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Title	**Exclusive enteral nutrition provides an effective bridge to safer interval elective surgery for adults with Crohn's disease.**
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SUMMARY

Background

Few studies have reported the systematic use of exclusive enteral nutrition in the perioperative setting.

Aims

We sought to test the hypothesis that exclusive enteral nutrition provides a safe and effective bridge to surgery and reduces post-operative complications in adult patients with Crohn's disease requiring urgent surgery for stricturing or penetrating complications.

Methods

Patients treated with exclusive enteral nutrition prior to surgery were each matched with two control patients for disease behaviour, type of surgery, age at diagnosis and disease duration. Data on disease phenotype, nutritional status, operative course, and post-operative complications were obtained.

Results

Twenty-five percent [13/51] patients treated with exclusive enteral nutrition avoided surgery. Exclusive enteral nutrition had no effect on pre-operative weight, but it significantly reduced serum CRP (median at baseline 36 [interquartile range (IQR) 13-91] vs. pre-operation 8 [4-31] mg/L, p=0.02). The median [IQR] length of surgery was shorter in patients pre-optimised with exclusive enteral nutrition than controls (3.0 [2.5-3.5] vs. 3.5 [3.0-4.0] hours respectively, p<0.001). Multivariable logistic regression analysis confirmed that going straight-to-surgery compared exclusive enteral nutrition pre-optimisation was associated with a nine-fold increase in the incidence of post-operative abscess and/or anastomotic leak (OR 9.1 95 %CI [1.2-71.2], p=0.04).

Conclusions

Exclusive enteral nutrition frequently down-stages the need for surgery in patients presenting with stricturing or penetrating complications of Crohn's disease and is associated with a reduction in systemic inflammation, operative times and the incidence of post-operative abscess or anastomotic leak. Further trials are needed to elucidate how exclusive enteral nutrition may improve operative outcomes.

Introduction

Despite improvements in medical care, about 70% patients diagnosed with Crohn's disease develop stricturing or penetrating complications necessitating surgery within the first 20 years of diagnosis [1,2]. Surgeries are frequently undertaken when patients have exhausted medical options, arguably when they are at the highest risk of post-operative complications because of the burden of intra-abdominal sepsis, immunosuppression and malnutrition [3]. In support of close attention to pre-surgical optimization, in particular the timing of surgery, mortality rates are higher in IBD patients undergoing emergency rather than planned surgery [4].

Exclusive enteral nutrition involves the use of a liquid nutrition formula to meet all of an individual's dietary requirements. For the management of Crohn's disease, exclusive enteral nutrition is typically provided for 4-6 weeks before food is re-introduced [5]. When tolerated, exclusive enteral nutrition is as effective as corticosteroids for induction therapy in adult patients with Crohn's disease [6–13] and in children is considered the treatment of choice for induction of remission of Crohn's disease because of the detrimental effects of corticosteroids, in particular on growth [5,14]. However, the higher cost compared to corticosteroids, and the perception that exclusive enteral nutrition is poorly tolerated, limit its use in adults[5].

Despite early data reporting that exclusive enteral nutrition improves nutritional status and inflammation in patients with complicated Crohn's disease too debilitated to undergo surgery, there is a paucity of data reporting its systematic use in the perioperative setting [12,15–17]. Whether exclusive enteral nutrition reduces inflammation and down-stages the need for urgent surgery is unknown.

We sought to test the hypothesis that exclusive enteral nutrition reduces post-operative complications in patients with Crohn's disease requiring surgery for stricturing or penetrating complications.

Methods

Study design and clinical setting

We conducted a retrospective case-control study to evaluate the incidence of post-operative complications in patients with stricturing or penetrating Crohn's disease who received pre-optimisation with exclusive enteral nutrition and subsequently underwent surgery, compared with patients who were not pre-optimised and went straight-to-surgery. Patients were matched for disease behaviour, type of surgery, age at diagnosis, and disease duration.

