Original article

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Association of mechanical bowel preparation with oral antibiotics and anastomotic leak following left sided colorectal resection: an international, multi-centre, prospective audit

The 2017 European Society of Coloproctology (ESCP) collaborating group

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Abstract

Introduction The optimal bowel preparation strategy to minimise the risk of anastomotic leak is yet to be determined. This study aimed to determine whether oral antibiotics combined with mechanical bowel preparation (MBP+Abx) was associated with a reduced risk of anastomotic leak when compared to mechanical bowel preparation alone (MBP) or no bowel preparation (NBP).

Methods A pre-planned analysis of the European Society of Coloproctology (ESCP) 2017 Left Sided Colorectal Resection audit was performed. Patients undergoing elective left sided colonic or rectal resection with primary anastomosis between 1 January 2017 and 15 March 2017 by any operative approach were included. The primary outcome measure was anastomotic leak.

Results Of 3676 patients across 343 centres in 47 countries, 618 (16.8%) received MBP+ABx, 1945 MBP (52.9%) and 1099 patients NBP (29.9%). Patients undergoing MBP+ABx had the lowest overall rate of anastomotic leak (6.1%, 9.2%, 8.7% respectively) in unadjusted analysis. After case-mix adjustment using a mixed-effects multivariable regression model, MBP+Abx was associated with a lower risk of anastomotic leak (OR 0.52, 0.30–0.92, $P = 0.02$) but MBP was not (OR 0.92, 0.63–1.36, $P = 0.69$) compared to NBP.

Conclusion This non-randomised study adds 'real-world', contemporaneous, and prospective evidence of the beneficial effects of combined mechanical bowel preparation and oral antibiotics in the prevention of anastomotic leak following left sided colorectal resection across diverse settings. We have also demonstrated limited uptake of this strategy in current international colorectal practice.

Keywords Colorectal surgery, colonic cancer, laparoscopic surgery, bowel preparation, anastomotic leak

What does this paper add to the literature?

This international study found that administration of combined oral antibiotics with mechanical bowel preparation halved the odds of anastomotic leak following left sided colorectal surgery compared to those with no bowel preparation; a finding consistent across sensitivity analyses. Despite this, only 16.8% of patients received this preparation strategy in contemporary practice.

Introduction

Anastomotic leak following left sided colorectal surgery is associated with increased morbidity and mortality, reduced quality of life and worse oncological outcomes [1,2]. As such, identifying perioperative measures that may reduce anastomotic failure rates is a major research focus.

The optimal preoperative bowel preparation regime in left sided colorectal surgery remains controversial. Current enhanced recovery after surgery (ERAS) recommendations states that mechanical bowel preparation (MBP) should not be used routinely in colonic surgery due to the distressing adverse effects that can be associated [3] with lack of evidence for benefit [4,5]. The majority of data on combined MBP with selective gastrointestinal decontamination with oral antibiotics

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comes from retrospective analyses of large North American databases. These demonstrate evidence of reduction in anastomotic leak and surgical site infection rates when compared to MBP alone, oral antibiotics alone or no preparation [6–11]. Evidence from several published clinical trials is consistent with this finding, but randomised evidence remains of low and moderate methodological quality with high risk of bias. In Europe [12], mechanical bowel preparation with concurrent oral antibiotics is the subject of a number of blinded, multi-centre randomised trials currently open to recruitment, but in the years before they report there remains no existing high quality prospective data to support this choice of preoperative bowel preparation strategy in elective colectomy [13].

The primary aim of this study was to explore associations between bowel preparation strategy and anastomotic leak after elective left sided colorectal resection with primary anastomosis. The secondary aims were to explore associations of anastomotic technique with anastomotic failure, and to assess the clinical impact of anastomotic leak.

Methods

Protocol

This prospective, observational, multi-centre audit was conducted in line with a pre-specified protocol (http://www.escp.eu.com/research/cohort-studies). An external pilot of the protocol and data capture system was conducted in five international centres prior to launch, allowing refinement of the study tool and delivery. This data was not included within the main study analysis.

Centre eligibility

Any unit performing gastrointestinal surgery was eligible to register to enter patients into the study. No minimum case volume, or centre-specific limitations were applied. The study protocol was disseminated to registered members European Society of Coloproctology (ESCP), and through national surgical or colorectal societies.

Patient eligibility

Adult patients (> 16 years) undergoing planned, elective left hemicolectomy, sigmoid colectomy or rectal resection with a single, primary anastomosis were extracted from the main audit database. Operations with multiple (> 1) anastomoses were excluded as were resections with formation of end colostomy without restoration of gastrointestinal continuity (e.g. abdominoperineal resection, Hartmann's procedure), more extensive colorectal resection (e.g. subtotal or total colectomy),, pouch formation, pelvic exenteration or multivisceral resection and reversal of colostomy. Both malignant and benign indications for surgery were eligible. Open, laparoscopic, laparoscopic-converted, robotic and robotic-converted procedures were all eligible, including those incorporating a perineal approach, both traditional or transanal.

Data capture

Consecutive sampling was performed of eligible patients over an 8-week study period in each included centres. Local investigators commenced data collection on any date between the 1 January 2017 and 15 March 2017, with the last eligible patient being enrolled on 10 May 2017. This study adopted the UK National Research Collaborative model for data collection and follow-up. Small teams of up to five surgeons or surgical trainees worked together to collect prospective data on all eligible patients at each centre. Quality assurance was provided by at least one consultant or attending-level surgeon. Data was recorded contemporaneously and stored on a secure, user-encrypted online platform (REDCap) without using patient identifiable information. Centres were asked to validate that all eligible patients during the study period had been entered, and to attain > 95% completeness of data field entry prior to final submission.

