**FROM PARIS TO MONTREAL: DISEASE REGRESSION IS COMMON DURING LONG TERM FOLLOW-UP OF PAEDIATRIC CROHN’S DISEASE**

*Mike Davies, MD1, Susanna Dodd, MD2, Morwenna Coultate, MD1, Andrew Ross, MD1, George Pears, MD1, Bruno Gnaneswaran, MD1, Christos Tzivinikos, MD3, Anastasia Konidari, MD3, Jeng Cheng, MD3, Marcus Karl-Heinz Auth, MD3, 4, Fiona Cameron, MD3, Sarang Tamhne, MD3, Elizabeth Renji, MD3, Manjula Nair, MD3, Colin Baillie, MD5, Paul Collins, MD1, Philip J Smith, MD1, Sreedhar Subramanian, MD1, 4\**

1Department of Gastroenterology, Royal Liverpool and Broadgreen University Hospital NHS Trust, Liverpool, UK

2Department of Biostatistics, University of Liverpool, Liverpool, UK

3Pediatric Gastroenterology, Hepatology and Nutrition, Alder Hey Children’s NHS Foundation Trust, Liverpool, UK

4University of Liverpool, Liverpool, UK

5Department of Surgery, Alder Hey Children’s NHS Foundation Trust, Liverpool, UK

\*Corresponding Author:

Dr Sreedhar Subramanian, Consultant Gastroenterologist and Honorary Senior Lecturer

Department of Gastroenterology

Royal Liverpool and Broadgreen University Hospital Trust and University of Liverpool

Prescot Street

Liverpool

UK

[sreedhar.subramanian@rlbuht.ns.uk](mailto:sreedhar.subramanian@rlbuht.ns.uk)

Tel: 0151 706 2000

Sources of funding and support: nil

URL (website address) and trial identification number: N/A

All authors concur with the submission. The material submitted for publication is not under consideration for publication elsewhere.

Word Count: 2075

Number of Tables: 1

Number of Figures: 3

**Conflicts of Interest and Source of Funding**

SS has received speaker fee from MSD, Actavis, Abbvie, Dr Falk pharmaceuticals, Shire and received educational grant from MSD, Abbvie, Actavis and is an advisory board member for Abbvie, Dr Falk pharmaceutics, Janssen and Vifor pharmaceuticals. MKHA has received speaker fees from Abbvie, and travel grants from Abbvie, Dr Falk pharmaceuticals, MSD/Janssen and Nutricia. CT has received speaker fees from Abbvie, Sanofi, Nutricia, Nestle and received travel grants from Abbvie and Merck. PC has received speaker fees from Shire, Abbvie, MSD, Warner-Chillcott and Falk pharma. He has received educational grants from Warner Chilcott, MSD and Ferring pharmaceuticals. He has served as an Advisory Board member for Falk pharma. PJS has received speaker fees from Abbvie and Janssen. MD, AK, AR, MC, BG, JC, FC, ST, ER, CB, MVN and GP report no conflicts of interest.

This study did not receive any funding support

**Author contributions:** MD, AR, MC, BG, GP and AK were involved in data collection and drafting of the manuscript. SS, JC and AK were involved in data analysis, drafting and final revision of the manuscript. SS and MD were involved in study design, data collection, analysis, drafting and revision of the manuscript. PC, PJS, MKHA, CT, ST, ER, CB and MVN were involved in the drafting of the final manuscript.

**Abstract**

**Introduction**

Paediatric Crohn’s disease (PCD) often presents with extensive and a frequent pan-enteric phenotype at onset. However, its long term evolution in to adulthood, especially since the widespread use of biological agents, is not well characterised. We conducted a single centre cohort study of all PCD patients transitioned to adult care to assess the long term disease evolution in the era of biologic therapy.