The Royal Devon & Exeter (RD&E) NHS Trust is a tertiary referral centre in the South West of England that serves approximately 3,500 paediatric, adolescent and adult patients with IBD. All of the colorectal surgeons operating in the Trust undertake urgent surgery on IBD patients.

Screening

Patients who were treated with exclusive enteral nutrition with a documented plan for future surgery for stricturing or penetrating complications of Crohn's disease were identified from our specialist dietician's database. Index cases were those patients who had received exclusive enteral nutrition and specialist dietician support, with or without concurrent antibiotic therapy, who had completed at least 2 weeks of exclusive enteral nutrition treatment prior to surgery. Patients who received exclusive enteral nutrition and whose symptoms resolved, such that they no longer required surgery, were excluded.

Matching

Diagnostic coding data were used to identify IBD patients who had undergone surgery between 2008 and 2015. In order to control for the type of complication and complexity of surgery, each index case was matched to two control patients according to disease behaviour and surgical procedure. In view of the increased severity and extent of Crohn's disease diagnosed in childhood [18,19] and that the accumulation of complications is associated with disease duration [1,2], we then matched for age at diagnosis (to within 3 years) and disease duration (to within 5 years). Where more than one potential match on the grounds of age at diagnosis was available, the two individuals with the closest disease duration were included.

Exclusive enteral nutrition regimen

All patients in the exclusive enteral nutrition group were assessed by a specialist dietician and a nutritional assessment undertaken. Energy requirements were calculated using the Henry equation adjusted for activity and a stress factor [20]. All patients were treated with oral Modulen IBD™ (Nestlé, Vevey, Switzerland): volumes were determined by energy requirements and an individual's tolerance of a 1 kcal/mL feed. Patients who were unable to tolerate this volume of feed were provided with a lower volume, more concentrated, regimen. Written information was provided after the first face-to-face consultation and patients were provided with outpatient or telephone support once-weekly. Food re-introduction diets were instituted after 6 weeks of exclusive enteral nutrition and dose adjustments to match calorie requirements were made to the volume of Modulen IBD™ prescribed. Where applicable (n=6), corticosteroid doses were rapidly weaned when patients were commenced on exclusive enteral nutrition.

Data acquisition

Data were recorded from the Trust's electronic patient record, our IBD database and the case-notes. Demographic data, smoking status and Charlson co-morbidity index [21] were recorded. The income measure from English Indices of Deprivation 2015 was determined from the patients' postcodes using the tool provided by OpenDataCommunities.org [22]. Disease duration, age at diagnosis, IBD phenotype according to the Montreal Classification [23], pre-operative medical therapy, previous Crohn's disease-related surgeries, weight and body mass index, as well as, laboratory and radiology results at baseline (defined as the day of commencement of exclusive enteral nutrition for index cases, and the day of surgery in the controls) were recorded.

Duration of exclusive enteral nutrition treatment, post-exclusive enteral nutrition (pre-operative) weight and body mass index as well as laboratory tests were recorded for index cases. The principal indication for surgery, surgery type and operative course; including operative time, formation of a stoma or primary anastomosis, time to first bowel movement and eating, overall length of stay and incidence and type of surgical complications, as well as, readmission and recurrence rates at 1 year were collected.

Statistical methods

All analyses were two tailed and p-values <0.05 were considered significant. Univariable analysis of baseline demographic data comparing patients pre-optimised with exclusive enteral nutrition and controls was carried out using chi-squared analyses for categorical data, Student's t-test for continuous normally distributed variables and Mann-Whitney U tests for nonparametric data. Paired t-tests and Wilcoxon signed rank tests were used to compare pre- and post-exclusive enteral nutrition laboratory indices. Univariable analyses using chi-squared analyses and Student's t-test tests were used to identify factors associated with post-operative abscesses and/or anastomotic leak. Checks were made for co-linearity and then these factors were entered into a stepwise forward multivariable logistic regression model along with the following clinical factors that influence post-operative complications: previous surgery, surgery type and operating surgeon.

Ethical consideration

This project was conducted as a service evaluation and so did not require formal ethical approval in accordance with the guidelines of the UK Health Research Authority [24].