There were three main phases of data collection for each patient, each represented by separate clinical reporting forms. Case report form (CRF) A collected baseline patient- and disease-specific characteristics including Age, Gender, American Society of Anaesthesiologists (ASA) classification grade, smoking history, body mass index, history of diabetes mellitus, cardiovascular disease, concurrent anticoagulant therapy, indication for surgery, disease location and urgency of surgery. CRF B collected information about the index operation and non-patient or disease related factors including operator grade (Consultant, Trainee), operator specialty interest (Colorectal, General Surgery), operative approach, level of proximal and distal transection, anastomosis type (handsewn, stapled), anastomotic configuration (side-to-side, side-to-end, end-to-end), distance of the anastomosis from the anal verge (in centimetres), whether an intraoperative leak test was performed, and whether a proximal defunctioning enterostomy (loop ileostomy, end ileostomy, loop colostomy) was formed.

Case report form C collected follow-up data on the primary and secondary outcome measures. This study was designed to bring efficiency by using normal post-operative follow-up pathways to obtain outcome data. Follow-up data was collected to 30 postoperative days through review of patient notes (paper and electronic) during their index admission, reviewing hospital systems to check for readmission or reoperation, and reviewing postoperative radiology reports. Where postoperative review at or before 30 postoperative days formed part of routine practice follow-up data was also obtained at this clinical review.

Outcome measure

The primary outcome measure was overall anastomotic leak, pre-defined as either (i) gross anastomotic leakage proven radiologically or clinically, or (ii) the presence of an intraperitoneal (abdominal or pelvic) fluid collection on post-operative imaging. The secondary outcome measures were the postoperative major complication rate, defined as Clavien-Dindo classification grade 3 to 5 (reoperation, reintervention, unplanned admission to critical care, organ support requirement or death), the postoperative length of stay (in whole days), with day of surgery as day zero, and the postoperative mortality rate, defined as death within 30 days of surgery.

Statistical analysis

This report has been prepared in accordance to guidelines set by the STROBE (strengthening the reporting of observational studies in epidemiology) statement for observational studies [14].

Patient, disease and operative characteristics were compared by type of bowel preparation (no bowel preparation (NBP), mechanical bowel preparation alone (MBP), mechanical bowel preparation and oral antibiotics (MBP + Abx) and by the primary outcome anastomotic leak using Student's *t*-test for normal, continuous data, Mann–Whitney *U* test for non-normal continuous data or Chi-squared test for categorical data. To test the association between overall anastomotic leak and the main explanatory variables of interest (type of bowel preparation, other non-patient and disease related factors described above), a mixed-effects logistic regression model was fitted. Clinically plausible patient, disease and operation-specific factors were entered into the model for risk-adjustment, treated as fixed effects. These were defined *a priori* within the study protocol, and included irrespective of their significance on univariate analysis. Hospitals were entered into the model as a random-

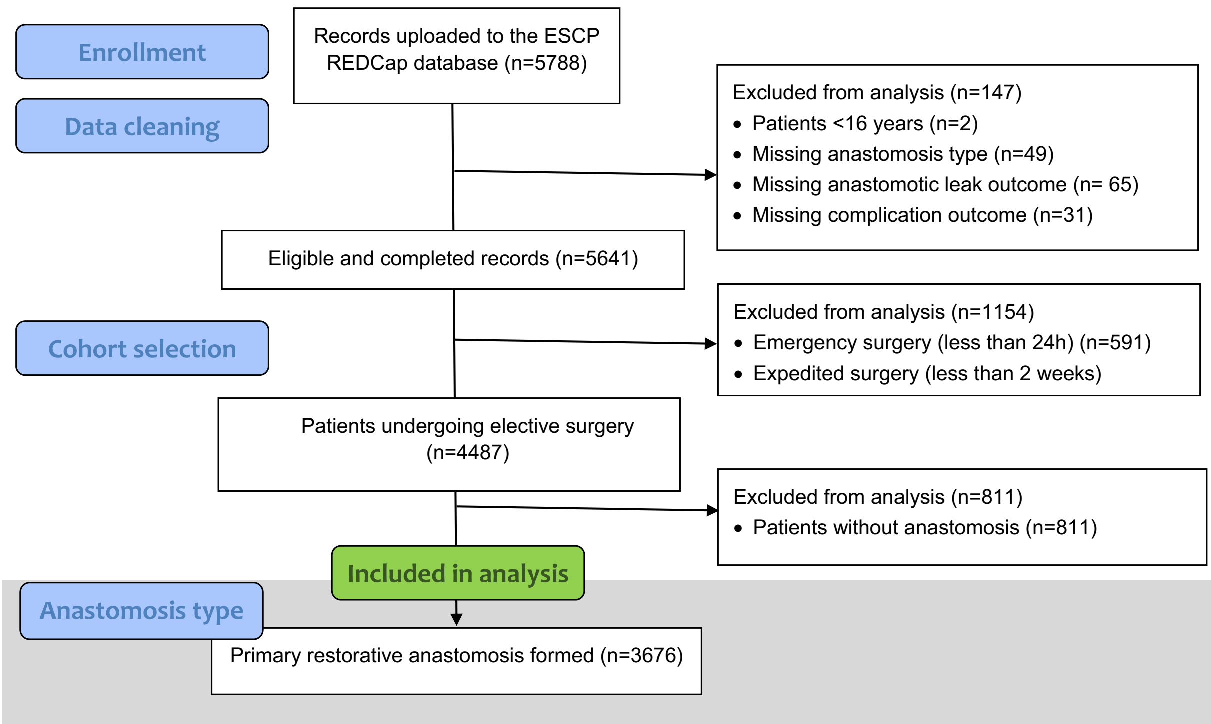

Figure 1 Flowchart for patients included in analysis of bowel preparation and intraoperative factors in elective left colorectal resection.

