

Oral antibiotic preparation in colorectal surgery: Is there more to debate?

Running Title – Oral antibiotic preparation in colorectal surgery

Katie E Rollins, MRCS¹, Dileep N Lobo, MS, DM, FRCS, FACS, FRCPE^{1,2}

¹Gastrointestinal Surgery, Nottingham Digestive Diseases Centre, National Institute of Health Research (NIHR) Nottingham Biomedical Research Centre, Nottingham University Hospitals and University of Nottingham, Queen's Medical Centre, Nottingham NG7 2UH, UK

²MRC/ARUK Centre for Musculoskeletal Ageing Research, School of Life Sciences, University of Nottingham, Queen's Medical Centre, Nottingham, NG7 2UH, UK

Corresponding Author & Request for Reprints:

Professor D. N. Lobo
Nottingham Digestive Diseases Centre
Nottingham University Hospitals NHS Trust,
Queen's Medical Centre
Nottingham NG7 2UH
UK
Tel: +44-115-8231149
Fax: +44-115-8231160
E-mail: dileep.lobo@nottingham.ac.uk

Word Count (excluding title page and references): 1029

Conflict of interest: The authors do not have a direct conflict of interest to declare.

Within the last three years, DNL has unrestricted received research funding from BBraun and speakers' honoraria from BBraun and Baxter Healthcare for unrelated work.

Funding: No external funding

Key words: oral antibiotics; bowel preparation; colorectal; surgery

The use of non-absorbable oral antibiotic preparation (OAB) in colorectal surgery was first proposed by Rosenberg and colleagues in 1971 (1), who in their randomised controlled trial (RCT) of combined mechanical bowel preparation (MBP) and one (phthalylsulphathiazole) or two oral antibiotics (phthalylsulphathiazole and neomycin) found a significant reduction in surgical site infection and anastomotic leak rates in a population of patients undergoing large bowel surgery after combined OAB and MBP when compared with those who received MBP alone. This was followed by studies (2,3) which demonstrated similar reductions in the incidence of postoperative infection. However, the preparation protocols typically required large volumes, prolonged preoperative hospital stays and carried a significant risk of electrolyte disturbance and dehydration. These issues resulted in combined preparation falling from favour, with MBP alone becoming an increasingly popular strategy. Relatively recent evidence from RCTs and meta-analyses (4,5) has suggested that MBP alone does not convey any benefit in patients undergoing colorectal surgery and, hence, it is no longer recommended as part of perioperative care protocols.

In recent years there has been a significant revival of interest in OAB (6) as it has been shown to reduce complications after colorectal surgery, with a decrease in surgical site infection (SSI) being the most common benefit (7). Much of the recent literature has been driven by large cohort studies (8-11), many of which have originated from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database. Meta-analyses (12,13) have been published recently with the aim of analysing the potential benefits of OAB more systematically, either with or without MBP, and have demonstrated significant

reductions in the incidence of SSI and anastomotic leaks with a combination of OAB and MBP, when both RCTs and cohort studies were considered. The use of OAB prior to elective colorectal surgery is currently very much a topic in evolution, with significant debate in the literature whether the combination of MBP and OAB is superior to OAB alone (14,15).

The most recent publication to arise from the ACS NSQIP database (16) focuses on a cohort of 5729 patients undergoing elective left-sided laparoscopic and open restorative colorectal surgery with or without faecal diversion and uses primary outcome measures of overall, superficial, deep and organ/space SSI. The authors found that combined MBP and OAB was associated with a significant reduction in the incidence of overall SSI when compared with no preparation (OR 0.46, 95% CI 0.36 to 0.59, $p < 0.0001$), with this combination remaining a predictor of the incidence of SSI on multivariate modelling. The OAB alone group had a trend towards a reduction in SSI, but this was not statistically significant (univariate OR 0.84, 95% CI 0.51 to 1.38, $p = 0.49$). The combination of MBP and OAB was associated with a reduction in SSI in patients undergoing both laparoscopic and open surgery. However, on multivariate analysis, this significance was lost for patients undergoing laparoscopic resection (adjusted OR 0.44, 95% CI 0.19 to 1.04, $p = 0.062$). Combined MBP and OAB also had a negative association with anastomotic leak rates, but there was no association between OAB alone and leak rates. Finally, the administration of MBP and OAB or OAB alone was not associated with any significant difference in *Clostridium difficile* infection rates when compared with no preparation (1.2% vs. 1.0% vs. 1.3%). This is in concordance with previous publications which have not reported an increased risk of *C. difficile* infection rates (12, 17).