Results

Screening & matching

Fifty-one patients who were treated with exclusive enteral nutrition prior to surgery for stricturing or penetrating complications of Crohn's disease were identified from our specialist dietician's database. Clinical status improved in 25% [13/51] patients such that they no longer required surgery (Figure 1). 9% [14/150] of potential control patients were excluded on the grounds of surgery type and disease behaviour and a further 40% [60/150] on the grounds of age at diagnosis and disease duration (Figure 1).

As a consequence of our matching, there was no difference in the age at diagnosis (median 31.5 [interquartile range (IQR) 25.1-38.5] vs. 30.6 [24.0-43.3] years), disease duration (1.1 [0.3-9.9] vs. 4.6 [0.8-8.8] years), disease location, disease behaviour (Table 1) or type of surgery (Table 2) between the exclusive enteral nutrition group and control group.

Demographic and socio-economic data

There were no differences in age, gender, ethnicity, income scores, smoking status or co-morbidities between index cases and controls (Table 1).

At the initiation of exclusive enteral nutrition, no differences were seen in the proportions of patients treated with 5-aminosalicylates (5-ASAs), immunomodulators (thiopurines or methotrexate) or biologic agents (infliximab and adalimumab) (Table 1). A small proportion of patients in both groups were treated with corticosteroids at baseline (Table 1). Patients treated with exclusive enteral nutrition were more frequently treated with antibiotics than matched controls (29% vs. 11% respectively, p=0.03). There were no differences in the proportions of cases and controls with radiological evidence of abscess or collection at baseline or in the proportions that had previous surgery (Table 1).

Body mass index was lower at baseline in the exclusive enteral nutrition group compared with controls (p=0.046, Table 2). No differences were seen in baseline full blood counts (FBC) or serum albumin levels. C-reactive protein (CRP) levels, however, were significantly higher at baseline in cases than controls (median 36 [IQR 13-91] vs. 7 [3-18] mg/L, p<0.0001). Baseline CRP levels were higher in patients co-prescribed antibiotics (p<0.001) but there was no difference in CRP levels in this sub-group immediately before surgery (Figure 2).

Exclusive enteral nutrition treatment

The mean [standard error of the mean (SEM)] duration of exclusive enteral nutrition therapy was 6.3 [0.4] weeks. Overall, 6% [3/51] patients were unable to tolerate at least 4 weeks of exclusive enteral nutrition. These patients then received courses of prednisolone and were bridged to thiopurine

158 therapy. Weight did not increase following exclusive enteral nutrition treatment (median 73 [IQR
159 60.5-81.6] vs. 73.5 [60.5-81.4] kg, p=0.92). There were no differences in weight or BMI immediately
160 before surgery between cases and controls (Table 2).
161 No differences were seen in full blood counts (FBC) or serum albumin levels after exclusive enteral
162 nutrition pre-optimisation; however, CRP levels in the exclusive enteral nutrition cases were
163 significantly lower before surgery than at baseline (pre-operation median 8 mg/L [IQR 4-31] vs.
164 baseline 36 [13-91] mg/L vs., p=0.004, Figure 2).
165 Exclusive enteral nutrition and antibiotic treatment, but not corticosteroid exposure, were
166 independently associated with significant reductions in serum CRP levels (Supplementary Table 1).
167 Given that more patients who were treated with exclusive enteral nutrition were co-prescribed
168 antibiotics, we repeated the model including antibiotics and exclusive enteral nutrition as interacting
169 variables; herein, treatment with exclusive enteral nutrition, but not antibiotics alone, was
170 associated with a reduction in CRP (Supplementary Table 2).
171 *Operative outcomes*
172 No differences were seen in the principal indication for surgery, surgical approach or the proportion
173 of patients that required a stoma (Table 2).
174 The median [IQR] length of surgery was shorter in patients pre-optimised with exclusive enteral
175 nutrition compared to the control group (3 [2.5-3] vs. 3.5 [3.5-4] hours respectively, p<0.001, Figure
176 2). Furthermore, the length of time to resume oral intake was also less in the exclusive enteral
177 nutrition cases compared with control patients (2 [1-3] vs. 3 [3-4] days, p<0.001). No differences
178 were seen in the time to first bowel movement or overall length of stay between cases and controls
179 (Table 2).
180 Overall, index patients pre-optimised with exclusive enteral nutrition patients had significantly fewer
181 surgical complications than control patients who went straight-to-surgery (3/38 [8%] vs. 52/78 [32%]
182 respectively, p< 0.001, Figure 3) including the rate of formation of an abscess, collections and/or
183 anastomotic leak (1/38 [3%] in exclusive enteral nutrition group vs. 15/78 [20%] in controls,
184 p=0.019). No statistically significant differences were seen in readmission or recurrence rates 1 year
185 after surgery (Table 2).