**Methods**

We conducted a retrospective observational, study of all PCD patients who were subsequently transferred to the care of an adult gastroenterology unit and had a minimum follow up of 2 years. We examined the case notes for evolution of disease location and behaviour. Disease location and behaviour was characterised using Paris classification at diagnosis and Montreal classification at last follow-up. In addition, we examined variables associated with complicated disease behaviour and the need for CD related intestinal resection.

**Results**

In total, 132 patients were included with a median age at diagnosis of 13 (IQR 11-14) and a median follow up of 11 years (range 4-14). At diagnosis, 23 (17.4%), 39 (29.6%) and 70 (53%) patients had ileal, colonic and ileocolonic disease. In addition, 31 (23.5%) patients had L4a or L4b disease at diagnosis (proximal or distal to the ligament of treitz respectively) and 13 patients (9.8%) had both whilst 27 (20.4%) patients had perianal disease. At diagnosis, 27 (20.4%) patients had complicated disease behaviour but 83 (62.9)% of patients had an extensive ‘pan-enteric’ phenotype. Of these patients only 55 (66.3%) retained the pan-enteric phenotype at last follow-up (p=0.0002). Disease extension was noted in 25 (18.9%) of patients and regression was noted in 47 (35.6%) of patients, whereas upper GI disease was noted in significantly fewer patients at last follow-up (21, 15.9%) (p=0.0001). More patients had complicated disease behaviour (46 patients, 34.9%, p=0.0018) at follow-up. There was a high exposure to both thiopurines 121 (91.7%) and biologics 84 (63.6%). The cumulative probability (95% CI) of surgery was 0.05 (0.02, 0.11) at 1 year, 0.17 (0.11, 0.24) at 3 years and 0.22 (0.15, 0.30) at 5 years. Neither disease location nor behaviour were associated with the need for intestinal resectional surgery.

**Conclusions**

Over the course of an extended follow-up period, there appeared to be changes in both disease location and behaviour in PCD. Interestingly, a significant proportion of patients had disease involution which may be related to a high rate of exposure to thiopurines and biologics. We were unable to identify any variables associated with the need for intestinal surgery.

**Introduction**

Crohn’s disease (CD) is usually diagnosed in the second and third decades of life1 but approximately 20-30% of patients are diagnosed during childhood2-4. The incidence and prevalence of paediatric Crohn’s disease (PCD) appears to be increasing globally5, 6. The increase in incidence has been noted in all paediatric age groups including the very-early onset group under 5 years of age6, 7.

Current literature, though conflicting, suggests some important differences between pediatric onset and adult onset Crohn’s disease. PCD reportedly has a more aggressive disease course, including more extensive disease location, a higher predilection to a pan-enteric phenotype, frequent upper gastrointestinal (GI) involvement, growth failure, more active disease, and need for more aggressive medical therapy, in predominantly hospital based studies8-10. However, other studies have suggested that pediatric disease behavior seems to parallel that of adults11.

Despite the widespread acknowledgement of an initial severe presentation, very few studies have examined if this severe phenotype persists in to adulthood. The literature regarding the evolution of PCD are conflicting and limited by short follow-up times. Hope *et al* followed up a cohort of Irish PCD patients for 2 years and reported a low rate of disease extension. To the contrary, studies from Scotland12, Slovenia13 and France14 reported disease extension rates of up to 40% with median follow-up periods ranging from 2 years to 84 months. Fewer studies still have examined the long term disease course in PCD after the advent of biological therapy. A recently published long-term extension study from a French population based PCD cohort showed that a high proportion of patients developed complicated disease behavior and had extensive disease at follow up15. However, this study was conducted prior to the widespread use of scheduled maintenance anti-TNF therapy in children potentially over-estimating the progression to complicated disease behavior. In light of this, we aimed to characterize the long term evolution of PCD in a contemporary cohort of patients.

