THE INFLUENCE OF THE INTRODUCTION OF BIOLOGIC AGENTS ON SURGICAL INTERVENTION IN PAEDIATRIC INFLAMMATORY BOWEL DISEASE

George S Bethell MPhil[1,2], James J Ashton PhD[3,4], Stephen Adams FRCS[2], Toby Johnson MBChB[1], R Mark Beattie FRCPCH[3,5], Nigel J Hall PhD[1,2] and Michael P Stanton MD[2]

1. University Surgery Unit, Faculty of Medicine, University of Southampton, Southampton, UK.
2. Department of Paediatric Surgery and Urology, Southampton Children's Hospital, Southampton, UK.
3. Department of Paediatric Gastroenterology, Southampton Children's Hospital, Southampton, UK.
4. Department of Human Genetics and Genomic Medicine, University of Southampton, Southampton, UK.
5. NIHR Southampton Biomedical Research Centre, University Hospital Southampton, Southampton, UK.

Correspondence to: Mr Michael Stanton, Department of Paediatric Surgery and Urology, Southampton Children's Hospital, Southampton, UK. 023 8120 6489. Michael.Stanton@uhs.nhs.uk.

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Abstract

Objectives

To determine how the use of biological therapy is associated with surgical intervention for paediatric inflammatory bowel disease (PIBD) at population level.

Methods

Hospital Episode Statistics data were obtained for all admissions within England, (1997-2015), in children aged 0-18 years, with an ICD-10 code for diagnosis of Crohn's disease (CD), ulcerative colitis (UC) or inflammatory bowel disease-unclassified (IBD-U). OPCS codes for major surgical resection associated with PIBD and for biological therapy were also obtained. Data are presented as median values (interquartile range).

Results

In total, 22,645 children had a diagnosis of PIBD of which 13,722 (61%) had CD, 7,604 (34%) UC and 1,319 (5.8%) cases IBD-U. Biological therapy was used in 4,054 (17.9%) cases. Surgical resection was undertaken in 3,212 (14%) cases, more commonly for CD than UC (17.5 *vs* 10.3%, $p<0.0001$). Time from diagnosis to major surgical resection was 8.3 (1.2-28.2) months in CD and 8.2 (0.8-21.3) months in UC. As the time-frame of the data-set progressed, there was a decreased rate of surgical intervention ($p=0.04$) and an increased use of biological therapy ($p<0.0001$). Additionally, the number of new diagnoses of PIBD increased.

Conclusion

The introduction of biologic agents has been associated with a reduction in cases undergoing surgery in children with a known diagnosis of PIBD. As time progresses we will be able to

determine whether biological therapies prevent the need for surgery altogether or just delay this until adulthood.

Key words

Paediatric inflammatory bowel disease; biological therapy; surgery; hospital episode statistics.

What is known?

- Biological therapies are the mainstays of treatment for paediatric inflammatory bowel disease and more recently top-down therapy has been recommended.
- Regional studies have found a reduction in surgical intervention since the introduction of biological therapies.

What is new?

- The number of surgical resections during childhood for paediatric inflammatory bowel disease has decreased nationally during the same time-frame that the use of biological therapy has rapidly increased.
- These data confirm that the number of new diagnoses of PIBD is increasing at a national level.

Introduction

The incidence of paediatric inflammatory bowel disease (PIBD) is increasing with 20-30% of cases of all IBD presenting prior to the age of 20 years old.(1) As many as 19% children with Crohn's disease (CD) and 10% of those with Ulcerative Colitis (UC) require surgical intervention prior to transitioning to adult services.(2) The most frequent intestinal operative procedure in CD is an ileo-caecal resection for stricturing disease of the terminal ileum, whereas patients with UC most commonly undergo subtotal colectomy with ileostomy. Biological therapies, primarily consisting of anti-tumour factor-α (anti-TNF) monoclonal antibodies, have been used in PIBD following their introduction into adult practice in 2003.(3) Use of biological therapy has increased in paediatric practice following reports of its effectiveness for treating CD in this population.(4) These agents were approved in the United States in 2006, the same year in which they started being recorded in the English hospital episode statistics dataset. An initial randomised control trial of infliximab in children in 2007 demonstrated that 56% of patients treated at 8 weekly intervals were in remission at 1 year.(4) Formal approval for use in Crohn's disease for patients aged <18 occurred in 2010 in UK, with more routine adoption for ulcerative colitis around 2012.(5) Anti-TNF agents were widely adopted prior to 2010, however use was limited to specific indications including fistulating disease, and only following optimisation of immunomodulation. It was not until 2021 that top-down therapy was formally recommended for extensive CD by consensus ESPGHAN-ECCO guidance.(6, 7) The safety and efficacy of these agents have been well demonstrated in children, and regional cohort studies have suggested that use of these decrease the need for surgical resection within childhood. (2, 8, 9)