186 *Factors associated with post-operative abscess/collection or anastomotic leak*
187 As described above, patients directed straight-to-surgery were more likely to suffer an anastomotic
188 leak, abscess or collection. In univariable analysis increasing length of operation (odds ratio (OR),
189 95% confidence interval) was also found to be associated with an increased incidence of an
190 anastomotic leak, abscess or collection (OR 3.3, 95%CI [1.1-11.2], p=0.043) Stepwise multivariable
191 logistic regression analysis incorporating previous surgeries, type of surgery and operating surgeon,

however, demonstrated that going straight-to-surgery was the only independent variable associated with the incidence of a post-operative abscess/collection or anastomotic leak (OR 9.1 95% CI 1.7-167.9], p=0.036).

Patients whose surgery was complicated by a post-operative abscess/collection or anastomotic leak had significantly longer length of stays and higher readmission rates than patients who had uncomplicated surgery (median [IQR] 8 [6-11] days vs. 6 [5-7] days, p=0.011).

Discussion

Several studies have reported the use of exclusive enteral nutrition for induction of remission in adults and children with active Crohn's disease; few, however, have been designed to evaluate the efficacy of exclusive enteral nutrition as a bridge to safer interval surgery and fewer operative complications. In addition to a more favourable adverse effect profile than corticosteroids and improved quality of life scores [25], exclusive enteral nutrition has been associated with higher rates of mucosal healing [26]; reductions in serum anti-TNFα levels [27]; increased insulin like growth factor-1 levels [28], improvements in nutritional status [29] and extensive modulation of the intestinal microbiota [30] that could conceivably improve post-operative outcomes.

We sought to test the hypothesis that exclusive enteral nutrition reduces post-operative complications in patients with stricturing or penetrating complications of Crohn's disease necessitating urgent surgery.

Key results and interpretation

In this study, 25% of the patients we treated with exclusive enteral nutrition because of stricturing or penetrating complications of Crohn's disease avoided surgery and were bridged to alternative immunosuppressant therapy. This is similar to rates reported from the early observational studies of exclusive enteral nutrition [12,15–17]. Despite the widely held belief that exclusive enteral nutrition is poorly tolerated in adults, 94% of our cohort were able to tolerate more than 4 weeks of exclusive enteral nutrition treatment, a rate similar to that reported in previous randomised controlled trials [6,8–10,12,31].

Unlike data from clinical trials of EEN in adults with Crohn's disease [6–13], EEN in our cohort had no effect on pre-operative weight; possibly because of the relatively short duration of treatment. In previous reports, significant changes in weight were only reported after 3 months of treatment [5,12].

In common with recent non-matched retrospective studies that reported surgical outcomes in Crohn's disease [32,33], and accepting that patients treated herein were more inflamed at baseline and more frequently co-prescribed antibiotics, exclusive enteral nutrition significantly reduced CRP prior

to surgery. When exclusive enteral nutrition and antibiotics were co-prescribed we found that their effects on CRP levels were synergistic. Going straight-to-surgery compared with exclusive enteral nutrition pre-optimisation was associated with a 9-fold increased risk of a post-operative abscess, collection or anastomotic leak. We also demonstrated that exclusive enteral nutrition was associated with shorter operation times. It is conceivable that exclusive enteral nutrition makes surgery technically easier by reducing the inflammatory burden, and that this leads to a reduction in complications.