**Methods**

*Patient population and variables:* We conducted a single-centre study of PCD patients diagnosed ≤16 years of age between February 1994 and December 2014 transitioned to adult care. The diagnosis of CD was based on standard clinical, endoscopic and histological criteria. Patients were transferred to the care of an adult gastroenterologist at approximately 16 years of age. Follow-up data was collected until August 2018 or the last contact with the clinician, whichever was latest. We only included patients with a minimum follow-up period of 2 years. Case notes were retrospectively interrogated to extract the following information: age, gender, year of diagnosis, disease location and behaviour at diagnosis and follow-up, time to initiation of immunomodulatory and biologic therapy and time to diagnosis of complications or surgery. Complication from CD was defined as the presence of a stricture or fistula or intra-abdominal abscess assessed by either endoscopy or cross-sectional imaging. Surgery was defined as the need for resection surgery such as small bowel or colonic resection. CD location and disease behaviour at diagnosis and maximal follow-up was collected according to Paris16 and Montreal17 classification respectively. Disease extension was defined as involvement of an additional location at last follow-up. If a previously involved segment at diagnosis was subsequently noted to be disease free at follow-up, it was categorised as disease regression. Pan-enteric phenotype was defined as extensive GI tract involvement (L4a, L4b and L3).

*Statistical analysis*

Categorical variables have been summarized as frequency (%) and continuous variables as median (interquartile range, IQR). Comparison of frequencies was performed using Pearson’s chi-square test. Hazard ratios (HR) from Cox proportional hazards models were used to quantify risk of surgery and complicated disease behaviour. All analyses were carried out using Stata v15.1 software (Stata Statistical Software, Release 15; StataCorp LP, College Station, Texas, USA).

*Ethical Considerations*

The study was performed using routine collected clinical data and as such is exempt from the need for ethics committee approval in the UK and the need to take written informed consent.

**Results**

*Demographics*

A total of 161 patients were transferred to adult care from the years 2002 to 2016. We excluded 29 due to insufficient follow-up and 132 were included in the final analysis. The median age at diagnosis was 13 (IQR 11-14) and 77 (58.3%) were male. The median follow up period was 11 years (range 4-24) and the median age at last follow up was 23.5 (IQR 20-26).

*CD location*

Ileocolonic disease location was the commonest (n=70, 53%) followed by colonic (n=39, 30%) and ileal (n=23, 17%) location at diagnosis (Figure 1). In addition, 21 (16%) and 10 (7.5%) patients had disease proximal (L4a) and distal to the ligament of Treitz respectively at diagnosis and 38 (29.7%) had perianal disease. Of these, 13 patients (9.8%) had disease both proximal and distal to the ligament of Treitz. Growth status was only available in 67 patients, of whom 43 (64%) had impaired status. At maximal follow up, disease location remained broadly similar except for upper GI (L4) disease with fewer patients (n=21, 15.9%, p=0.0001) compared to diagnosis (Figure 1). There was a non-significant increase in the proportion of patients with perianal disease at diagnosis (20.4%) and maximal follow-up (23.5%). At diagnosis, 83 (62.9%) of patients had an extensive ‘pan-enteric’ phenotype but of these patients only 55 (66.3%) retained the phenotype at last follow-up (p=0.0002). Disease extension was noted in 25 (18.9%) of patients and regression was noted in 47 (35.6%). The rate of exposure to biological therapy was similar in patients with disease regression (32/47, 68.1%) and disease extension (21/25, 84%).

*CD Behaviour*

Most patients had inflammatory (n=105, 80%) phenotype at diagnosis but disease behaviour changed significantly over time (Figure 2). Complicated disease behaviour was noted in 27 (20%) patients at diagnosis with stricturing phenotype in 11 (8.3%), penetrating in 15 (11.4%) and a combination of both in 1 (0.8%). At last follow up, 20 (15.2%) and 26 (19.7%) patients had stricturing and penetrating phenotypes respectively. We examined the association of a number of variables including early exposure to biologics and immunosuppressants with complicated disease behaviour at diagnosis or follow up (Table 1). None of the examined variables were associated with the need for surgery and reached the pre-specified significance threshold of 5% to be included in a multi-variate analysis. Only the presence of perianal disease was associated with complicated disease behaviour at follow-up in both uni- and multi-variate analysis (Odds ratio 3.31, 95% CI 1.23-8.85, P=0.017).