Table 1 Patient and disease characteristics of patients by bowel preparation strategy.

Factor	Levels	No bowel prep	MBP only	MBP and pre-op oral ABx	*P*-value
Age	< 55	254 (23.1)	371 (19.1)	115 (18.6)	0.002
	55–70	451 (41.0)	887 (45.6)	265 (42.9)	
	70–80	296 (26.9)	516 (26.5)	170 (27.5)	
	> 80	98 (8.9)	171 (8.8)	65 (10.5)	
	Missing	0 (0.0)	0 (0.0)	3 (0.5)	
Gender	Female	493 (44.9)	784 (40.3)	242 (39.2)	0.029
	Male	606 (55.1)	1161 (59.7)	376 (60.8)	
ASA class	Missing	0 (0.0)	5 (0.3)	24 (3.9)	< 0.001
	Low risk (ASA 1–2)	828 (75.3)	1288 (66.2)	434 (70.2)	
	High risk (ASA 3–5)	271 (24.7)	652 (33.5)	160 (25.9)	
BMI	Normal weight	361 (32.8)	552 (28.4)	193 (31.2)	< 0.001
	Underweight	33 (3.0)	37 (1.9)	13 (2.1)	
	Overweight	443 (40.3)	837 (43.0)	262 (42.4)	
	Obese	241 (21.9)	497 (25.6)	113 (18.3)	
	Missing	21 (1.9)	22 (1.1)	37 (6.0)	
History of IHD/CVA	Missing	1 (0.1)	0 (0.0)	1 (0.2)	0.009
	No	960 (87.4)	1619 (83.2)	542 (87.7)	
	Yes	138 (12.6)	326 (16.8)	75 (12.1)	
History of diabetes mellitus	Missing	1 (0.1)	0 (0.0)	2 (0.3)	0.038
	No	969 (88.2)	1651 (84.9)	533 (86.2)	
	Diabetes: any control	129 (11.7)	294 (15.1)	83 (13.4)	
Smoking history	Non-smoker	893 (81.3)	1669 (85.8)	527 (85.3)	0.017
	Current	200 (18.2)	260 (13.4)	84 (13.6)	
	Missing	6 (0.5)	16 (0.8)	7 (1.1)	
Indication	Benign	335 (30.5)	321 (16.5)	124 (20.1)	< 0.001
	Malignant	764 (69.5)	1624 (83.5)	494 (79.9)	
Anastomosis height	Missing	5 (0.5)	2 (0.1)	0 (0.0)	< 0.001
	Left colon	159 (14.5)	175 (9.0)	76 (12.3)	
	Sigmoid colon	350 (31.8)	394 (20.3)	157 (25.4)	
	High rectum	318 (28.9)	417 (21.4)	134 (21.7)	
	Mid rectum	150 (13.6)	412 (21.2)	124 (20.1)	
	Low rectum	117 (10.6)	545 (28.0)	127 (20.6)	
	APER	0 (0.0)	0 (0.0)	0 (0.0)	
For malignant disease (n = 2888)					
Neoadjuvant therapy	Missing	11 (1.0)	5 (0.3)	4 (0.6)	< 0.001
	Chemotherapy only	29 (2.6)	51 (2.6)	18 (2.9)	
	Long course CRTx	40 (3.6)	298 (15.3)	97 (15.7)	
	Short course radiotherapy	7 (0.6)	75 (3.9)	17 (2.8)	
	None	674 (61.3)	1193 (61.3)	357 (57.8)	
Pre-treatment T stage	Missing	48 (4.4)	31 (1.6)	28 (4.5)	< 0.001
	T1	92 (8.4)	159 (8.2)	62 (10.0)	
	T2	150 (13.6)	432 (22.2)	102 (16.5)	
	T3	359 (32.7)	806 (41.4)	226 (36.6)	
	T4	112 (10.2)	194 (10.0)	75 (12.1)	

P-value derived from χ^2 test for categorical variables. % shown by column. NBP, no bowel preparation; MBP, mechanical bowel preparation only; MBP+ABx, mechanical bowel preparation and oral antibiotics; SD, standard deviation; IQR, interquartile range; IHD, ischemic heart disease; CVA, cerebrovascular accident; N/A, not applicable.

effect, to adjust for hospital-level variation in outcome. Sensitivity analyses were performed for proven anastomotic leakage only. Effect estimates are presented as odds ratios (OR) with 95% confidence intervals (95% CI) and two-tailed *P*-values. An alpha level of 0.05 was used throughout. Data analysis was undertaken using R Studio V3.1.1 (R Foundation, Boston, USA).

Ethical approval

All participating centres were responsible for compliance to local approval requirements for ethics approval or indemnity as required. In the UK, the National Research Ethics Service tool recommended that this project was not classified as research, and the protocol was registered as clinical audit in all participating centres.

Results

Patient and disease characteristics

This analysis included 3676 patients from 343 centres in 47 countries (Figure 1). The mean age of included patients was 66 years (range 18–99 years), 58.4% (2149/3676) were male, and the majority were low preoperative risk (69.5% ASA 1–2, 2558/3676). Resection involved colon only in 35.8% (1317/3676) and the rectum in 64.2% (2359/3676). The primary indication for surgery was malignant disease in 78.7% (2894/3676) and benign disease in 21.3% (782/3676). The abdominal approach was laparoscopic in 56.2% (2065/3676), robotic in 3.9% (144/3676), and a transanal perineal approach was used in 10.0% (369/3676). Pre-operatively, 15.1% (556/3676) of included patients were on enteral and 0.8% (29/3676) on parenteral nutritional supplementation. An intra-abdominal abscess was present preoperatively in 3.0% (111/3676). Few patients were on exogenous steroid therapy at the time of surgery (10/3676). Amongst those with a malignant indication for surgery 21.9% (634/2894) had undergone neoadjuvant therapy, with long-course chemoradiotherapy being most common strategy (437/634, 66.7%). The majority of oncological resections were for T2 and T3 disease (686/2894, 23.7%; 1399/2894, 48.3% respectively).

