

Complications and Disease Recurrence after Ileocecal Resection in Pediatric Crohn's Disease: A Retrospective Study

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Abstract

Objective: The aim of this retrospective study was to describe the risk of post-operative recurrence after ileocecal resection, the occurrence of surgical complications and identify predictors of these adverse postoperative outcomes in pediatric Crohn's disease (CD).

Patients and methods: All the children less than 18 years of age with a diagnosis of CD, who underwent primary ileocecal resection for CD between January 2006 and December 2016 in our tertiary centre, were considered for inclusion. Factors related to post-operative recurrence were investigated. POR of CD was defined as an increase in the PCDAI of 12.5 points accompanied by either radiological (ultrasound or MRI) or endoscopic confirmation of recurrent CD.

Results: A total of 377 children were followed for CD during 2006 and 2016. During this period, 45 (12%) children needed an ileocecal resection. Post-operative recurrence was diagnosed in 16% (n=7) at one year and 35% (n=15) at the end of the follow-up, with a median follow-up of 2.3 years (Q1-Q3 1.8-3.3). Median duration of the postoperative clinical remission was 1.5 years (range 0.5-2). Multivariate Cox regression analysis identified only young age at diagnosis as a risk factor for post-operative recurrence. Seven of the 43 patients (16%) developed severe postoperative complications. The only risk factor was intraoperative abscess.

Conclusion: Only young age at diagnosis was associated with POR. This information could be useful to develop targeted therapeutic strategies for young CD children. At the end of follow-up with a median follow-up of 2.3 years (Q1-Q3 1.8-3.3), there was no surgical post-operative recurrence: endoscopic dilatation for post-operative recurrence should be considered in order to delay or prevent surgery.

Keywords: Crohn's disease; Ileocecal resection; Post-operative recurrence

Introduction

The clinical course of childhood-onset Crohn's Disease (CD) is more severe with more extensive disease, more aggressive disease behavior and an earlier exposure to major postsurgical sequelae [1]. By 5 years, 14% to 47% of pediatric CD patients require surgery, and the most common surgery is ileocecal resection with a range of 44% to 71% [2]. Surgery may be considered as an alternative to medical therapy when a patient has active disease limited to a short segment despite optimized medical treatment; and also in children in prepubertal or pubertal stage if growth velocity for bone age is reduced over a period of 6 to 12 months despite optimized medical and nutritional therapy [3]. Surgical resection is not curative for CD. Relapse, both at the area of anastomosis and at other sites, frequently occurs within 5 years' post-surgery [4-6]. The post-operative recurrence (POR) rate in adults varies according to the definition used, be it clinical, endoscopic, radiological, or surgical. Smoking, prior intestinal surgery, absence of prophylactic treatment, penetrating disease at index surgery, perianal location, granulomas in resection specimen, and myenteric plexitis are considered predictors of early POR after ileocolic resection [7]. In pediatric CD, clinical POR varies from 18% [8] to 50% [6] at one year, and from 34% [9] to 73% [6] at 5 years. Diffuse ileocolic disease, penetrating and stricturing disease, severe disease, complex disease, age less than 14 at diagnosis, and failure of medical management increase the risk for recurrence [2]. The aim of this study was to describe the risk of POR after ileocecal resection, the occurrence of surgical complications and identify predictors of these adverse postoperative outcomes in pediatric CD.

Methods

Patients

All the children under 18 years of age with a diagnosis of CD according to the revised Porto criteria [10], who underwent primary ileocecal resection for CD between January 2006 and December 2016 in our tertiary centre, were considered for inclusion in this retrospective study. Patients were collected using the hospital medico-administrative database PMSI (*Programme de Médicalisation des Systèmes d'Information*) and the national register CEMARA (*CEntre des MALadies RAres*) for our centre [11]. The extraction with these 2 information systems allowed the selection of all the children under 18 years of age with a diagnosis of CD, who were followed between January 2006 and December 2016 in our tertiary centre. The study was approved by the Institutional Review Boards for the ethical approval and the French national data protection agency (Commission Nationale de l'informatique et des libertés n°19811722). All patients were informed.