*Treatments*

A high proportion of patients were exposed to thiopurines (N=121, 91.7%) either alone (N-40, 30.3%) or in combination with a biologic agent (N=81, 61.4%). Eighty-one (61.4%) patients received an anti-TNF agent during their disease course. Of the patients who failed anti-TNF therapy a further 12 patients (9%) received ustekinumab (9%) and 6 (4.5%) patients received vedolizumab. Most patients were commenced on thiopurines early (median 0 years, IQR 0-1) whereas the median time to starting an anti-TNF agent was 5 years (IQR 2-8).

*Surgery:*

The cumulative probability (95% CI) of surgery was 0.05 (0.02, 0.11) at 1 year, 0.17 (0.11, 0.24) at 3 years, 0.22 (0.15, 0.30) at 5 years and 0.43 (0.34, 0.53) at 10 years (Figure 3). Overall, 56 (42.4%) of the entire cohort had surgery at the end of follow-up. We assessed the contribution of a number of variables (disease location, behaviour, early exposure to thiopurines and anti-TNF agents) to the risk of intestinal surgery but none of the examined variables showed a significant association (Table 2).

**Discussion**

We report that both disease location and behaviour in PCD evolve during an extended follow-up period into adulthood in our cohort of patients with a high exposure rate to biological therapy. Our findings of a high prevalence of extensive pan-enteric phenotype at presentation are similar to previously reported studies12, 14. Similarly, the proportion of patients with perianal fistulising disease in our cohort is similar to that reported in previous population based 14, 18 and hospital based cohorts12. An additional novel finding in our study is that a greater proportion of patients experienced involution of disease location compared to disease extension. Up to a third of patients with a pan-enteric phenotype at presentation subsequently had less extensive disease. Our findings differ from previous studies which have investigated the change of disease location over time12, 15, 19-21 in pediatric cohorts with the majority of studies reporting disease extension rather than regression. In a Danish study from Copenhagen county (1962–1987; n=23), disease location progressed in 67% of children until the end of the follow-up 20. In a French population-based cohort (1988–2002; n=281), 31% of children were reported to have disease extension at maximal follow-up 14, 15. A similar extension rate was described in a national cohort from Scotland (n= 276), where 39.1% of children experienced disease progression 2 years after diagnosis12. In contrast, a lower rate of disease extension (15%) was observed in an unselected cohort from Sweden (1990–2007, n=200), during a median follow-up of 8.8 years21. Finally, no significant change in disease location was observed in two Irish inception cohorts, but the number of patients included was quite small and follow-up time limited19. A major difference between our cohort and other studies is the high rate of exposure to biologics and thiopurines and this may be relevant to our observation. However, there is limited data on the impact of biological therapy on regression of disease location in CD. Of note, a single population based Danish cohort of adult CD patients22 found that biologic therapy protected against a change in disease location which is in keeping with our observation. Scheduled maintenance anti-TNF therapy was introduced to routine clinical practice at our centre in 2009. Only a minority of patients (n=41, 30%) were diagnosed after 2009. Of that cohort, 28 (68.3%) were treated with biologic but the proportion of patients with early exposure to biological therapy (within 2 years) was relatively low. Due to the low number of patients, we were unable to meaningfully assess the impact of routine maintenance anti-TNF therapy after its introduction to our clinical practice.

We noted a high rate of inflammatory phenotype at diagnosis consistent with previous studies23, 24. However, just over a third of patients developed either a stricturing or penetrating phenotype during follow-up. The rate of progression reported in our cohort is broadly comparable to previous reports of between 24-43% and 14-44% developing a stricturing and penetrating phenotype respectively8, 14, 23, 24. Despite the high rate of exposure to biologicals, it is surprising that the rate of complicated disease behaviour in our study is not significantly lower than reported previously. This could be readily explained by differences in study population and the fact that the median disease duration prior to treatment with biological agents was 5 years in our cohort. In keeping with this, a recent prospective study in PCD showed that only early initiation of anti-TNF agents (within 90 days of diagnosis) was associated with a reduction in intestinal penetrating complications25. Interestingly, we did not find an association between early anti-TNF therapy and disease behaviour but our study was under-powered to address this question. Overall, it is yet unclear whether anti-TNF agents halt the progression to a complicated phenotype with some studies suggesting a protective effect26, 27 whilst others do not28.