Practice of bowel preparation and use of preoperative antibiotics

Overall 1099 patients received no bowel preparation (29.9%), 1945 received MBP (52.9%) and 618 (16.8%) received MBP+ABx. Information on type of bowel preparation was not obtained in 14 patients. The patient and disease characteristics of included patients, grouped by choice of preparation strategy, is shown in Table 1. Compared to those received MBP alone, patients undergoing MBP+ABx were older, lower risk, less likely to be obese, and less likely to have a history of cardiovascular disease in comparison to those receiving NBP. When compared to those receiving NBP, those receiving MBP+ABx were less likely to be current smokers and were more likely to have disease involving the low or middle rectum (Figure 2).

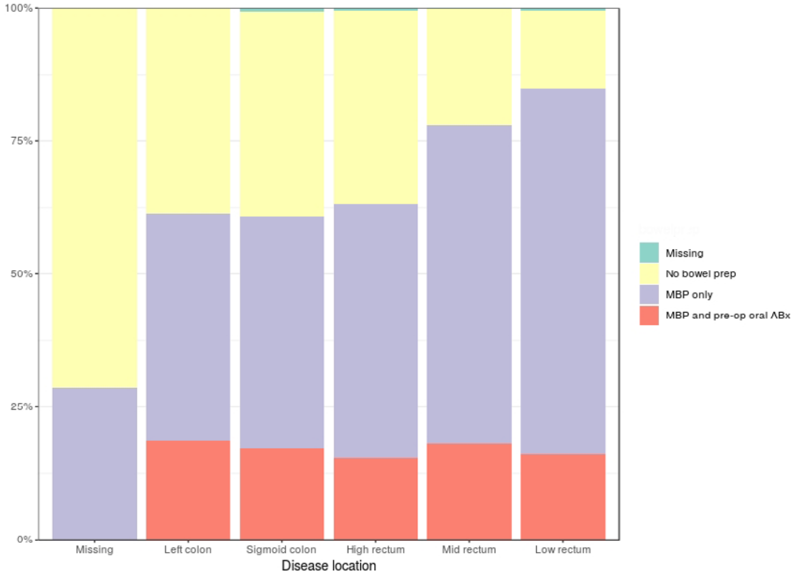

Figure 2 Choice of bowel preparation strategy by height of anastomosis.

Table 2 Patient and disease characteristics of patients who suffered anastomotic leak.

Factor	Levels	Anastomosis		*P*-value
		No leak	Leak	
For all patients (*n* = 3676)				
Total		3364	312	–
Age	< 55	672 (20.0)	68 (21.8)	0.499
	55–70	1480 (44.0)	130 (41.7)	
	70–80	901 (26.8)	86 (27.6)	
	> 80	309 (9.2)	27 (8.7)	
	Missing	2 (0.1)	1 (0.3)	
Gender	Female	1443 (42.9)	84 (26.9)	< 0.001
	Male	1921 (57.1)	228 (73.1)	
ASA class	Low risk (ASA 1–2)	2348 (69.8)	210 (67.3)	0.584
	High risk (ASA 3–5)	988 (29.4)	100 (32.1)	
	Missing	28 (0.8)	2 (0.6)	
BMI	Normal weight	1025 (30.5)	87 (27.9)	0.212
	Underweight	74 (2.2)	9 (2.9)	
	Overweight	1416 (42.1)	128 (41.0)	
	Obese	781 (23.2)	76 (24.4)	
	Missing	68 (2.0)	12 (3.8)	
History of IHD/CVA	No	2874 (85.4)	260 (83.3)	0.073
	Yes	489 (14.5)	51 (16.3)	
	Missing	1 (0.0)	1 (0.3)	
History of diabetes mellitus	No	2898 (86.1)	268 (85.9)	0.303
	Diabetes: any control	464 (13.8)	43 (13.8)	
	Missing	2 (0.1)	1 (0.3)	
Smoking history	Non-smoker	2846 (84.6)	255 (81.7)	0.343
	Current	491 (14.6)	55 (17.6)	
	Missing	27 (0.8)	2 (0.6)	
Indication	Benign	716 (21.3)	66 (21.2)	0.957
	Malignant	2648 (78.7)	246 (78.8)	
Anastomosis height	Left colon	376 (11.2)	34 (10.9)	< 0.001
	Sigmoid colon	842 (25.0)	65 (20.8)	
	High rectum	822 (24.4)	51 (16.3)	
	Mid rectum	635 (18.9)	52 (16.7)	
	Low rectum	683 (20.3)	109 (34.9)	
	Missing	6 (0.2)	1 (0.3)	
For malignant disease (*n* = 2888)				
Total	2643	2643	245	
Neoadjuvant therapy	Chemotherapy only	92 (3.5)	6 (2.4)	0.014
	Long course CRTx	388 (14.7)	49 (20.0)	
	Short course radiotherapy	83 (0.1)	16 (6.5)	
	None	2060 (77.9)	173 (70.6)	
	Missing	20 (0.8)	1 (0.4)	
Pre-treatment T stage	T1	293 (11.1)	20 (8.2)	0.206
	T2	631 (23.9)	55 (22.4)	
	T3	1262 (47.7)	137 (55.9)	
	T4	356 (13.5)	27 (11.0)	
	Missing	101 (3.8)	6 (2.4)	

P-value derived from χ^2 test for categorical variables. % shown by column. SD, standard deviation; IQR, interquartile range; IHD, ischemic heart disease; CVA, cerebrovascular accident; N/A, not applicable.