Exclusive enteral nutrition pre-treatment and operation time were the only factors associated with post-operative abscess, collection or anastomotic leak, with the use of EEN the only independent variable remaining on multivariable analysis. In contrast to previous studies, we did not demonstrate associations with smoking status [34], corticosteroids [35] or anti-TNF exposure [36] and the occurrence of post-operative abscess, collection or anastomotic leak.

Strengths and limitations

Our matched study has several strengths. By comparing our exclusive enteral nutrition cohort with controls matched for disease behaviour, surgery type, age at diagnosis and duration of diagnosis, we attempted to avoid selection bias and confounding by differences in disease severity. However, this will have led to selection of patients with more severe phenotypes with, arguably, an increased risk of complications than previously reported case series [32,33]. Furthermore, given this is a single centre cohort from a tertiary IBD centre, the patients were each accurately phenotyped, allowing us to look for differences between demographic characteristics, disease phenotype, and treatment regimens. Moreover, there was no difference in the proportions of patients with intra-abdominal sepsis/collection at baseline thus minimising the potential for confounding by severity.

Conversely, this work has a number of limitations. Because of our retrospective data collection, in particular for the Montreal classification and surgical disease course, our results are potentially subject to interpretation bias, and bias because of missing data. Our results might be confounded by incomplete matching of disease severity. However, despite higher baseline levels of inflammation, the complication rate was lower in the EEN-treated group. We acknowledge too, that the sample size is relatively small and that we used a composite primary outcome measure, and that consequently our conclusions may be subject to a type II error.

Conclusion

Exclusive enteral nutrition frequently downstages the need for urgent surgery, in patients presenting with stricturing or penetrating complications of Crohn's disease. Compared with patients who went straight-to-surgery matched for surgical type and disease behaviour, age at diagnosis and disease duration, patients pre-treated with EEN had fewer post-operative complications. This suggests that exclusive enteral nutrition may be used as a bridge to semi-elective, and arguably therefore, safer surgery in patients with complicated Crohn's disease. A randomised-controlled trial is needed to elucidate how exclusive enteral nutrition may improve operative outcomes and to confirm that exclusive enteral nutrition provides a safe and effective bridge to surgery.

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TA and JRG conceived and designed the study. NH screened the outpatient populations and matched the cohorts. BT collated the EEN dataset. NH and PH collated the control dataset. NH, JRG and NAK analysed the dataset and prepared the manuscript. GH, GW, CC, RMB, SDM and TA contributed to interpretation of the study results and writing of the manuscript. All authors approved the final manuscript.

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Figures

Figure 1: STROBE [37] diagram outlining the screening, matching and inclusion of cases and controls. Each index case that was treated EEN was matched on surgical procedure, disease behaviour, age at diagnosis (to within 3 years) and then disease duration (to within 5 years) to two patients that went straight-to-surgery. Where more than one potential match on the grounds of age at diagnosis was available, the individual with the closest disease duration was included.