The rate of surgery in our cohort is broadly comparable to findings from other studies. This is

in line with figures from elsewhere reporting surgery proportions ranging from 14% to 20% after 3 years of follow-up29, 30. The 5-year probability of surgery in our cohort and this figure is higher than the 15% resection rates in recent studies of PCD patients with a lower frequency of exposure to biological agents22, 31. Interestingly, higher rates of surgery have been reported from selected hospital units with up to 24% during 4 years of follow-up32 and up to 44% during 2 years of follow-up33. It is noteworthy that the surgical rate in our cohort is high despite the extensive use of biologics. This is consistent with findings from a Danish nationwide cohort study which reported no significant change in surgical rates over time despite an increase in the use of biologic agents22. Moreover, many of the patients treated in our cohort were treated with biologic agents later on in the disease course.

Our study has some notable strengths and limitations. All the patients in our cohort were closely followed up clinically, endoscopically and radiologically allowing for robust measures of disease location and complication rates. In addition, the length of follow-up and the contemporary nature of our study are particular strengths. Almost all of the previous studies were done prior to the widespread use of biologic agents hampering conclusions on the impact of biological therapy on the evolution of PCD. Our study population was derived from a tertiary centre IBD practice and consequently included patients with extensive and complicated disease history and may not be representative of other population based PCD cohorts. This is consistent with a high rate of exposure to biological agents in our study population. Finally, structured data on biomarkers or mucosal healing were not available to examine the impact of these factors on risk of surgery.

In summary, we conclude that the severe phenotype of PCD at presentation was attenuated at follow up in a proportion of patients, likely due to the regular use of biological therapy.

**Table 1: Uni- and multi-variate analysis\* of factors associated with complicated disease behaviour**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Diagnosis characteristics** | **Hazard ratio** | **95% CI** | **p-value** | **N** |
| Age <10 | 1.68 | (0.54, 5.22) | 0.372 | 15 |
| Male sex | 0.70 | (0.35, 1.42) | 0.328 |  |
| Location: baseline L2 (n= 39) |  |  | 0.322 |  |
| L1 | 1.15 | (0.41, 3.22) |  | 23 |
| L3 | 1.78 | (0.81, 3.94) |  | 70 |
| L4 | 1.77 | (0.83, 3.74) | 0.138 | 44 |
| Perianal disease | 3.31 | (1.23, 8.85) | 0.017 | 38 |
| Early exposure to thiopurines (<2 years from diagnosis) | 0.74 | (0.35, 1.55) | 0.421 | 90 |
| Early exposure to biologics  (<2 years from diagnosis) | 0.74 | (0.23, 2.42) | 0.618 | 12 |

\*Both uni-and multi-variate analysed yielded identical results

**Table 2: Univariate analysis of factors associated with the need for intestinal surgery in paediatric Crohn’s disease**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Diagnosis characteristics** | **Hazard ratio** | **95% CI** | **p-value** | **N** |
| Age <10 | 0.75 | (0.34, 1.68) | 0.487 | 15 |
| Male sex | 0.66 | (0.39, 1.12) | 0.122 |  |
| Location: baseline L2 (n= 39) |  |  | 0.144 |  |
| L1 | 2.19 | (1.00, 4.79) |  | 23 |
| L3 | 1.34 | (0.72, 2.50) |  | 70 |
| L4 | 0.999 | (0.58, 1.73) | 0.996 | 44 |
| Behaviour: baseline B1 (n= 105) |  |  | 0.318 |  |
| B2 | 0.70 | (0.22, 2.26) |  | 11 |
| B3 | 1.72 | (0.77, 3.82) |  | 15 |
| Perianal disease | 1.70 | (0.93, 3.12) | 0.087 | 38 |
| Early exposure to thiopurines (<2 years from diagnosis) | 1.14 | (0. 64, 2.03) | 0.644 | 90 |
| Early exposure to biologics  (<2 years from diagnosis) | 0.63 | (0 .15, 2.59) | 0.518 | 12 |