Table 3 Intraoperative characteristics of patients who suffered anastomotic leak.

Factor	Levels	Anastomosis No leak	Anastomosis Leak	*P*-value
Bowel preparation	NBP	1003 (29.8)	96 (30.8)	0.077
	MBP	1767 (52.5)	178 (57.1)	
	MBP+Abx	580 (17.2)	38 (12.2)	
	Missing	14 (0.4)	0 (0.0)	
Anastomotic configuration	End to end	2525 (75.1)	239 (76.6)	0.364
	Side to side	301 (8.9)	19 (6.1)	
	Side to end	537 (16.0)	54 (17.3)	
	Missing	1 (0.0)	0 (0.0)	
Anastomotic technique	Handsewn	445 (13.2)	54 (17.3)	0.044
	Stapled	2919 (86.8)	258 (82.7)	
Stapler Type	Circular stapler	2734 (81.3)	243 (77.9)	0.224
	Linear stapler	182 (5.4)	15 (4.8)	
	No stapled anastomosis	445 (13.2)	54 (17.3)	
	Missing	3 (0.1)	0 (0.0)	
Leak test performed	No	1184 (35.2)	110 (35.3)	0.689
	Yes	2172 (64.6)	202 (64.7)	
	Missing	8 (0.2)	0 (0.0)	
Defunctioning stoma	Yes	866 (25.7)	116 (37.2)	< 0.001
	No	2496 (74.2)	196 (62.8)	
	Missing	2 (0.1)	0 (0.0)	
Approach	Laparoscopic	1910 (56.8)	155 (49.7)	0.054
	Open	1324 (39.4)	143 (45.8)	
	Robotic	130 (3.9)	14 (4.5)	
	Missing	0 (0.0)	0 (0.0)	
Operator specialty	Colorectal	2733 (81.2)	259 (83.0)	0.662
	General surgery	628 (18.7)	53 (17.0)	
	Missing	3 (0.1)	0 (0.0)	
Operator training grade	Consultant	3097 (92.1)	292 (93.6)	0.573
	Trainee	264 (7.8)	20 (6.4)	
	Missing	3 (0.1)	0 (0.0)	
Critical care admission	None	2449 (72.8)	172 (55.1)	
	Planned from theatre	872 (25.9)	102 (32.7)	
	Unplanned from theatre	20 (0.6)	14 (4.5)	
	Missing	3 (0.1)	0 (0.0)	

P-value derived from Chi2 test for categorical variables. % shown by column. NBP, no bowel preparation; MBP, mechanical bowel preparation only; MBP+ABx, mechanical bowel preparation and oral antibiotics; SD, standard deviation; IQR, interquartile range; IHD, ischemic heart disease; CVA, cerebrovascular accident; N/A, not applicable.

Intraoperative and technical characteristics

Attempted laparoscopy was the most common initial operative approach (56.2%, 2065/3676), with a conversion rate of 15.9% (328/2065). 39.9% (1467/3676) of patients underwent open surgery and 3.9% (144/3676) robotic surgery (of which 16/144, 11.1% underwent conversion). 86.4% (3177/3676) underwent stapled anastomosis, of which 93.7% (2977/3177) used a circular stapler. 13.6% (499/3676) of anastomoses were handsewn.

Anastomotic leak

The overall anastomotic leak rate was 8.5% (312/3676). Patient and disease characteristics (Table 2) and intraoperative and technical characteristics (Table 3) differed between groups of patients who did and did not have anastomotic leak. In the unadjusted analysis, patients with leak were more likely to be male, have undergone a low or middle rectal anastomosis, neoadjuvant therapy, a handsewn anastomosis, a defunctioning ileostomy, or had a planned admission to critical care from theatre.

Outcomes of patients by bowel preparation strategy

In the unadjusted analysis (Table 4), the rate of anastomotic leak was 6.1% (38/618) in those with MBP+ABx, 9.2% (178/1945) in those with MBP and 8.7% (96/1099) in those with NBP. Correspondingly, the major complication rates in those with MBP+Abx was lower than in the other two groups (8.6%; 11.5%; 11.5% respectively). The mean length of stay was significantly higher in those with MBP alone (7.8 days; 8.9 days; 7.8 days respectively, $P < 0.001$).

In the univariate analysis, no significant association was seen between choice of bowel preparation strategy and anastomotic leak (Table 5). Male gender (OR 1.89, 1.37–2.62; $P < 0.001$) and a low rectal anastomosis (OR 2.37, 1.19–5.42; $P = 0.02$) carried an increased risk of anastomotic failure. Side-to-side configuration (OR 0.39, 0.15–0.81; $P = 0.02$), stapled anastomosis (OR 0.65, 0.44–1.01; $P = 0.04$), and not having a defunctioning stoma (OR 0.56, 0.42–0.76; $P < 0.001$) conveyed a statistically significant benefit.

In the multilevel model (Figure 3), MBP+Abx was the only bowel preparation strategy associated with lower risk of anastomotic failure (OR 0.52, 0.30–0.92, $P = 0.02$) than NBP (reference). This association was consistent in a sensitivity analysis for 'proven' anastomotic leak alone (Table 6, OR 0.48, 0.26–0.89, $P = 0.02$). Male gender remained significantly associated with a higher rate of anastomotic leak, and middle age and side-to-side anastomosis a lower rate of anastomotic leak. The model had acceptable discrimination (AUC: 0.69).