This study (16) provides additional information surrounding the beneficial effects of combined MBP and OAB in left-sided restorative colectomy with pelvic anastomosis with or without faecal diversion and was able, through careful uni- and multi-variate analysis, analyze the factors associated with SSI and anastomotic leak rates. It also provides more detailed information than many previous studies regarding the impact of these bowel preparation regimens in open compared with laparoscopic surgery. It represents another of a multitude of studies originating from the ACS NSQIP database, many of which have been likely to have presented data and conclusions based upon the same patient populations. However, whereas many of the previous publications have focused upon 2012-2014 (12), this study is based on data from 2015 and is, therefore, less likely to be subject to duplication of participants than previous studies originating from the same database.

As with other retrospective database studies on the subject, the proportion of patients receiving OAB alone was low, representing just 3.5% of the overall cohort (16). This makes interpretation of any conclusions based on OAB alone difficult. There were also several potentially significant sources of bias in the baseline patient populations, including an increased prevalence of medical comorbidities in those participants in the no preparation and MBP alone group, as measured by the American Society of Anesthesiology class, and this may have impacted upon the incidence of postoperative complications. In addition, there was a greater proportion of patients with diabetes in the no preparation group compared with other groups, which again is likely to have exerted a significant selection bias and resulted in an increased incidence of surgical infection in this group which may not be wholly explained by the lack of preparation. Moreover, the benefit of OAB with or without

MBP in patients undergoing laparoscopic surgery is not proven when compared with those undergoing open surgery both in the cohort study being discussed (16) and a recent meta-analysis (12).

As has been identified by the authors (16), a definitive large four-arm RCT seems necessary to more definitively answer the question regarding the best method for preparation of the colon prior to elective colorectal surgery. Participants should be stratified according to whether they have open or laparoscopic surgery and then randomised to a) no bowel preparation, b) MBP, c) OAB and d) OAB + MBP.

Several recent survey-based studies have documented low rates of routine prescription of OAB, either alone or when combined with MBP, particularly in the UK and Europe (18,19), suggesting that despite the ongoing publication of studies supporting the role of MBP and OAB prior to elective colorectal surgery, this is yet to have an impact upon clinical practice. Definitive evidence from a large scale, well designed and conducted RCT may be necessary before this becomes routine clinical practice.

References

1. Rosenberg IL, Graham NG, De Dombal FT, Goligher JC. Preparation of the intestine in patients undergoing major large-bowel surgery, mainly for neoplasms of the colon and rectum. *Br J Surg* 1971;58:266-9. PMID: 5108232.
2. Washington JA, 2nd, Dearing WH, Judd ES, Elveback LR. Effect of preoperative antibiotic regimen on development of infection after intestinal surgery: Prospective, randomized, double-blind study. *Ann Surg* 1974;180:567-72. PMID: 4606495.
3. Nichols RL, Condon RE, DiSanto AR. Preoperative bowel preparation. Erythromycin base serum and fecal levels following oral administration. *Arch Surg* 1977;112:1493-6. PMID: 931637.
4. Rollins KE, Javanmard-Emamghissi H, Lobo DN. Impact of mechanical bowel preparation in elective colorectal surgery: A meta-analysis. *World J Gastroenterol* 2018;24:519-36. PMID: 29398873. doi: <https://dx.doi.org/10.3748/wjg.v24.i4.519>.
5. Cao F, Li J, Li F. Mechanical bowel preparation for elective colorectal surgery: updated systematic review and meta-analysis. *Int J Colorectal Dis* 2012; 27:803-10. PMID: 22108902. doi: <https://dx.doi.org/10.1007/s00384-011-1361-y>.
6. Cirocco WC. The fatal flaw of outcome studies comparing colorectal operations with and without mechanical bowel preparation: The absence of oral antibiotics! *Dis Colon Rectum* 2016;59(8):e421. PMID: 27384100. doi: <https://dx.doi.org/10.1097/DCR.0000000000000645>.
7. McSorley ST, Steele CW, McMahon AJ. Meta-analysis of oral antibiotics, in combination with preoperative intravenous antibiotics and mechanical bowel preparation the day before surgery, compared with intravenous antibiotics and mechanical bowel preparation alone to reduce surgical site infections in elective colorectal surgery. *BJS Open* 2018;2:185-94. PMID: 30079387. doi: <https://dx.doi.org/10.1002/bjs5.68>.
8. Scarborough JE, Mantyh CR, Sun Z, Migaly J. Combined mechanical and oral antibiotic bowel preparation reduces incisional surgical site infection and anastomotic leak rates after elective colorectal resection: An analysis of colectomy-targeted ACS NSQIP. *Ann Surg* 2015;262:331-7. PMID: 26083870. doi: <https://dx.doi.org/10.1097/sla.0000000000001041>.
9. Kiran RP, Murray AC, Chiuzan C, Estrada D, Forde K. Combined preoperative mechanical bowel preparation with oral antibiotics significantly reduces surgical site infection, anastomotic leak, and ileus after colorectal surgery. *Ann Surg* 2015;262:416-25; discussion 423-5. PMID: 26258310. doi: <https://dx.doi.org/10.1097/sla.0000000000001416>.
10. Ohman KA, Wan L, Guthrie T, Johnston B, Leinicke JA, Glasgow SC, et al. Combination of oral antibiotics and mechanical bowel preparation reduces surgical site infection in colorectal surgery. *J Am Coll Surg* 2017;225:465-71. PMID: 28690206. doi: <https://dx.doi.org/10.1016/j.jamcollsurg.2017.06.011>.
11. Althumairi AA, Canner JK, Pawlik TM, Schneider E, Nagarajan N, Safar B, et al. Benefits of bowel preparation beyond surgical site infection: A retrospective study. *Ann Surg* 2016;264:1051-57. PMID: 26727098. doi: <https://dx.doi.org/10.1097/sla.0000000000001576>.