**References:**

1.Shivashankar R, Tremaine WJ, Harmsen WS, et al. Incidence and Prevalence of Crohn's Disease and Ulcerative Colitis in Olmsted County, Minnesota From 1970 Through 2010. Clin Gastroenterol Hepatol 2017;15:857-863.

2.Adamiak T, Walkiewicz-Jedrzejczak D, Fish D, et al. Incidence, clinical characteristics, and natural history of pediatric IBD in Wisconsin: a population-based epidemiological study. Inflamm Bowel Dis 2013;19:1218-23.

3.Farrokhyar F, Swarbrick ET, Irvine EJ. A critical review of epidemiological studies in inflammatory bowel disease. Scand J Gastroenterol 2001;36:2-15.

4.Kugathasan S, Judd RH, Hoffmann RG, et al. Epidemiologic and clinical characteristics of children with newly diagnosed inflammatory bowel disease in Wisconsin: a statewide population-based study. J Pediatr 2003;143:525-31.

5.Ashton JJ, Cullen M, Afzal NA, et al. Is the incidence of paediatric inflammatory bowel disease still increasing? Arch Dis Child 2018;103:1093-1094.

6.Benchimol EI, Bernstein CN, Bitton A, et al. Trends in Epidemiology of Pediatric Inflammatory Bowel Disease in Canada: Distributed Network Analysis of Multiple Population-Based Provincial Health Administrative Databases. Am J Gastroenterol 2017;112:1120-1134.

7.Henderson P, Wilson DC. The rising incidence of paediatric-onset inflammatory bowel disease. Arch Dis Child 2012;97:585-6.

8.Abraham BP, Mehta S, El-Serag HB. Natural history of pediatric-onset inflammatory bowel disease: a systematic review. J Clin Gastroenterol 2012;46:581-9.

9.de Bie CI, Paerregaard A, Kolacek S, et al. Disease phenotype at diagnosis in pediatric Crohn's disease: 5-year analyses of the EUROKIDS Registry. Inflamm Bowel Dis 2013;19:378-85.

10.Pigneur B, Seksik P, Viola S, et al. Natural history of Crohn's disease: comparison between childhood- and adult-onset disease. Inflamm Bowel Dis 2010;16:953-61.

11.Levine A. Pediatric inflammatory bowel disease: is it different? Dig Dis 2009;27:212-4.

12.Van Limbergen J, Russell RK, Drummond HE, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. Gastroenterology 2008;135:1114-22.

13.Urlep D, Trop TK, Blagus R, et al. Incidence and phenotypic characteristics of pediatric IBD in northeastern Slovenia, 2002-2010. J Pediatr Gastroenterol Nutr 2014;58:325-32.

14.Vernier-Massouille G, Balde M, Salleron J, et al. Natural history of pediatric Crohn's disease: a population-based cohort study. Gastroenterology 2008;135:1106-13.

15.Fumery M, Pariente B, Sarter H, et al. Long-term outcome of pediatric-onset Crohn's disease: A population-based cohort study. Dig Liver Dis 2018.

16.Levine A, Griffiths A, Markowitz J, et al. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. Inflamm Bowel Dis 2011;17:1314-21.

17.Satsangi J, Silverberg MS, Vermeire S, et al. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut 2006;55:749-53.

18.Schwartz DA, Loftus EV, Jr., Tremaine WJ, et al. The natural history of fistulizing Crohn's disease in Olmsted County, Minnesota. Gastroenterology 2002;122:875-80.