Data collection

Data were retrospectively obtained from medical files and recorded in an anonymous standardized form. The following baseline characteristics were recorded for each patient: gender, age at diagnosis, CD classification according to Paris classification [12], disease activity according to PCDAI score [13]. Pre and postoperative data

including age at surgery, disease activity (PCDAI), the use of CD-related medication, endoscopy, radiographic imaging such as ultrasound or Magnetic Resonance Imaging (MRI). Preoperative data were collected at the preoperative workup. Post-operative data were collected at the last visit without recurrence and at the recurrence. Pubertal status was not available. Surgical variables included type of surgical approach, type of anastomosis, additional surgical procedures, stoma placement, operating time, pathology report of the resected segment, postoperative complications according to Dindo and Clavien [14].

Outcomes

Complications: Severe post-operative complications were defined as requiring surgical, endoscopic or radiological intervention (clavien Dindo) [14]. Intra-Abdominal Septic Complications (IASC) were defined as anastomotic leak, enterocutaneous fistula, and intraabdominal abscesses de novo. Risk factors for IASC were investigated.

Disease POR: In our study, POR of CD was defined as an increase in the PCDAI of 12.5 points [15] accompanied by either radiological (ultrasound or MRI) or endoscopic confirmation of recurrent CD. PCDAI was collected postoperatively at each visit (every 3 months). Radiological recurrence was defined as increased gut wall thickness and increased vascular pattern or echogenicity (ultrasound) or contrast enhancement (MRI) extending from the anastomosis proximally, either in ultrasound or in MRI [16,17]. Surgical POR was defined as recurrence requiring a new surgery. Risk factors for POR were explored. Endoscopic recurrence was described using the Rutgeerts score [18].

Statistical analysis

Categorical variables were described as frequencies and percent's. Continuous variables were described as the median (Interquartile Range [IQR]), means and standard deviations. Univariate analyses were performed using the nonparametric Mann-Whitney test for continuous variables and the chi-square test, or Fischer's exact test as appropriate for categorical variables. Predictors for POR were identified by multivariate Cox regression analysis. Eight variables were chosen a priori based on literature review: age at diagnosis, L4 location, penetrating behavior, perianal disease, granulomas in resection specimen and myenteric plexitis and inflammation of the ileocecal valve, treatment with biologics after the first surgery [7,19]. A P level <0.05 was considered significant. Analyses were conducted using RStudio 1. (Rstudio, Inc).

Results

Ileocecal resection

A total of 377 children were followed for CD at Robert Debré hospital during 2006 and 2016 (Figure 1). During this period, 45 (12%) children needed an ileocecal resection for CD, 16 (37%) by laparoscopy, 27 (63%) by assisted laparoscopy. Follow-up was available for 43, with a median follow-up of 2.3 years (Q1-Q3 1.8-3.3). Sixteen (37%) ileocecal resections were done before 2011, 27 (63%) after. The indications for ileocecal resection were biologics therapy refractory inflammation (49%, n=22), intra-abdominal abscesses (24.4%, n=11), active disease limited to a short segment associated to growth delay (13.3%, n=6), surgery rather than anti-TNF (11.1%, n=5), digestive perforation (2.2%, n=1). Table 1 depicts patients' demographic and surgical characteristics at time of ileocecal resection and details regarding the surgery.