Whilst some data has pointed to a reduction in the need for surgical resection since more widespread use of biologic therapy, this has not yet been demonstrated at a population level. The aim of this study was to determine whether the introduction of anti-TNF therapy in England was associated with a change in the number of children requiring intestinal surgery.

Methods

Data collection

Hospital Episode Statistics (HES) data were acquired from NHS Digital and were available from April 1997 to April 2015 for children aged less than 18 years in England. All hospital admissions for children were included in analysis if they had a diagnosis of inflammatory bowel disease, identified with ICD-10 coding, during the study period. Crohn's disease (CD), ulcerative colitis (UC) and IBD-unclassified (IBD-U) were identified using the ICD-10 codes K50, K51 and K52.3 respectively. Where children had a subsequent ICD-10 code, on future admission, that differed from initial ICD-10 code (e.g. K52.3 followed by K50) they were managed using the following rules: 1. If, initially coded as IDC, but subsequently coded as UC, then diagnosis was taken as UC; 2. If, initially coded as IDC, but subsequently coded as CD, then diagnosis was taken as CD; 3. If, initially coded as UC, but subsequently coded as CD, then diagnosis was taken as CD; 4. If, initially coded as CD, but subsequently coded as UC, then diagnosis was taken as CD; 5. If, initially coded as CD or UC, but subsequently coded as IDC, then diagnosis taken as initial CD or UC. IBD-U in HES data represents indeterminate colitis where it is not possible to determine between CD and UC on colonoscopy and histology however, most patients with this initial diagnosis evolve to have a definite diagnosis.(10)

Use of biological therapy was identified from 2006 when they were introduced into the HES dataset, using the Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures, 4th revision, (OPCS-4) codes X29.2, X35.3, X89.1, X89.2, X89.3, X89.8, X89.9 and X96.1. Major surgical resection was also identified using OPCS-4 codes which were G58-61, G69, G70.2, G72-74, G78, H04-16, H29, H33 (supplementary data 1). In paediatric practice all initial biological therapy is given in hospital, with routine infliximab infusions also being recorded as a hospital episode and therefore available within the dataset. Administration of biological therapy attracts a high cost drug code that appears in HES data to allow payments to NHS trusts for this.

Children were tracked over time using a quasi-anonymised NHS number to determine the chronology of events (i.e. temporal relationship of biologic therapy and surgery) even if events occurred in a different hospital within England.

Outcomes

Outcomes of interest were the number of children receiving biological therapy per year, number of surgical resections per year, and the duration between these events for individual children.

Ethical approval

Access and permission to use HES data for this study were obtained from NHS digital. Additional ethical approval was not required as this study used existing data which is fully anonymised.

Statistical analysis

Statistical analysis took place using StataSE v15 (StataCorp LLC, Texas, USA). Chi-squared was used for categorical data 2x2 analysis and Mann Whitney U was used for non-parametric continuous data. Linear regression was used to assess trends over time focussing on trend before and after the introduction of biological therapy into the HES database in 2006. Data are reported as median with interquartile range, or number with percentage as appropriate. P<0.05 was considered significant. Graphs have been created using GraphPad Prism v9 (GraphPad Software, La Jolla California USA).

Results

Cases identified

Over the 18-year study period, there were 22,645 children (12,844 [57%] male) with a diagnosis of PIBD including CD (n=13,722 [61%]), UC (n=7,604 [34%]) and IBD-U (n=1,319 [5.8%]).

Biological therapy

Biological therapy was used in 4,054 (17.9%) of children and was used more commonly in CD than UC (3303 [24%] *vs* 750 [9.9%] children, p<0.0001). Time from diagnosis to first administration of biological therapy was 6.9 (1.2-18.4) months in CD and 5.9 (0.8- 17.1) months in UC. The number of hospital admission episodes where biological therapy was administered increased between 2006 and 2014, figure 1. The number of new diagnoses per year of PIBD, CD and UC increased during the study. The year-on-year use of biological therapy increased, figure 2a-c.