19.Hope B, Shahdadpuri R, Dunne C, et al. Rapid rise in incidence of Irish paediatric inflammatory bowel disease. Arch Dis Child 2012;97:590-4.

20.Langholz E, Munkholm P, Krasilnikoff PA, et al. Inflammatory bowel diseases with onset in childhood. Clinical features, morbidity, and mortality in a regional cohort. Scand J Gastroenterol 1997;32:139-47.

21.Malmborg P, Grahnquist L, Idestrom M, et al. Presentation and progression of childhood-onset inflammatory bowel disease in Northern Stockholm County. Inflamm Bowel Dis 2015;21:1098-108.

22.Larsen MD, Qvist N, Nielsen J, et al. Use of Anti-TNFalpha Agents and Time to First-time Surgery in Paediatric Patients with Ulcerative Colitis and Crohn's Disease. J Crohns Colitis 2016;10:650-6.

23.Kim HJ, Oh SH, Kim DY, et al. Clinical Characteristics and Long-Term Outcomes of Paediatric Crohn's Disease: A Single-Centre Experience. J Crohns Colitis 2017;11:157-164.

24.Rinawi F, Assa A, Hartman C, et al. Evolution of disease phenotype in pediatric-onset Crohn's disease after more than 10 years follow up-Cohort study. Dig Liver Dis 2016;48:1444-1450.

25.Kugathasan S, Denson LA, Walters TD, et al. Prediction of complicated disease course for children newly diagnosed with Crohn's disease: a multicentre inception cohort study. Lancet 2017;389:1710-1718.

26.Peyrin-Biroulet L, Oussalah A, Williet N, et al. Impact of azathioprine and tumour necrosis factor antagonists on the need for surgery in newly diagnosed Crohn's disease. Gut 2011;60:930-6.

27.Safroneeva E, Vavricka SR, Fournier N, et al. Impact of the early use of immunomodulators or TNF antagonists on bowel damage and surgery in Crohn's disease. Aliment Pharmacol Ther 2015;42:977-89.

28.Jeuring SF, van den Heuvel TR, Liu LY, et al. Improvements in the Long-Term Outcome of Crohn's Disease Over the Past Two Decades and the Relation to Changes in Medical Management: Results from the Population-Based IBDSL Cohort. Am J Gastroenterol 2017;112:325-336.

29.Benchimol EI, Guttmann A, To T, et al. Changes to surgical and hospitalization rates of pediatric inflammatory bowel disease in Ontario, Canada (1994-2007). Inflamm Bowel Dis 2011;17:2153-61.

30.Leonor R, Jacobson K, Pinsk V, et al. Surgical intervention in children with Crohn's disease. Int J Colorectal Dis 2007;22:1037-41.

31.Benchimol EI, Mack DR, Nguyen GC, et al. Incidence, outcomes, and health services burden of very early onset inflammatory bowel disease. Gastroenterology 2014;147:803-813 e7; quiz e14-5.

32.Blackburn SC, Wiskin AE, Barnes C, et al. Surgery for children with Crohn's disease: indications, complications and outcome. Arch Dis Child 2014;99:420-6.

33.Aloi M, Viola F, D'Arcangelo G, et al. Disease course and efficacy of medical therapy in stricturing paediatric Crohn's disease. Dig Liver Dis 2013;45:464-8.

**Legends**

Figure 1 A and B: Disease location according to Paris classification at diagnosis (1A) and Montreal classification (1B) at maximal follow up

Figure 2: Crohn’s disease behaviour at diagnosis and last follow-up. A significant change in disease behaviour towards a complicated phenotype was noted over time.

Figure 3: Cumulative risk of first intestinal resection in Paediatric Crohn’s disease (N=132)

Table 1: Uni- and multi-variate analysis of factors associated with complicated disease behaviour

Table 2: Uni-variate analysis of factors associated with the need for intestinal surgery in paediatric Crohn’s disease