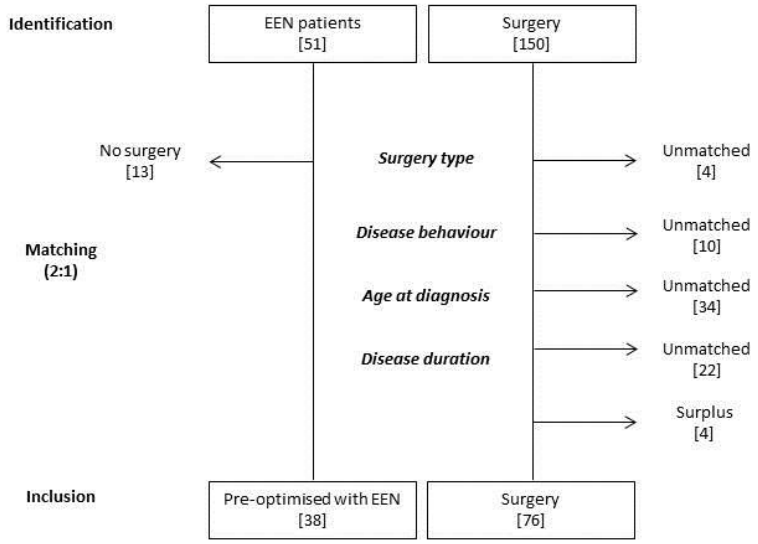
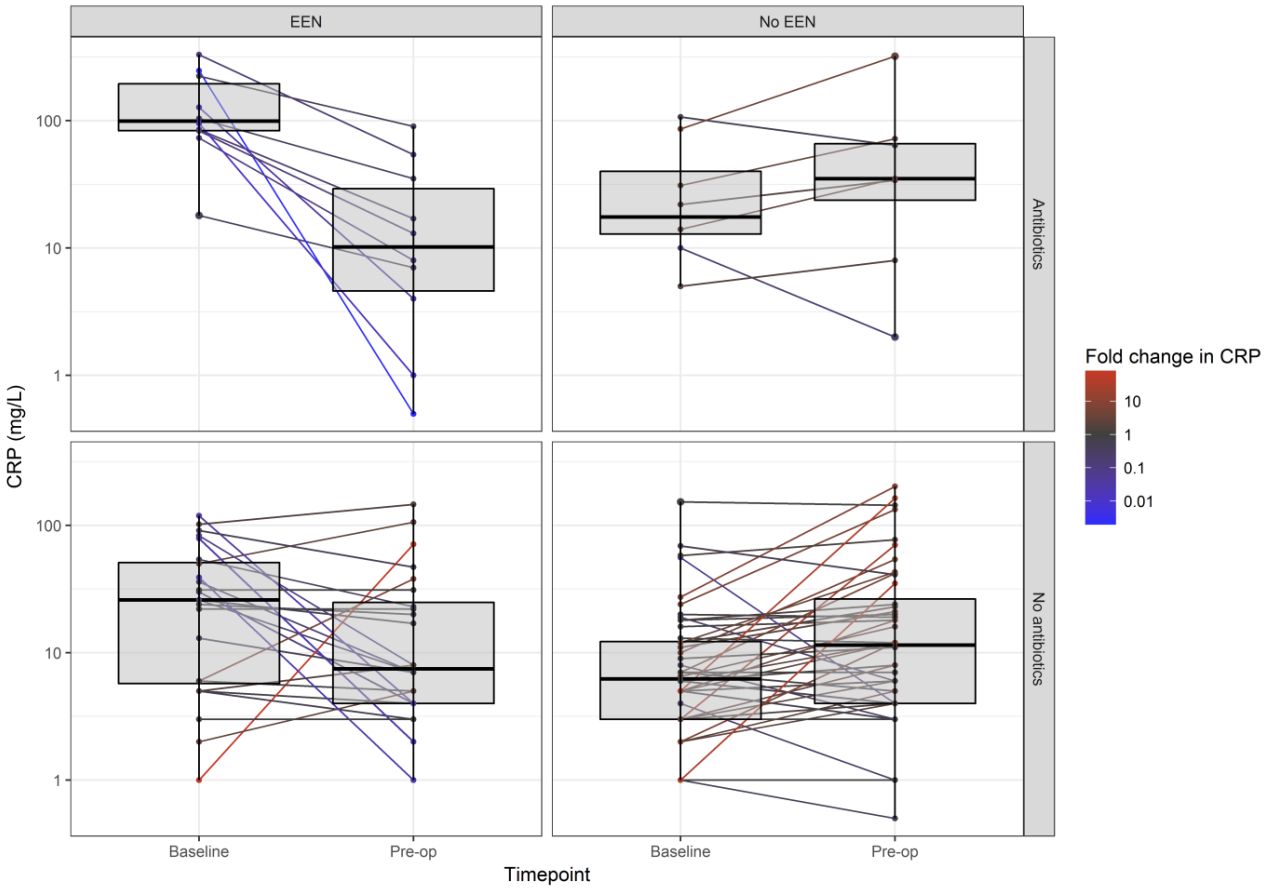


Figure 2: Fold change in CRP in patients treated with or without exclusive enteral nutrition with or without antibiotics.