Surgical resection

Major surgical resection was required in 3,212 (14%) children and was more often required in CD than UC (2,399 [17.5%] *vs* 782 [10.3%], p<0.0001). Between 1997 and the introduction of coding for biological therapy into the database in 2006, the number of children undergoing surgical resection increased (slope gradient=5.2, R^2=0.81 and p=0.004), whereas after 2006 this number decreased (slope gradient=-6.4, R^2=0.54 and p=0.04) in all children with PIBD (Figures 3a and 3b). In CD the number of children undergoing surgical resection prior to 2006 increased (slope gradient=5.7, R^2=0.72 and p=0.002) whereas after 2006 this number decreased (slope gradient=-6.3, R^2=0.62 and p=0.02). In UC, there was no statistically significant difference in the number of children undergoing surgical resection before or after 2006 (slope gradient=-0.64, R^2=0.07 and p=0.47; and slope gradient=0.14, R^2=0.002 and p=0.90 respectively). The median time from diagnosis of PIBD to surgical resection was 8.3 (1.2-28.2) months in CD and 8.2 (0.8-21.3) months in UC. The median time from first dose of biological therapy to surgical resection was 10.8 (4.1-18.2) months in CD and 7.2 (2.8-10.3) months in UC. The year-on-year number of surgical resections decreased, with an increased incidence of PIBD in the dataset, figure 2a-c. Early administration of biological therapy, defined as less than one month from confirmed diagnosis of CD, was not associated with an increase in surgical resections (9.5 *vs* 11.0%, p=0.43) compared to those who commenced biological therapy more than one month after diagnosis or not at all.

Surgical resection free survival analysis was undertaken comparing those receiving biological therapy prior to surgical resection to those not in both CD and UC (supplementary figure). Those receiving biological therapy had reduced resection free survival compared to those not receiving biological therapy prior to surgical intervention.

Discussion

This population-based study confirms the steady increase in the use of biological therapies to treat PIBD following their introduction into the HES database in 2006. This precedes a decrease in the absolute number of children undergoing surgical resection during childhood (<18 years of age). These data also demonstrate the well-established increase in PIBD incidence, equating to a larger relative decrease in surgical resection, that is relative to the number of individuals at risk.

Following introduction of anti-TNF monoclonal antibody therapy in adult IBD, there has also been a rapid increase in their use in PIBD.(8, 11) ESPGHAN-ECCO guidelines, published in 2014, suggested that these agents should be used where previous therapies have been unsuccessful, in fistulating disease or in moderate to severe disease.(7) Whilst these data indicate a steady rise in monoclonal therapy use in PIBD, it is not possible to determine from this study dataset whether biological therapies have been used in line with the guidelines. More recent ESPGHAN-ECCO guidelines now suggest a top-down approach to all but mild to moderate, purely inflammatory disease, which is likely to further increase the prevalence of anti-TNF therapy.(6) These data should be interpreted in the context of the known increasing PIBD incidence, whilst the phenotype appears to remain equally severe.(12, 13) Taken as a whole, this appears likely to reflect an increased prevalence of anti-TNF therapy, alongside the increase in absolute patient numbers.

There appears to be concurrent reduction in the absolute number of surgical resections, despite the increased disease incidence. This finding has been reported in smaller, regional studies. In Wessex, the rate of children with PIBD receiving biological therapy increased from 5.1% in 2007 to 27.1% in 2017. At the same time the rate of surgical resection fell from 7.1%

to 1.5% despite a year on year increase of new diagnoses of disease.(2) The merits of a regional study are that it is possible to be confident about the prevalence of disease as it is known that no patients left the region during the study. Confirming these findings at population level is important and supports that the rate of surgery decreased whilst use of biological therapy increased nationally.

Differences between patients with Crohn's disease and ulcerative colitis are important. Previous data has indicated no change in the rates of resection for patients with ulcerative colitis over a 20-year period.(2) Our data demonstrate a similar trend, with no change in ulcerative colitis resection number over time. Increases and decreases in resections were driven by Crohn's disease patients only.