Clinical impact of anastomotic leak

Patients with anastomotic leak were five times more likely to die postoperatively than those without (Table 7, 0.5% versus 3.5%, $P < 0.001$). Anastomotic leak was also associated with double the postoperative length of stay (17.2 days versus 7.9 days, $P < 0.001$). The definition of anastomotic leakage chosen as the primary outcome of this study included the presence of an intraperitoneal (abdominal or pelvic) fluid collection on post-operative imaging as well as those leaks 'proven' on radiological or clinical examination. Despite giving a rate nearly double that of the 'proven' leaks alone, the impact on mortality rates and length of stay was remarkably similar when the two groups are compared.

Discussion

This analysis of a large, multicentre prospective audit of elective left colorectal resections demonstrated a benefit for mechanical bowel preparation with oral antibiotics in the reduction of anastomotic failure, which was consistent across sensitivity analyses. The overall rate of usage of this bowel preparation strategy remained low, at less than one-fifth of the international cohort. Anastomotic leak was associated with worse short-term survival, more critical care usage and a prolonged length of stay.

This study adds to a growing body of evidence to support the addition of oral antibiotics to mechanical bowel preparation regimes for left sided colorectal surgery. A comprehensive systematic review published in 2018 described six randomised controlled trials testing MBP+ABx, failing to find a benefit upon meta-analysis [15,16]. However, half of included studies (three of six) were of unclear methodological quality and published more than 20 years ago. Anastomotic outcomes from these studies are unlikely to be comparable to those in a modern era of minimally invasive surgery and modernised stapling devices and thus may lack relevance to current clinical practice. Of the more contemporary randomised studies, all three were single-centre and of

Table 4 Outcomes of patients undergoing different types of bowel preparation strategy.

		Bowel preparation strategy			
Outcome	Levels	NBP	MBP only	MBP+ABx	*P* value
Leak	No leak	1003 (91.3)	1767 (90.8)	580 (93.9)	0.077
	Leak	96 (8.7)	178 (9.2)	38 (6.1)	
Post-operative complication	No major complication	973 (88.5)	1722 (88.5)	565 (91.4)	0.106
	Major complication	126 (11.5)	223 (11.5)	53 (8.6)	
Length of stay	Mean (SD)	7.9 (5.6)	8.9 (5.4)	7.8 (5.1)	< 0.001
Post-operative mortality	No	1091 (99.3)	1935 (99.5)	615 (99.5)	0.862
	Yes	8 (0.7)	10 (0.5)	3 (0.5)	

P-values derived from χ^2 test for categorical variables and Student's *T*-test for parametric continuous variables, % shown by column. NBP, no bowel preparation; MBP, mechanical bowel preparation only; MBP+ABx, mechanical bowel preparation and oral antibiotics.

Table 5 Univariable and multilevel models for overall anastomotic leak (primary outcome measure).