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Characteristic		**EEN pre-surgery (38)**	**Matched-controls (76)**	***p* - value**
Age	Age (yrs)	36.3 [30.1-46.6]	39.9 [28-49.5]	0.77
Sex	Male	21 [55%]	36 [47%]	0.55
Ethnicity	White	38 [100%]	78 [100%]	1.0
Socio-economic status	Index of Multiple Deprivation Score	0.11 [0.009]	0.11 [0.006]	0.59
Smoking	Current Ex Never	13 [34%] 5 [13%] 20 [53%]	25 [33%] 9 [12%] 42 [55%]	0.28
Comorbidity	Charlson score	0 (0-3)	0 (0-6)	0.31
Disease Duration †	Disease duration (yrs)	1.1 [0.3-9.9]	4.6 [0.8-8.8]	0.16
	Age at diagnosis (yrs)	31.5 [25.1-38.5]	30.6 [24-43.3]	0. 84
Montreal Classification †	A1: Age <17 A2: 17-40 A3: >40	3 [8%] 28 [74%] 7 [18%]	3 [4%] 47 [62%] 26 [34%]	0.17
	L1: Ileal L2: Colonic L3: Ileocolonic	19 [50%] 1 [3%] 18 [47%]	46 [61%] - 30 [40%]	0.22
	+ L4: Upper GI	7 [18%]	12 [16%]	0.79
	B1: Inflammatory B2: Stricturing B3: Penetrating	- 18 [47%] 20 [53%]	- 36 [47%] 40 [53%]	1.00
	+ p: Perianal	3 [8%]	5 [7%]	1.00
Medications	5 ASA	0 [0%]	5 [7%]	0.17
	Corticosteroids	6 [16%]	8 [11%]	0.43
	Thiopurine	10 [26%]	29 [38%]	0.20
	Methotrexate	0 [0%]	2 [3%]	0.55
	Anti-TNF	3 [8%]	9 [12%]	0.51
	Antibiotics	11 [29%]	9 [11%]	0.03
Prior surgeries‡	None	26 [68%]	50 [66%]	0.94
	Small bowel resection	4 [11%]	7 [9%]	
	Ileocaecal resection	7 [18%]	10 [13%]	
	Right hemicolectomy	1 [3%]	9 [12%]	
Radiology	Collection/abscess	8[21%]	17[22%]	1.0
Laboratory indices	Haemoglobin (g/L) mean [SEM]	127 [2.6]	129 [1.5]	0.62
	MCV (fL) mean [SEM]	85.5 [1.0]	87.2 [0.9]	0.23
	White cell count ($x10^9$/L) mean [SEM]	9.3 [0.5]	8.1[0.4]	0.07
	Platelet count ($x10^9$/L) mean [SEM]	331 [16.7]	308 [11.3]	0.25
	Albumin (g/L) mean [SEM]	41.8 [0.8]	42.6 [0.5]	0.35
	C-reactive protein (mg/L) median [IQR]	36 [13-91]	7 [3-18]	<0.0001

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444 **Table 1: Baseline demographic, disease phenotype, concurrent medications, previous surgeries**
445 **and laboratory indices in cases and controls.** Median and interquartile range (IQR) are presented
446 unless otherwise stated. SEM denotes standard error of the mean. Differences between parametric
447 continuous variables and in non-parametric and/or discrete variables were sought using Student's t-
448 test and the Mann-Whitney U test respectively. Differences between categorical variables were
449 sought using chi-squared analyses, where n<6 Fisher's exact test was used. † matching criteria: only
450 the age at diagnosis and disease behaviour components of the Montreal classification were
451 matched. ‡ denotes chi-squared analysis between surgery and no surgery.
452