Intestinal surgical resection in PIBD is reserved for the most severe cases which are refractory to medical therapies, have fibrotic stricturing disease or complex intestinal fistulating disease.(14) This most frequently consists of subtotal colectomy in UC and ileo-caecal resection for terminal ileal strictures in CD.(15, 16) For some patients, surgical intervention offers the potential to significantly reduce disease burden, however early and late complications are common.(15, 17) Optimising nutritional state prior to surgery, minimising active disease and ensuring patients are off corticosteroid therapy are all beneficial to short and long-term surgical success.(18) It is also clear that surgery may be utilised as effective primary treatment in some cases of PIBD rather than as a last resort, and timely intervention can prevent subsequent complications if there is disease progression. An example of this is a study by *Hojsak et al.* which utilised elective ileo-caecal resection in active, localised CD leaving 79% of children in disease remission at 1 year.(19) Data in this current study suggest that surgical resection free survival is greater in those not receiving biological therapies. These

data should be interpreted with caution however as HES data does not contain information on severity of disease. Hence, those with more severe disease are most likely to be started on biological therapy and require surgical resection.

The primary non-response to anti-TNF therapy may be as high as 30% in the published literature, with the upper estimates of secondary loss of response being nearly 50%.(20) Optimising therapy also improves patient outcome, although the role of proactive therapeutic drug monitoring on long-term outcomes in paediatric practice remains controversial.(21) In the context of surgery, active anti-TNF therapy does not appear to impact on surgical outcomes to the same extent as concurrent corticosteroid treatment, although there is some evidence there are still more early complications in patients with Crohn's disease.(22)

Our data demonstrate that the number of children undergoing surgery prior to 2009 increased, with a subsequent decrease from 2009-2014, chronologically associated with the more routine use of anti-TNF therapy from 2006. These data should be interpreted in the context of increasing PIBD incidence.(13) At a population level, fewer patients with IBD are undergoing surgery before their 18th birthdays. What is not clear from this study, however, is what happens to these patients after childhood, and whether the requirement for surgical intervention is only delayed, or whether surgery is completely avoided. Determination of the long-term outcomes of these patients will be extremely important to determine the optimal timing for surgery. Whilst we may be delaying the inevitable, optimised use of anti-TNF therapy may also shrink any inflammatory component of stricturing Crohn's disease, perhaps resulting in a shorter bowel resection, and improved intestinal outcomes. Interestingly, when assessing quality of life in PIBD, patients on monoclonal therapy had worse scores compared to those who were not treated.(23) However, this may purely reflect higher disease activity

in those receiving biologics. Considering surgery, there was no difference in quality of life found between those who had previous undergone surgery, and those who had not.

This study is limited by its use of administrative data but benefits from a population-based approach and demonstrates association but not causation. It is possible that some subsequent doses of biological therapy such as Adalimumab did not involve hospital admission and therefore not appears in the HES database, however routine practice is that all initial administrations of these drugs take place during admission to allow monitoring of the children and payment to the NHS trusts for these high cost drugs. The children in this study are followed to 18 years of age but not into adulthood. It is also not possible to interrogate other factors that may be associated with changes to number of children undergoing surgical intervention. However, these findings do mirror those found in smaller, non population-based, reports.(2) These data do not assess the impact of monoclonal therapy on surgery related to perianal fistulating disease.

Conclusion

This population-based study of PIBD has shown an association between the introduction of biological therapies and a subsequent reduction in the number of children with PIBD undergoing intestinal resection. This may be reassuring to children and families of those with disease. Follow-up into adulthood is required to determine long-term prognosis.