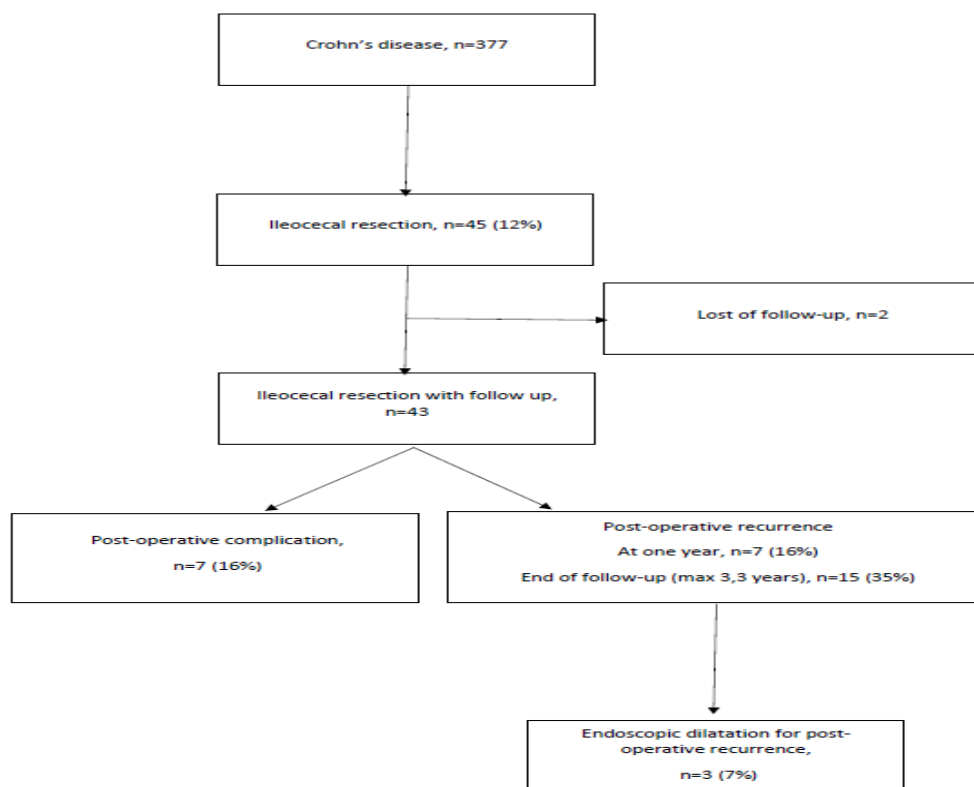


Figure 1: Flow chart.

Table 1: Demographic and surgical characteristics of patients at time of ileocecal resection

Characteristics	Total N=43	Recurrence N=15	No recurrence N=28	P
Female, n (%)	23 (51)	7 (47)	16 (57)	0.5
Age at surgery mean (\pm SD)	15.19 (1.76)	14.47 (1.99)	15.57 (1.53)	0.05
Years since diagnosis Median (Q1-Q3)	2 (0.5-4)	3.3 (1.5-4.5)	1.8 (0.4-3.3)	0.15
Age at diagnosis median (Q1-Q3)	12 (10.5-15)	11 (9.5-14)	14 (11-16)	0.05
Paris classification, n (%)				
A1a	7 (16)	4 (27)	3 (11)	
A1b	36 (84)	11 (73)	25 (89)	
Disease location, n (%) at diagnosis				
L1	30 (69)	8 (53)	22 (79)	0.16
L2	0 (0)	0 (0)	0 (0)	
L3	13 (31)	7 (47)	6 (21)	
L4	13 (33)	7 (54)	6 (23)	0.07
Disease behavior, n (%)				
B1	2 (5)	2 (13)	0 (0)	0.17
B2	26 (60)	9 (60)	17 (61)	