Factor	Levels	Overall anastomotic leak		OR (univariable)	OR (multilevel)
		No leak	Leak		
Bowel preparation	NBP	547 (25.2)	47 (23.9)	*Reference*	*Reference*
	MBP	1260 (58.1)	130 (66.0)	1.20 (0.85–1.72, *P* = 0.303)	0.92 (0.63–1.36, *P* = 0.688)
	MBP+ABx	360 (16.6)	20 (10.2)	0.65 (0.37–1.09, *P* = 0.113)	0.52 (0.30–0.92, *P* = 0.024)
Age	< 55	448 (20.7)	54 (27.4)	*Reference*	*Reference*
	55–70	960 (44.3)	81 (41.1)	0.70 (0.49–1.01, *P* = 0.054)	0.64 (0.43–0.95, *P* = 0.025)
	70–80	589 (27.2)	49 (24.9)	0.69 (0.46–1.04, *P* = 0.073)	0.59 (0.38–0.94, *P* = 0.025)
	> 80	170 (7.8)	13 (6.6)	0.63 (0.32–1.16, *P* = 0.157)	0.61 (0.30–1.22, *P* = 0.159)
Gender	Female	915 (42.2)	55 (27.9)	*Reference*	*Reference*
	Male	1252 (57.8)	142 (72.1)	1.89 (1.37–2.62, *P* < 0.001)	1.91 (1.35–2.69, *P* < 0.001)
ASA class	Low risk (ASA 1–2)	1536 (70.9)	137 (69.5)	*Reference*	*Reference*
	High risk (ASA 3–5)	631 (29.1)	60 (30.5)	1.07 (0.77–1.46, *P* = 0.693)	1.04 (0.71–1.52, *P* = 0.834)
BMI	Normal weight	700 (32.3)	64 (32.5)	*Reference*	*Reference*
	Underweight	41 (1.9)	7 (3.6)	1.87 (0.74–4.09, *P* = 0.146)	1.95 (0.81–4.67, *P* = 0.134)
	Overweight	952 (43.9)	84 (42.6)	0.97 (0.69–1.36, *P* = 0.837)	0.94 (0.66–1.35, *P* = 0.741)
	Obese	474 (21.9)	42 (21.3)	0.97 (0.64–1.45, *P* = 0.880)	0.93 (0.61–1.44, *P* = 0.760)
History of IHD/CVA	No	1858 (85.7)	163 (82.7)	*Reference*	*Reference*
	Yes	309 (14.3)	34 (17.3)	1.25 (0.84–1.83, *P* = 0.253)	1.44 (0.91–2.27, *P* = 0.119)
History of diabetes mellitus	No	1874 (86.5)	170 (86.3)	*Reference*	*Reference*
	Diabetes: any control	293 (13.5)	27 (13.7)	1.02 (0.65–1.53, *P* = 0.942)	0.97 (0.62–1.52, *P* = 0.883)
Smoking history	Non-smoker	1853 (85.5)	159 (80.7)	*Reference*	*Reference*
	Current	314 (14.5)	38 (19.3)	1.41 (0.96–2.03, *P* = 0.071)	1.25 (0.84–1.85, *P* = 0.277)
Indication	Benign	379 (17.5)	34 (17.3)	*Reference*	*Reference*
	Malignant	1788 (82.5)	163 (82.7)	1.02 (0.70–1.52, *P* = 0.935)	0.79 (0.51–1.23, *P* = 0.298)
Approach	Laparoscopic	1171 (54.0)	100 (50.8)	*Reference*	*Reference*
	Open	895 (41.3)	87 (44.2)	1.14 (0.84–1.54, *P* = 0.398)	1.16 (0.84–1.61, *P* = 0.369)
	Robotic	101 (4.7)	10 (5.1)	1.16 (0.55–2.19, *P* = 0.670)	0.86 (0.42–1.77, *P* = 0.680)
Anastomosis height	Left colon	126 (5.8)	8 (4.1)	*Reference*	*Reference*
	Sigmoid colon	373 (17.2)	24 (12.2)	1.01 (0.46–2.46, *P* = 0.975)	0.91 (0.38–2.17, *P* = 0.836)
	High rectum	501 (23.1)	32 (16.2)	1.01 (0.47–2.39, *P* = 0.988)	0.91 (0.39–2.13, *P* = 0.827)
	Mid rectum	543 (25.1)	39 (19.8)	1.13 (0.54–2.66, *P* = 0.758)	1.07 (0.45–2.52, *P* = 0.882)
	Low rectum	624 (28.8)	94 (47.7)	2.37 (1.19–5.42, *P* = 0.023)	2.14 (0.91–5.03, *P* = 0.081)
Anastomotic configuration	End to end	1594 (73.6)	150 (76.1)	*Reference*	*Reference*
	Side to side	165 (7.6)	6 (3.0)	0.39 (0.15–0.81, *P* = 0.025)	0.38 (0.15–0.94, *P* = 0.036)
	Side to end	408 (18.8)	41 (20.8)	1.07 (0.74–1.52, *P* = 0.722)	0.96 (0.65–1.42, *P* = 0.840)
Anastomotic technique	Handsewn	219 (10.1)	29 (14.7)	*Reference*	*Reference*
	Stapled	1948 (89.9)	168 (85.3)	0.65 (0.44–1.01, *P* = 0.044)	0.72 (0.44–1.18, *P* = 0.197)
Leak test performed	No	733 (33.8)	73 (37.1)	*Reference*	*Reference*
	Yes	1434 (66.2)	124 (62.9)	0.87 (0.64–1.18, *P* = 0.360)	1.04 (0.72–1.51, *P* = 0.832)
Defunctioning stoma	No	1410 (65.1)	101 (51.3)	0.56 (0.42–0.76, *P* < 0.001)	0.96 (0.64–1.44, *P* = 0.841)
	Yes	757 (34.9)	96 (48.7)	*Reference*	*Reference*
Operator type	Colorectal	1745 (80.5)	161 (81.7)	*Reference*	*Reference*
	General surgery	422 (19.5)	36 (18.3)	0.92 (0.63–1.33, *P* = 0.683)	1.03 (0.68–1.56, *P* = 0.886)
Training grade	Consultant	2016 (93.0)	185 (93.9)	*Reference*	*Reference*
	Trainee	151 (7.0)	12 (6.1)	0.87 (0.45–1.52, *P* = 0.642)	1.05 (0.55–1.98, *P* = 0.889)
AIC: 1340.3. Area Under the Receiver Operating Curve: 0.69					

Overall anastomotic leak was pre-defined as either (i) gross anastomotic leakage proven radiologically or clinically, or (ii) the presence of an intraperitoneal (abdominal or pelvic) fluid collection on post-operative imaging. Odds ratio (OR) presented with 95% confidence intervals. % shown by column. SD, standard deviation; IQR, interquartile range; IHD, ischemic heart disease; CVA, cerebrovascular accident; N/A, not applicable.

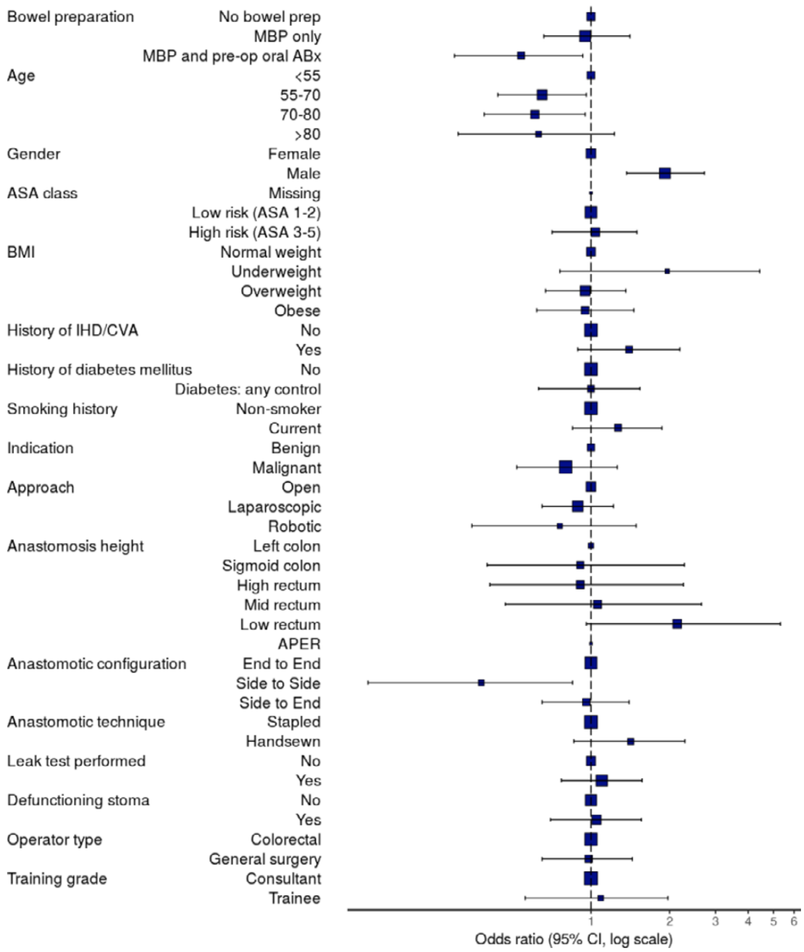

Figure 3 Forest plot for mixed-effects model demonstrating factors associated with overall anastomotic leak.