Figure legends

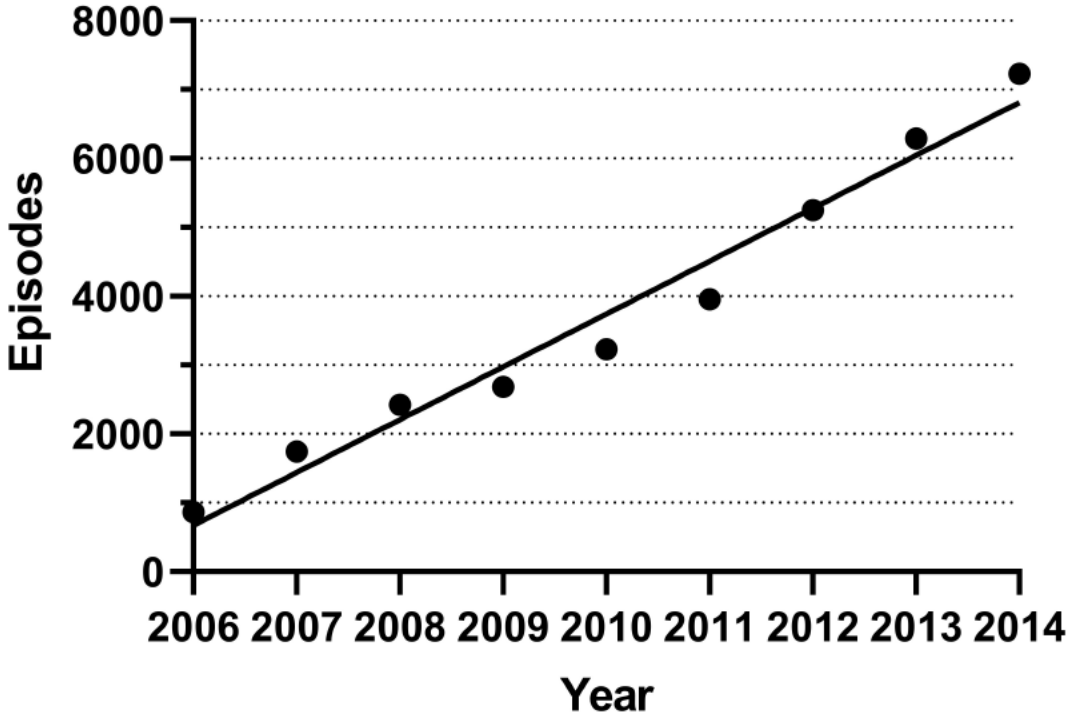

Figure 1 – Episodes of biological therapy administered per year of study, from 2006, onwards. Slope gradient=768, R^2=0.97 and p<0.0001.