B3 or B2B3	15 (36)	4 (27)	11 (39)	0.50
Perianal location, n (%)	2 (5)	2 (14)	0 (0)	0.11
Extra-intestinal manifestations, n (%)	7 (18)	3 (21)	4 (15)	
Intestinal occlusion, n (%)	4 (9)	1 (7)	3 (11)	
Medical therapy before surgery, n (%)				
Steroids	12 (28)	3 (20)	9 (32)	0.5
Immunosuppressive therapy	19 (44)	6 (40)	13 (46)	0.4
Biologics	24 (56)	9 (60)	15 (54)	0.3
antibiotics	18 (42)	8 (53)	10 (36)	0.5
Medical therapy after surgery, n (%)	42 (98)	15 (100)	27 (96)	
Immunosuppressive therapy	25 (58)	8 (53)	17 (61)	
Biologics	17 (40)	7 (47)	10 (36)	0.5
Laboratory				
C reactive proteine >10mg/L, n (%)	31 (76)	13 (93)	18 (67)	0.12
Albuminemia <30g/L, n (%)	15 (36)	8 (53)	7 (26)	0.10
Hemoglobin <11g/dL	16 (38)	6 (43)	10 (36)	
Surgical access, n (%)				
Laparoscopy	16 (37)	5 (33)	11 (39)	
Assisted laparoscopy	27 (63)	10 (66)	17 (61)	
Type of anastomosis, n (%)				
Side to side	30 (70)	10 (67)	20 (71)	
Stapled	19 (44)	5 (33)	14 (50)	0.4
intracorporeal	18 (42)	5 (33)	13 (46)	0.5
Protective stoma, n (%)	3 (7)	1 (7)	2 (7)	
Operating time, Median (Q1-Q3), min	175 (127-214)	174 (123-212)	175 (129-212)	
Length of ileal resection >30 cm N (%)	7 (17)	4 (27)	3 (11)	0.2
Length of stay after surgery Median (Q1-Q3), days	7 (6-12)	9 (6-12.5)	7 (6-12)	0.7
Postoperative complications, n (%)	7 (16)	3 (20)		

The Eleven patients with an abscess were treated with antibiotics before surgery, 4 only with enteral nutrition and antibiotics, 2 with immunosuppressants and antibiotics, 3 with enteral nutrition, immunosuppressant and antibiotics and 2 with anti-TNF and antibiotics. Nine patients underwent ileocecal resection without complication and surgery resolved the abscess. An intraoperative abscess complicated the ileocecal resection for the 2 patients treated with anti-TNF before surgery, requiring a protective per operative stoma placement. Surgery was performed for growth delay associated to active disease for 6 patients. Three patients were receiving enteral nutrition before surgery. Height velocity (cm/years) increased from 1.1 cm/year (Q1-Q3 0-3.3) to 5.8 cm/year (Q1-Q3 3.1-8.4) after surgery. One patient had a digestive perforation with a sepsis requiring a stoma nine months before the ileocecal resection. During surgery 3 patients required a protective stoma placement: two patients for an intraoperative abscess and 1 patient for a severe digestive and joint disease requiring heavy immunosuppressive drugs (steroids and anti-TNF and methotrexate). Patients received systematically peri-operative antibiotics. Immunosuppressants were delayed after surgery with a median of 12 days (Q1-Q3 6-34). Severe postoperative complications. Seven of the 43 patients (16%) developed severe postoperative complications (**Figure 1**). One patient developed anastomotic leak requiring a stoma, and six intra-abdominal abscess de novo after resection including the 2 intraoperative abscess. The only risk factor for IASC was intraoperative abscess. Risk factors for IASC are analyzed in **Table 2**.

Table 2: univariate analyses: Risk factors for intra-abdominal septic complications.

Characteristics	No postoperative complication N=36	Postoperative complication N=7	P
Age at surgery, mean (\pm SD), years	15.06 (1.84)	15.86 (1.21)	0.28
Pre-operative biologics, n (%)	18 (50)	6 (86)	0.11
Pre-operative steroids, n (%)	11 (31)	1 (14)	0.6
Disease behavior B3 or B2B3, n (%)	8 (22)	3 (43)	0.35
Albumin<30g/L, n (%)	12 (33)	3 (43)	0.7
CRP>10mg/L, n (%)	26 (72)	5 (71)	
Intracorporeal anastomosis, n (%)	13 (36)	5 (71)	0.11
Intraoperative abscess, n (%)	0 (0)	2 (5.5)	0.02
Operating time, Median (Q1-Q3), min	174 (124-213)	197 (146-218)	0.5

