Abstract

Surgical site infection (SSI) is a major cause of morbidity following elective colorectal resection worldwide. Reduction in SSI rates can be achieved with the use of SSI reduction bundles. Debate about the role of mechanical bowel preparation and oral antibiotics (MOAB) in reducing SSI has persisted over decades with considerable variation in international practice. This article summarises the arguments for and against the routine use of MOAB in the elective setting, highlighting the areas of controversy and evidence gaps and provides pragmatic suggestions for colorectal practice.

What does this paper add to the literature?

This paper summaries the arguments for and against the routine use of MOAB in routine colorectal practice. It highlights the areas where evidence is lacking but awaited, and possible areas of concern if adopted widely. It provides a suggested pragmatic outline for its use in contemporary elective practice.

The use of oral antibiotics and mechanical bowel preparation in elective colorectal resection for the reduction of surgical site infection

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Surgical site infection (SSI) following elective colorectal resection continues to be a major source of morbidity affecting up to 20% of patients [1-3]. Reducing SSI requires a multi-faceted approach [4] and can be achieved by the use of SSI reduction bundles [5]. Such bundles include prophylactic intravenous antibiotics [6] which represent an undisputed standard of care [4]. They do not include the use of mechanical bowel preparation (MBP) alone which is not recommended in elective colonic resection to reduce SSI [7-9], although may offer an advantage in elective rectal resection [10].

A long-standing area of controversy is the use of mechanical and oral antibiotic bowel preparation (MOAB) prior to elective colorectal resection [11, 12]. Marked differences exist between clinicians worldwide [13]. Recent guidelines from the American Society of Colon and Rectal Surgeons strongly recommend the use of MOAB in elective colorectal resection to reduce SSI [14, 15]. Other international bodies have recognised the increasing body of evidence and altered their recommendations in a more conservative manner but stop short of endorsing this practice because of the lack of level 1 evidence [16]. This paper summarises the arguments for and against the use of MOAB in elective colorectal resection, highlighting the controversies surrounding this issue (Figure 1).

Arguments supporting the use of MOAB

The combination of MOAB in elective colorectal resection is associated with lower rates of SSI. Numerous reports from the North American Surgical Quality Improvement programmes (NSQIP) show improved clinical outcomes after varying versions of preoperative MOAB [17-31]. These observational studies include many thousands of patients undergoing elective surgery and show that the combination of MOAB in comparison to MBP alone is associated with a reduction in SSI of about 50%. Similar reductions are seen in numerous randomised controlled trials (RCTs) [32-37], observational studies [13] and meta-analyses; both in meta-analyses of RCTs alone [2, 38-40] and in those analysing both RCTs and observational studies [41, 42].

There seem to be additional patient benefits in using MOAB. Over the last decade, accumulating reports have highlighted reductions in anastomotic leak (AL), ileus, readmission rates, re-operation rates and even mortality. However, these findings are not consistent across all studies. Positive effects of MOAB have been seen in multiple retrospective studies [13, 18, 19, 21-31, 43]. The beneficial effects may be more evident in left-sided colonic resections or rectal resections [22, 29, 44]. Several underpowered RCTs however have shown no difference in AL rates [36, 45]. Meta-analyses vary in their conclusions regarding the additional benefits of MOAB. No differences in AL rates were seen in a meta-analysis including 16 RCTs published between 1979 and 2007 [38] nor in a recent network meta-analysis including 8458 patients in 38 RCTs; whereas significant multiple additional benefits were reported in 2 large recent meta-analyses, although these effects were less evident when OAB were considered alone [41, 42]. Developing evidence implicating intraluminal bacteria in the pathogenesis of AL and reduction in AL with locally administered antibiotics and selective gut decontamination regimes [46] may go part way to explaining the reduction in AL seen with MOAB.

The consequences of infectious complications, such as SSI and AL, may persist for years and are associated with a reduction in Quality of Life (QoL) years after the initial surgery [47]. There is

extensive evidence to show that SSI is a risk factor for the development of incisional hernia [48-50] which is a common, complex and costly complication of colorectal surgery associated with considerable morbidity. Septic complications increase the permanent stoma rate and in rectal resections supposedly temporary diverting ileostomies are not reversed in more than a third of cases [51], almost always due to a septic anastomotic complication. There is also evidence to support increased risk of local and distant cancer recurrence and reduced survival following anastomotic leak [52-56].

Reducing these complications by using MOAB is therefore a very attractive proposition yet possible widespread reintroduction of this policy has raised concerns that the incidence of Clostridium Difficile related infections (CDI) may rise. A large body of evidence refutes this concern. Only two published studies show an increase in CDI rates [57] or readmissions due to CDI [18], whereas two retrospective studies show a beneficial effect. Kim et al [19] showed that patients having MOAB had a lower CDI rate than those with no bowel preparation (0.5% vs 1.8%, p=0.01) while Al-Mazrou [58] showed a similar reduction with OAB alone. The majority of studies show no differences in CDI rates in patients exposed to OAB. This holds true for retrospective studies [30, 31, 59-61], RCTs [33-37, 45] and in meta-analysis [42]. There is no evidence of harm in terms of increase in CDI rates by using MOAB.

