previous studies from the EPIMAD registry<sup>1,2,6</sup> showed that pediatric-onset IBD is characterized by a severe phenotype with extensive complicated disease. Good conditions are required to operate on these patients: antibiotic prophylaxis and thromboembolic prophylaxis must be prescribed in accordance with the ECCO recommendation because patients with IBD have an increased risk of developing a thromboembolic complication.<sup>15</sup> In our study, 68 patients (64%) received low-molecular-weight heparin. No prospective study on thromboembolic prevention in patients with pediatric-onset IBD requiring surgery has previously been performed. The frequency of thromboembolic complications is 3 times higher after intestinal surgery for IBD<sup>16</sup> than in other indications. Another study<sup>17</sup> reported that in a hospitalized children cohort regardless of the cause, the rate of phlebitis was increased in all pediatric age groups (<1, 1–5, 6–11, and 12–17 yr). This risk increased over time and was the highest in the group of children less than 1 year of age (prevalence from 18.1/10<sup>5</sup> from 1994 to 49.6/10<sup>5</sup> in 2009). Lazzarini et al<sup>18</sup> showed that thromboembolic disease was 4 times higher in children with UC than those with CD. Results of our study approached those reported by Lazzarini, because only UC was significantly associated with an increased risk of POC. Another study performed in a Danish population-based IBD cohort<sup>19</sup> reported a 6-fold higher risk of thromboembolic complications in IBD in patients below 20 years than in other age groups.

Our study confirms that pediatric UC presents the highest risk of POC with a mean number of 1.32 POC per patient. Some studies performed in referral centers reported the same conclusions. In a small pediatric UC cohort<sup>20</sup> requiring colectomy, 33% of patients had at least 1 POC. Similarly, Alexander et al<sup>21</sup> reported, in a population of 151 patients with IBD who had undergone surgery and were below 21 years of age, that 31 presented an early POC (21%) including 10% of abscesses or pelvic infection. In this cohort, 68 patients had at least 1 late POC (45%) including 25% infectious complications and 12% small bowel obstruction. An American study performed in a large pediatric UC cohort (n = 218) requiring colectomy reported<sup>22</sup> a surgical complication rate of 49% in children including a third attributed to infectious complications.

In our study, active smoking was not found to be an associated factor of POC. Little information is available in the literature about smoking and POC in IBD in young adults. Abbas et al<sup>23</sup> reported that smoking more than 20 packs per year was associated with an increased risk of wound dehiscence ( $P < 10^{-3}$ ; OR 3.7) regardless of the indication for intestinal resection.

In our study, 50% of early POC was infectious. In a population of 204 patients, Patel et al<sup>24</sup> described an infectious POC rate of 32% in a small cohort (29 patients). Some factors must be considered as causes of infectious POC such as the context of emergency surgery or preoperative exposure to steroids. In our study, we found a significant association between preoperative exposure to SS and infectious POC in univariate but not in

multivariate analysis. This is probably because preoperative SS exposure is associated with severe acute colitis more frequently in UC. In a pediatric UC cohort of 51 patients requiring colectomy, 78% were exposed to SS in the 60 days before surgery, and 43% developed a wound infection versus 9% in patients who were not exposed to SS ( $P < 0.05$ ).<sup>24</sup> The meta-analysis performed by Subramanian<sup>25</sup> confirmed these data in adults with an increased risk of infectious POC (OR 1.7; 95% CI, 1.2–2.3) in patients exposed to SS in the preoperative period, particularly if the dose was higher than 40 mg per day (OR 2.0 [1.3–3.3]). In our study, multivariate analysis showed no significant association between SS and POC, but results can be explained by a lack of power. In this study, exposure to IS during the 3 months before surgery was not associated with POC (OR 1.3; 95% CI, 0.8–2.0). Two other studies performed in pediatric UC cohorts requiring colectomy reported the same results.<sup>26,27</sup>

The association between anti-TNF exposure and POC was not studied in our population-based cohort because of a lack of power and the prebiologic era of IBD diagnosis (98 patients were exposed to anti-TNF between diagnosis and first intestinal resection in our cohort between 1988 and 2004). This is a weakness in our study.

The major strength of our study was that data were gathered from a large population-based registry with long postoperative follow-up. It is more representative of the reality of the natural history of IBD. It thus allowed us to avoid the bias of recruitment that would have resulted in a group of patients recruited from referral centers, a large proportion having severe disease and thus at a high risk of POC. However, there are limitations to our study. First, data were retrospectively collected, and we were not able to collect data on clinical and endoscopic disease activity. Second, if we have shown that the type of IBD (UC) was associated with POC, it was not possible for us to isolate other associated factors because of the lack of power. Third, this study included patients diagnosed from 1988 to 2004 and who were thus in most cases managed in the prebiologic era.

In conclusion, in this population-based cohort, half of the patients with IBD and who had undergone surgery before 18 years of age presented POC. Although the frequency of severe complications was similar in the 2 IBD, UC was the only factor associated with POC. These data are very important when a therapeutic choice must be made between medical or surgical treatment in children.