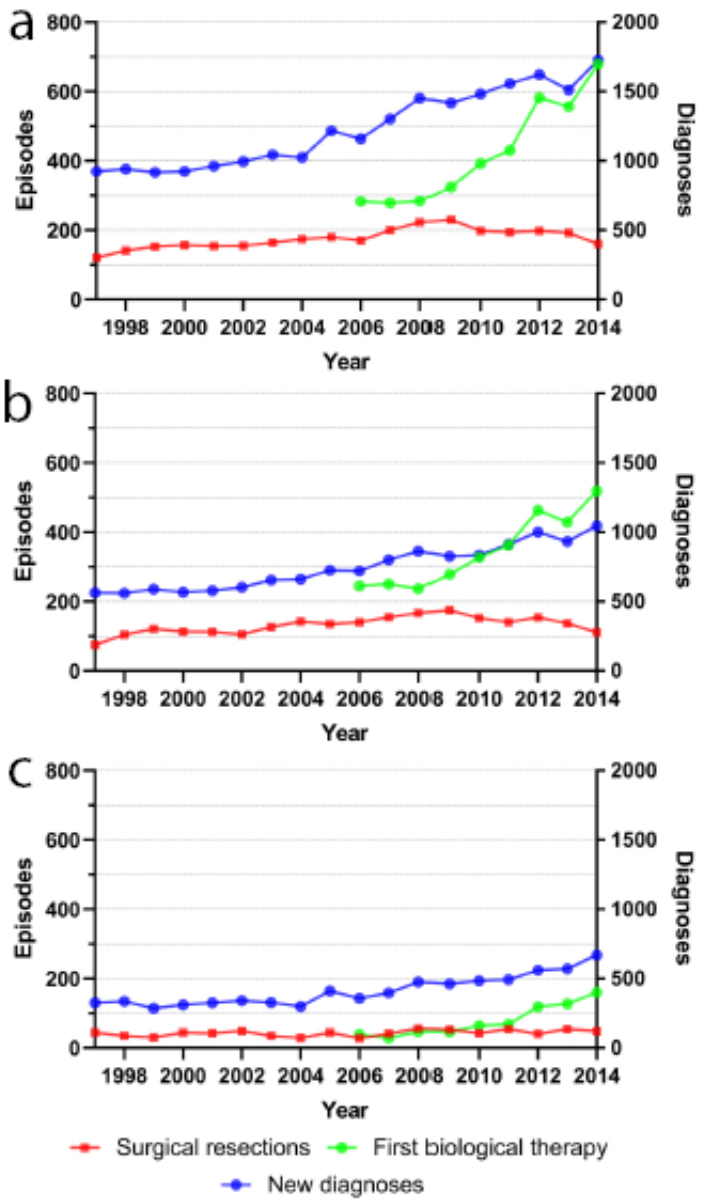

Figure 2. a - Comparison of new diagnoses of paediatric inflammatory bowel disease per year (blue, right sided Y-axis) to surgical resections (red, left sided Y-axis) and first coded episode of biological therapy use (green, left sided Y-axis). b - Comparison of new diagnoses of Crohn's disease per year (blue, right sided Y-axis) to surgical resections (red, left sided Y-axis) and first coded episode of biological therapy use (green, left sided Y-axis). c - Comparison of new diagnoses of Ulcerative Colitis per year (blue, right sided Y-axis) to surgical resections (red, left sided Y-axis) and first coded episode of biological therapy use (green, left sided Y-axis).

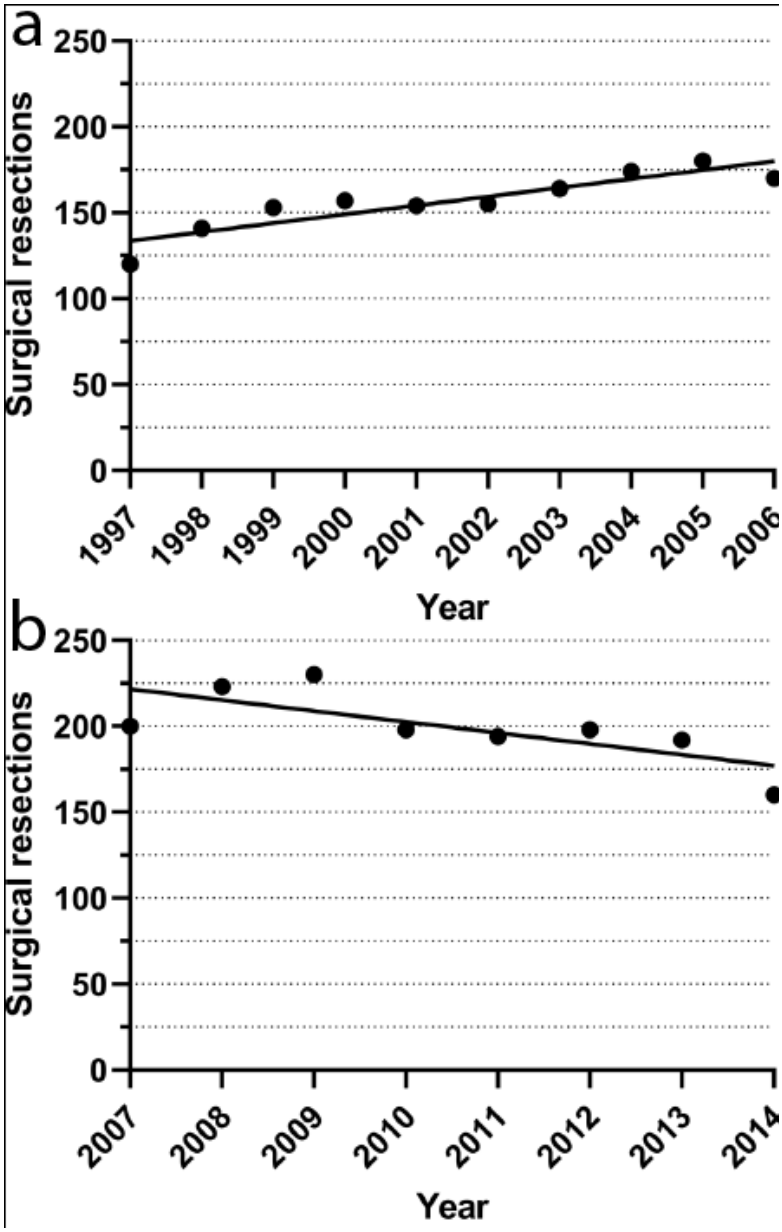

Figure 3. a – Number of children undergoing surgical resection for paediatric inflammatory bowel disease from 1997 to 2006. Slope gradient=5.2, R^2=0.81 and p=0.004. b – Number of children undergoing surgical resection for paediatric inflammatory bowel disease from 2007 to 2014. Slope gradient=-6.4, R^2=0.54 and p=0.04.