Table 6 Univariable and multilevel models for 'proven' anastomotic leak only (sensitivity analysis).

		Proven anastomotic leak			
Factor	Levels	No leak	Leak	OR (univariable)	OR (multilevel)
Bowel preparation	NBP	554 (25.2)	40 (24.1)	*Reference*	*Reference*
	MBP	1279 (58.2)	111 (66.9)	1.20 (0.83–1.77, P = 0.336)	0.94 (0.63–1.42, P = 0.780)
	MBP+ABx	365 (16.6)	15 (9.0)	0.57 (0.30–1.02, P = 0.069)	0.48 (0.26–0.89, P = 0.021)

Proven anastomotic leak was defined as gross anastomotic leakage proven radiologically or clinically. Patient, disease and operative factors included in the model are described in Table 5.

limited methodological rigor [17–19]. The highest quality of these included just 579 patients, was open-label, and examined anastomotic leak as a secondary outcome with no clear outcome definition or assessment criteria stated.

The most convincing current evidence supporting MBP+Abx is found in retrospective analyses of the large American College of Surgeons' National Surgical Quality Improvement Program (ACS-NSQUIP) database. Seven analyses of this dataset have been published to date, including around 147 000 patients [6–11,20]. These share common criticisms including the low fidelity of retrospectively collected clerical data, high percentages of missing data fields and a high propensity for selection and reporting bias [6–10]. When meta-analysis has been performed on these observational datasets a 40% reduction in odds of anastomotic leak has been described [16].

Table 7 The clinical impact of anastomotic leak.

	Total	Length of stay (median, IQR)	30-day mortality (%, *n*)
No leak	3364	7 (5–9)	0.5% (18)
Anastomotic leak and/or collection*	312	15 (11–26)	3.5% (11)
'Proven' anastomotic leak only	166	16 (11–26)	3.6% (6)

*Primary outcome for this study – defined as either or both (i) gross anastomotic leakage proven radiologically or clinically or (ii) the presence of an intraperitoneal (abdominal or pelvic) fluid collection on post-operative imaging. Proven anastomotic leak included only gross anastomotic leakage proven radiologically or clinically. % shown by row. SD, standard deviation; *n*, count.

This analysis represents the first prospective observational assessment of the relationship of MBP+ABx and anastomotic leak, demonstrating a significant benefit in elective left sided colorectal anastomoses, which prevailed after risk adjustment for patient, operation and disease factors. Few other modifiable intraoperative or technical characteristics had a significant association with anastomotic leak in univariate or multilevel models. Side-to-side anastomotic configuration (common in left sided colonic, rather than rectal resections) appeared to convey a benefit in multivariable analysis, which may reflect other unmeasured confounders, such as technical ease of the procedure and the number of stapler firings in circular stapled rectal anastomoses. Whilst this study was underpowered to detect a difference in the primary outcome within many of these smaller subgroups, variation within our data suggests that an optimal technique for left sided colorectal anastomosis is yet to reach consensus. Whilst a number of acceptable modifications are likely to exist, standardisation of techniques for anastomotic formation may improve outcomes by reducing unacceptable variation.

The ESCP Left Sided Colorectal Resections 2017 audit used the same combined outcome measure of radiologically or clinically 'proven' anastomotic leak or intraabdominal collection that has been previous described in the ESCP 2015 audit of Right Sided Resections [21]. Again the data demonstrated an increase in adverse postoperative events (death, length of stay, critical care requirement) of similar magnitude for both the combined and 'proven' anastomotic leak groups, validating the use of our primary outcome measure in left sided disease. We recommend that this combined outcome measure is used in future prospective randomised and non-randomised studies.

This study presents a multicentre evaluation of bowel preparation practice and its outcomes using a validated 'snap-shot' methodology that combines pragmatism with high-quality, protocolised data collection performed by frontline teams of clinicians in a multicentre, international setting [22–28]. Randomised trials are sometimes criticised for being performed in highly controlled settings (i.e. explanatory trials), and treatment effects described are not realised when adopted into widespread clinical practice. This study adds to the literature by demonstrating that a signal for benefit in combined oral antibiotics and bowel preparation is also seen in a 'real world' setting. We attempted to minimise the impact of selection bias on our findings by the application of mixed-effects models adjusting for the effects of patient, disease, operative and centre level variation. However we lack the fidelity in this dataset to examine in detail specific centre level characteristics regarding those centres applying MBP+ABx in routine practice (for example surgical resection volume, availability of adjuncts to testing anastomotic integrity). There are also likely to be a number of unmeasured patient and intraoperative risk factors for anastomotic leak that we were unable to adjust for with this observational study.

A large, international randomised trial is needed to determine whether antibiotics alone are sufficient, or whether it is the combination with mechanical bowel preparation that is mechanistic. Although the current evidence base has been stated as being conclusive, incomplete penetration into clinical practice as demonstrated within this study and the relatively weak existing data mean a major trial is warranted. Further efforts to explore reasons for the low rate of adoption of combined antibiotics and bowel preparation amongst the international surgical community will support future quality improvement efforts.

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Conflicts of interest

None to declare.

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