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## REFERENCES

- Vernier-Massouille G, Balde M, Salleron J, et al. Natural history of pediatric Crohn's disease: a population-based cohort study. *Gastroenterology*. 2008;135:1106–1113.
- Gower-Rousseau C, Dauchet L, Vernier-Massouille G, et al. The natural history of pediatric ulcerative colitis: a population-based cohort study. *Am J Gastroenterol*. 2009;104:2080–2088.
- Turunen P, Ashorn M, Auvinen A, et al. Long-term health outcomes in pediatric inflammatory bowel disease: a population-based study. *Inflamm Bowel Dis*. 2009;15:56–62.
- Van Limbergen J, Russell RK, Drummond HE, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. *Gastroenterology*. 2008;135:1114–1122.
- Vasseur F, Gower-Rousseau C, Vernier-Massouille G, et al. Nutritional status and growth in pediatric Crohn's disease: a population-based study. *Am J Gastroenterol*. 2010;105:1893–1900.
- Chouraki V, Savoye G, Dauchet L, et al. The changing pattern of Crohn's disease incidence in northern France: a continuing increase in the 10- to 19-year-old age bracket (1988–2007). *Aliment Pharmacol Ther*. 2011;33:1133–1142.
- Auvin S, Molinié F, Gower-Rousseau C, et al. Incidence, clinical presentation and location at diagnosis of pediatric inflammatory bowel disease: a prospective population-based study in northern France (1988–1999). *J Pediatr Gastroenterol Nutr*. 2005;41:49–55.
- Molinié F, Gower-Rousseau C, Yzet T, et al. Opposite evolution in incidence of Crohn's disease and ulcerative colitis in Northern France (1988–1999). *Gut*. 2004;53:843–848.
- Hellers G. Crohn's disease in Stockholm county 1955–1974. A study of epidemiology, results of surgical treatment and long-term prognosis. *Acta Chir Scand Suppl*. 1979;490:1–84.
- Agrez MV, Valente RM, Pierce W, et al. Surgical history of Crohn's disease in a well-defined population. *Mayo Clin Proc*. 1982;57:747–752.
- Peyrin Biroulet L, Loftus EV, Harmsen WS, et al. Postoperative complications in a population-based cohort of Crohn's disease. *Gastroenterology*. 2010;138:S–70.
- Gower-Rousseau C, Salomez JL, Dupas JL, et al. Incidence of inflammatory bowel disease in northern France (1988–1990). *Gut*. 1994;35:1433–1438.
- Satsangi J, Silverberg MS, Vermeire S, et al. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut*. 2006;55:749–753.
- Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240:205–213.
- Fumery M, Xiaocang C, Dauchet L, et al. Thromboembolic events and cardiovascular mortality in inflammatory bowel diseases: a meta-analysis of observational studies. *J Crohns Colitis*. 2014;8:469–479.
- Mangram AJ, Horan TC, Pearson ML, et al. Guideline for Prevention of Surgical Site Infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. *Am J Infect Control*. 1999;27:97–132.
- Boulet SL, Grosse SD, Thornburg CD, et al. Trends in venous thromboembolism-related hospitalizations, 1994–2009. *Pediatrics*. 2012;130:812–820.
- Lazzerini M, Bramuzzo M, Maschio M, et al. Thromboembolism in pediatric inflammatory bowel disease: systematic review. *Inflamm Bowel Dis*. 2011;17:2174–2183.
- Kappelman MD, Horvath-Puho E, Sandler RS, et al. Thromboembolic risk among Danish children and adults with inflammatory bowel diseases: a population-based nationwide study. *Gut*. 2011;60:937–943.
- Soon IS, Wrobel I, deBruyn JCC, et al. Postoperative complications following colectomy for ulcerative colitis in children. *J Pediatr Gastroenterol Nutr*. 2012;54:763–768.
- Alexander F, Sarigol S, DiFiore J, et al. Fate of the pouch in 151 pediatric patients after ileal pouch anal anastomosis. *J Pediatr Surg*. 2003;38:78–82.
- Kelley-Quon L, Tseng C, Jen H, et al. Postoperative complications and health care use in children undergoing surgery for ulcerative colitis. *J Pediatr Surg*. 2012;47:2063–2070.
- Abbas SM, Hill AG. Smoking is a major risk factor for wound dehiscence after midline abdominal incision; case-control study. *ANZ J Surg*. 2009;79:247–250.
- Patel HI, Leichtner AM, Colodny AH, et al. Surgery for Crohn's disease in infants and children. *J Pediatr Surg*. 1997;32:1063–1067.
- Subramanian V, Saxena S, Kang JY, et al. Preoperative steroid use and risk of postoperative complications in patients with inflammatory bowel disease undergoing abdominal surgery. *Am J Gastroenterol*. 2008;103:2373–2381.
- Markel TA, Lou DC, Pfefferkorn M, et al. Steroids and poor nutrition are associated with infectious wound complications in children undergoing first stage procedures for ulcerative colitis. *Surgery*. 2008;144:540–545.
- Schaufier C, Lerer T, Campbell B, et al. Preoperative immunosuppression is not associated with increased postoperative complications following colectomy in children with colitis. *J Pediatr Gastroenterol Nutr*. 2012;55:421–424.