Disease POR

POR was diagnosed in 16.3% (n=7) at one year and 35% (n=15) at the end of the follow-up, median 2.3 years (range 1.8-3.3) (**Table 1 and Figure 1**). Median duration of the postoperative clinical remission was 1.5 years (range 0.5-2). Median increase in PCDAI was 20 (Q1-Q3 15-35). An endoscopy was available for 9 patients. Proximal spread of disease was seen in 4 patients (i3 n=4). A flare up on the colonic side was also seen in 2 of these 4 patients. In 5 patients, lesions were confined to the ileocolonic anastomosis with stenosis in 3 (i2 n=2, i4 n=3). For 6 patients' clinical recurrence was confirmed by radiology, showing an increased gut wall thickness

extending from the anastomosis proximally. At the time of ileocecal resection, 44% (n=19) were treated with immunosuppressive therapy, 40% (n=6) in the POR group and 46% (n=13) in the no POR group. 56% (n=24) were treated with biologics, 60% (n=9) in the POR group and 54% (n=15) in the no POR group. After resection, only one patient was just followed up, 25 patients (58%) were treated with immunosuppressive therapy (azathioprine n=18, 6 mercaptopurine n=4, methotrexate n=3), and 17 (40%) with biologics (anti-TNF n=15, ustekinumab n=2). Fecal calprotectine was not available during follow-up. Endoscopy was performed only for 19 (9 symptomatic and 10 asymptomatic) patients at a median of 14 months after surgery (Q1-Q3 5- 20.5), at time of clinical recurrence for 9 patients. Only two patients had endoscopic remission and 89% endoscopic recurrence (n=17, endoscopic AND clinical recurrence n=9, only endoscopic recurrence with no symptoms n=8) (Rutgeerts score>i2). At the end of follow-up, there was no surgical POR. Three patients (7%) needed an endoscopic dilatation for POR during follow-up (min 25 months, max 45 months) for anastomotic stricture. Multivariate Cox regression analysis identified only young age at diagnosis as a risk factor for POR (**Table 3**). The median of age at diagnosis was 11 for patients with POR, and 14 for patients without POR (p=0.05). Surgery was performed within a median of 3.3 years after CD diagnosis for POR patients and 1.8 years for those without POR.

Table 3: Multivariate Cox regression analysis: Risk factors for post-operative recurrence.

	HR	95% CI	P
Age at diagnosis	0.73	0.54-0.98	0.04
Disease location L4	4.11	0.70-24.04	0.12
Disease behavior B3 or B2B3	3.06	0.42-22.34	0.27
Perianal location	1.33	0.52-3.28	0.55
granulomas in resection specimen	0.73	0.11-4.71	0.74
Myenteric plexitis in resection specimen	3.21	0.55-18.66	0.19
Inflammation of the ileocecal valve in the resection specimen	0.75	0.22-2.53	0.64
Postoperative biologics	0.44	0.08-2.30	0.20

Discussion

In this retrospective study, 12% of CD patients needed ileocecal resection. To our knowledge, only three studies report ileocecal resection in children alone and not intestinal resections of different extent and location [20-22], but focused on POR rates. The rate of primary surgery in literature is variable: from a cumulative incidence of 5 to 7% at 1 year, 15 to 20% at 5 years and 30 to 34% at 5 years [23-25] in pediatric CD. The rate of primary surgery in our center was in the same range. The cohort considered was uniformly diagnosed, and uniformly treated. ESPGHAN recommendations stating that “anti-TNF therapy as primary induction therapy may be