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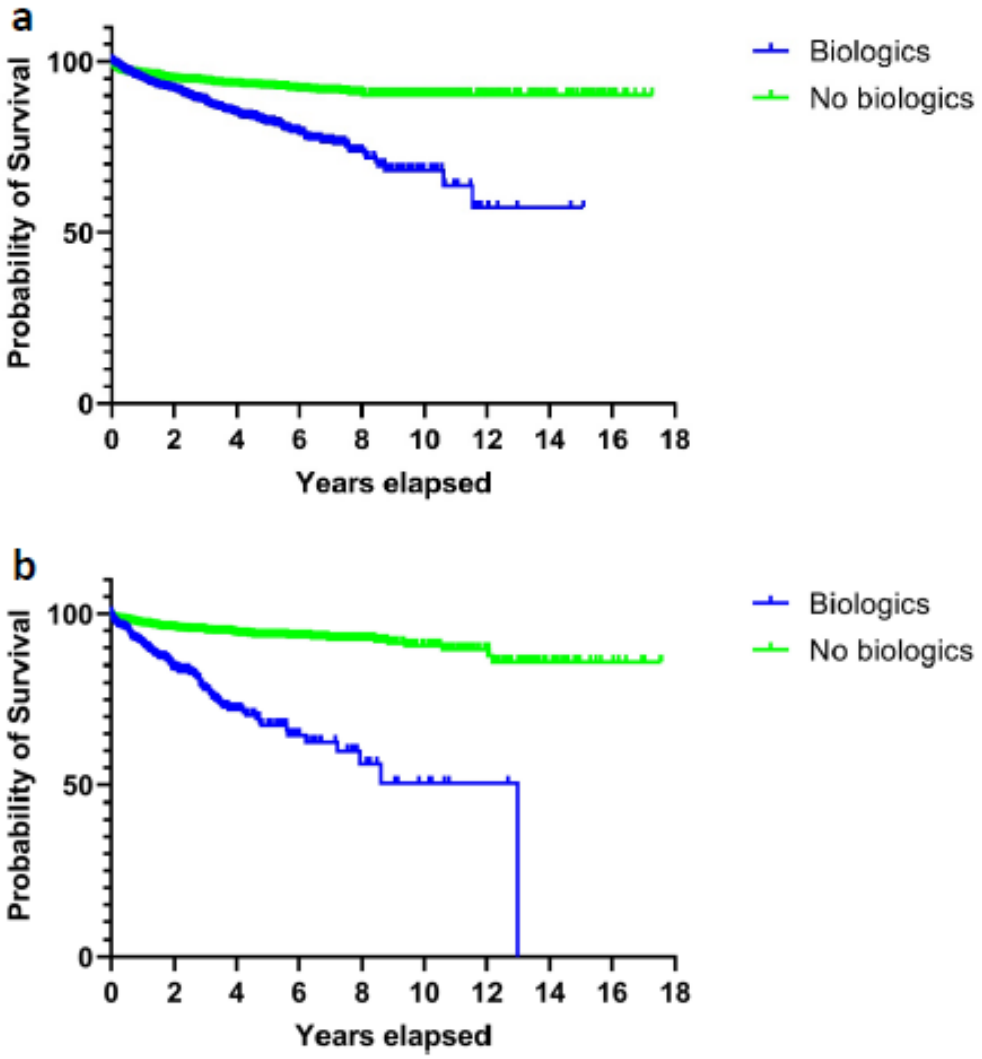
Supplementary data - OPCS-4 codes used to identify major surgical resection

Surgical procedure	**OPCS-4 codes**
Excision of jejunum with/without jejunostomy	G58-61
Excision of ileum with/without ileostomy	G69, G70.2, G72-74, G78
Excision of colon with/without colostomy	H04-16, H29, H33



Supplementary figure – Survival curves for Crohn's disease (a) and Ulcerative Colitis (b) comparing surgical resection free follow-up in children receiving biological therapy prior to surgical resections (blue line) versus no biological therapy prior to surgical resection (green line). Log-rank test (a) $p<0.0001$ and (b) $p<0.0001$. Children were only included in these analyses if born after the start of the dataset.