Characteristic		**EEN pre-surgery (38)**	**Matched controls (76)**	***p* - value**
Nutritional status	Baseline weight (kg)	71.5 [59.0-77.8]	74.8 [61.8-83.5]	0.13
	Baseline BMI	23.0 [19.5-26.7]	24.6 [21.5-28.3]	0.46
	Weight pre-surgery	71.1 [59.5-78.0]	74.8 [61.8-83.5]	0.18
	Weight post-surgery	74.8 [59.8-79.9]	74.2 [62.8-84.7]	0.37
Pre-operative medications	Corticosteroids	4 [11%]	8[11%]	1.0
	Antibiotics	11[29%]	9[11%]	0.04
Pre-op laboratory indices	Haemoglobin (g/L) mean [SEM]	130 [2.3]	129 [1.7]	0.72
	MCV (fL) mean [SEM]	85.5 [1.0]	87.2 [0.9]	0.23
	White cell count ($x10^9$/L) mean [SEM]	9.3[0.5]	8.1[0.4]	0.07
	Platelet count ($x10^9$/L) mean [SEM]	306[14.1]	294 [9.4]	0.52
	Albumin (g/L) mean [SEM]	42.4[1.0]	41.3[0.7]	0.38
	C-reactive protein (mg/L)	8 [4-29]	14 [5-43]	0.30
Indication for surgery	Stricturing	18[47%]	40[53%]	0.11
	Penetrating	20[53%]	36[47%]	
Surgical approach	Open	16 [42%]	44[58%]	0.11
	Laparoscopic	22 [58%]	32 [42%]	
Surgery type †	Small bowel resection	3 [8%]	6[8%]	0.99
	Ileocaecal resection	30 [79%]	60 [79%]	
	Right hemicolectomy	3[8%]	7[9%]	
	Colectomy	2[5%]	3[4%]	
Stoma	Primary anastomosis	37[97%]	70 [92%]	0.42
	Stoma	1[3%]	6 [8%}	
Operative course	Length of surgery (hrs)	3 [2.5-3.5]	3.5 [3.0-4.0]	<0.001
	Time to first bowel movement (days)	3 [2-4]	3 [3-4]	0.28
	Time to eating (days)	2 [1-3]	3 [3-4]	<0.001
	Length of stay (days)	6 [5-7]	6 [5-7]	0.97
Surgical complications	Anastomotic leak, abscess or collection	1 [3%]	15 [20%]	0.02
	Wound dehiscence	2 [5%]	6 [8%]	0.72
	High stoma output	-	2 [3%]	-
	Rectal bleeding	-	1 [1%]	-
	Ileus	-	1 [1%]	-
Readmission	Within 28 days	1 [3%]	11[14%]	0.11
	29-72 days	-	3[4%]	0.55
Disease activity at 1 year	Recurrence	11 [29%]	31 [41%]	0.30
	Remission	27 [71%]	45 [59%]	

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Table 2: Peri-surgical, nutritional and laboratory indices, indication for surgery, surgical approach, type, stoma formation, operative course and complications in cases and controls. Median and interquartile range (IQR) are presented unless otherwise stated. SEM denotes standard error of the mean. Differences between parametric continuous variables and in non-parametric and/or discrete variables were sought using Student's t-test and the Mann-Whitney U test respectively. Differences between categorical variables were sought using chi-squared analyses, where n<6 Fisher's exact test was used. † denotes matching criteria.

Variable	Parameter estimate	LCI	UCI	*p* - value
(Intercept)	1.88	1.27	2.78	0.002
EEN	0.24	0.13	0.44	<0.0001
Antibiotics (baseline)	0.35	0.16	0.74	0.008

Supplementary Table 1: Simultaneous multivariable linear regression of factors independently associated with fold-change in CRP.

Variable	Parameter estimate	LCI	UCI	*p* - value
(Intercept)	1.66	1.12	2.46	0.014
EEN	0.35	0.18	0.69	0.003
Antibiotics (baseline)	0.85	0.30	2.43	0.767
EEN and antibiotics (baseline)	0.17	0.04	0.75	0.021

Supplementary Table 2: Simultaneous multivariable linear regression including EEN and antibiotics as an interacting variable with fold-change in CRP.