considered for selected children at high risk for poor outcome” were adopted in our centre after 2018 [26]. Only 24 patients (56%) were treated with antiTNF at the time of ileocecal resection. POR was observed in 16.3% of patients at 1 year and 35% at the end of follow-up (median 2.3 years (range 1.8-3.3)), with a median duration of remission for 1.5 years (range: 0.5-2). In other pediatric series, ileocecal resection resulted in clinical recurrence of 20% of the patients at one year and 44% during the entire follow-up of 30 months [20]. For Diederens et al. [22], clinical recurrence was observed in 49.2% of subjects at 5 years from resection. Clinical disease recurrence was previously reported in 65% of adult patients [25], and in 60% of pediatric patients [28] at 5 years from ileocecal resection. Our recurrence rate was slightly lower from other series, but we defined POR as an increase in the PDAI of 12.5 points [15] accompanied by either radiological or endoscopic confirmation of recurrent CD. The objective of the radiologic confirmation was to confirm recurrence. Functional abdominal disorders can indeed increase PDAI (abdominal pain, diarrhea). Fecal calprotectin was available only for a few patients. To circumvent this methodological difficulty, we add radiological data to our POR definition. In this cohort, 44% of patients received immunosuppressive therapy and 56% biologics before surgery, and 58% and 40% respectively after. Patients receiving immediate postoperative therapy are known to develop less clinical and surgical recurrence. A recent systematic review and meta-analysis reported that after the year 2000, the surgical rates at 1, 5 and 10 years have significantly decreased. It is unclear whether this decrease can be solely attributable to the introduction of biologics, the more effective use of thiopurine dosing with monitoring or perhaps earlier disease recognition and early use of effective interventions [29]. Despite small sample size, endoscopic recurrence rate was 38% at 6th month for Zarubova et al. [21]. Bobanga et al. [27] reported a recurrence rate of 87% in patients younger than 16 years who underwent endoscopy during mean 3 years’ follow-up compared to 70% in patients older than 16. In our series, endoscopy was performed only for 19 patients during long-term follow-up. Only 2 patients had endoscopic remission and 89% endoscopic recurrence. Moreover, endoscopy was in most cases performed after clinical relapse (68%). It is an important limitation of our study: endoscopy should have been performed systematically as recommended. Indeed, endoscopy is the standard for evaluation of POR and endoscopic assessment within 1 year of surgical resection is recommended. Endoscopic recurrence precedes the onset of clinical symptoms. It is important to identify asymptomatic patients at risk for clinical recurrence and disease complication with early endoscopic surveillance [30]. In this retrospective study, the inconsistent use of endoscopy was a weakness. Nevertheless, MRI is better accepted than endoscopy by children, is less invasive and has shown a reliable accuracy to detect endoscopic activity in CD patients [17,31]. We use MRI for the evaluation of the postoperative course of CD, dependent on our center’s experience/availability and patient preference. At the end of follow-up, there was no surgical POR, three patients (7%) needed an endoscopic dilatation for POR, whereas surgical recurrence was observed in 11.9% of subjects in other pediatric series [22]. The aims of endoscopic treatment are to relieve the obstruction and obstruction-associated symptoms, delay or prevent surgery [32], thereby preserving the bowel from chronic intestinal failure [33]. We found an association between young age at disease onset and at surgery and POR: the median age at diagnosis was 11 for POR patients and 14 for no POR patients $p=0.05$. L4 location at diagnosis was present in 7 (54%) patients with POR and in 6 (23%) patients without, $p=0.07$. Boualit found that a young age (less than 14 years) at diagnosis, complicated behavior, and an L4 location were risk factors for undergoing second surgery, moreover a first intestinal resection performed within 3 years after diagnosis was associated with reduced need for further IS

and/or anti-TNF- α treatment and a better catch-up of height and weight. We found that surgery was performed within a median of 3.3 years after CD diagnosis for POR patients and 1.8 years for those without POR. Delaying surgery could also be associated with a poor outcome. CD in children is known to be more severe and more aggressive [1]. Young age is a risk factor for disease severity. Young patients less than 14 and even more if less than 11 should be more monitored. Delaying surgery after 3 years could be a factor of poor outcome. The occurrence of severe complications in this cohort was 16%, and all were infectious. This is more than previous reports in adults (11-13%) [34,35] and in children and adolescents (10-12%) [4,22]. The only risk factor for IASC was intraoperative abscess. In our cohort, in which 56% of patients received biologics before and 40% after first surgery, biologics had no impact on IASC.

Conclusion

Only young age at diagnosis was associated with POR. This information could be useful to develop targeted therapeutic strategies for young CD children less than 14 and more specifically less than 11. Surgery should not be delayed in order to prevent poor outcome. At the end of follow-up, there was no surgical post-operative recurrence: endoscopic dilatation for post-operative recurrence should be considered to delay or prevent surgery.

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