12. Rollins KE, Javanmard-Emamghissi H, Acheson AG, Lobo DN. The role of oral antibiotic preparation in elective colorectal surgery: A meta-analysis. *Ann Surg* 2018 [Epub ahead of print]. PMID: 30570543. doi: <https://dx.doi.org/10.1097/SLA.0000000000003145>.
13. Chen M, Song X, Chen LZ, Lin ZD, Zhang XL. Comparing mechanical bowel preparation with both oral and systemic antibiotics versus mechanical bowel preparation and systemic antibiotics alone for the prevention of surgical site infection after elective colorectal surgery: A meta-analysis of randomized controlled clinical trials. *Dis Colon Rectum* 2016;59:70-8. PMID: 26651115. doi: <https://dx.doi.org/10.1097/DCR.0000000000000524>.
14. Klinger AL, Green H, Monlezun DJ, Beck D, Kann B, Vargas HD, et al. The role of bowel preparation in colorectal surgery: Results of the 2012-2015 ACS-NSQIP data. *Ann Surg* 2017 [Epub ahead of print]. PMID: 29064902. doi: <https://dx.doi.org/10.1097/sla.0000000000002568>.
15. Garfinkle R, Abou-Khalil J, Morin N, et al. Is there a role for oral antibiotic preparation alone before colorectal surgery? ACS-NSQIP analysis by coarsened exact matching. *Dis Colon Rectum* 2017;60:729-37. PMID: 28594723. doi: <https://dx.doi.org/10.1097/dcr.0000000000000851>.
16. Toh JWT, Phan K, Ctercteko G, Pathma-Nathan N, El-Khoury T, Richardson A, et al. The role of mechanical bowel preparation and oral antibiotics for left-sided laparoscopic and open elective restorative colorectal surgery with and without faecal diversion. *Int J Colorectal Dis* 2018;33:1781-91. PMID: 30238356. doi: <https://dx.doi.org/10.1007/s00384-018-3166-8>.
17. Al-Mazrou AM, Hyde LZ, Suradkak K, Kiran RP. Effect of inclusion of oral antibiotics with mechanical bowel preparation on the risk of *Clostridium difficile* infection after colectomy. *J Gastrointest Surg* 2018;22:1968-75. PMID: 29967968. doi: <https://dx.doi.org/10.1007/s11605-018-3837-3>.
18. Devane LA, Proud D, O'Connell PR, Panis Y. A European survey of bowel preparation in colorectal surgery. *Colorectal Dis* 2017;19(11): O402-O406. PMID: 28975694. doi: <https://dx.doi.org/10.1111/codi.13905>.
19. Battersby CLF, Battersby NJ, Slade DAJ, Soop M, Walsh CJ. Preoperative mechanical and oral antibiotic bowel preparation to reduce infectious complications of colorectal surgery – the need for updated guidelines. *J Hosp Infect* 2018 [Epub ahead of print]. PMID: 30579970. doi: <https://dx.doi.org/10.1016/j.jhin.2018.12.010>.