Arguments against the use of MOAB

There is still a lack of high quality supporting level 1 evidence, coupled with concerns around antimicrobial stewardship, choice of antibiotics, negative patient experience and the unknown, little understood, short, medium and long-term consequences on the microbiome and what this may mean for other oncological outcomes.

The majority of the evidence showing benefit from MOAB is from big datasets, such as NSQIP and the European Society of Coloproctology (ESCP) snapshot audit [62]. The North American registry data has influenced the American guidelines strongly where it is summarised as Level 1b (strong recommendation; moderate-quality evidence) [15]. This recommendation arises from the inclusion of 'exceptionally strong evidence from observational studies'. However, these data have been criticised [11] for use of multiple retrospective reports using the same overlapping data sets and heterogeneity between groups. In many reports, the groups that receive MOAB tend to be younger, fitter, with fewer co-morbidities, lower corticosteroid use and earlier stage disease which may contribute to their lower SSI rates. Despite the large numbers in these datasets, this evidence may not be robust.

Irrespective of data quality, arguments against the routine introduction of MOAB prior to elective bowel resection centre around the fact that SSI reduction bundles alone can achieve low rates of SSI without necessarily including MOAB. In addition, it is also questioned whether OAB alone are enough to reduce SSI.

Evidence based care bundles focused on reducing SSI rates have been successfully implemented in many institutions over the last ten years. In the UK, SSI bundles have been created based on guidelines from the National Institute for Health and Care Excellence, the World Health Organisation and Health Protection Scotland with additional components added from the published literature [4, 63, 64]. In the United States, similar national guidelines have been formulated by the American College of Surgeons and the Centers for Disease Control and Prevention [65, 66]. Application of SSI care bundles form a recommended component of enhanced recovery guidelines [14].
The content of SSI care bundles varies but will contain common and variable components. Common shared components include prophylactic intravenous antibiotics, preoperative bathing, hair removal and maintenance of normoglycaemia and normothermia. Less uniformly used interventions include smoking cessation, MRSA screening, 2% alcoholic chlorhexidine skin preparation, wound protectors, antibiotic impregnated sutures, change of gloves and instruments prior to skin closure, novel wound closure devices and MOAB. Compliance to care bundles can be challenging and resource intensive [67] and requires continual audit and real-time feedback to alter practice [68].

Financial incentives and penalties in North America surrounding potentially preventable SSIs have resulted in significant reductions in SSI in major institutions showing that this can be achieved in practice and sustained over time [69, 70].

Implementation of SSI care bundles has been shown to reduce SSI rates by up to 40% [68, 69, 71-74]. The majority of the published studies are cohort studies. However, 2 RCTs have been carried out [75, 76].   Despite clear heterogeneity between these studies two meta-analyses have also demonstrated effectiveness of SSI care bundles [5, 77]. The results clearly show that SSI bundles are effective in reducing SSI rates irrespective of whether MOAB form part of the bundle. Individual institutions can achieve rates of SSI with implementation of SSI reduction bundles as low as 1.8% [78]. However, arguably it is more important to define which of the components of SSI bundles contribute the most to the effectiveness of the intervention. A recent meta-analysis [77] attempted to address this through sub-group analysis and identified MOAB, a separate sterile instrument closure tray and glove change prior to closure as providing 'significantly greater SSI risk reduction'. Interestingly, the one study in this meta-analysis that failed to show effectiveness of bundle implementation was a well-designed RCT which omitted MOAB from the experimental arm of the trial. These studies presented also suffer from differences in compliance levels and how SSI rates were calculated as well as publication bias. Cumulatively, SSI bundles are evidently effective and should be standard of care [79].

It has been assumed that MBP is a requirement in order for OAB to be effective. The administration of MBP prior to elective colectomy is considered unpleasant by many patients, but few studies have taken patient satisfaction into consideration. Taking bowel preparation, often for the second time in a few weeks, may add considerably to the anxiety and distress experienced by the patient before major elective colorectal surgery. The available bowel cleansing agents are often poorly tolerated, time consuming and have unpleasant side-effect profiles, resulting in reduced compliance and poor bowel preparation [80]. Preparations containing polyethylene glycols (PEG) are diluted in large volumes of water (up to 4 litres) and have an unpalatable taste [81]. Elderly patients, in particular, find it hard to drink the large volumes of fluid required [82]. Sodium phosphate preparations are better tolerated due to the smaller volume of liquid (300ml water) and palatability [83] but are associated with safety concerns such as major fluid and electrolyte shifts and so should be avoided in patients with chronic kidney disease, congestive cardiac failure, cirrhosis or in patients with electrolyte disturbances [81]. Difficulties in administering MBP may also be anticipated in other patient groups including patients with poor reading skills, immobility or frailty or patients taking multiple medications.

Patient concerns about taking MBP underline the need to question whether SSI reduction may be brought about by OAB alone? The need for an RCT to determine this has long been discussed [17, 84, 85], because data on OAB alone are contradictory. Different reports show that the use of OAB alone is worse than [24, 25, 27, 29-31, 43, 86], equivalent to [22, 26, 28, 42, 87] or better than [17, 20, 32] the MOAB combination in reduction of SSI. The problems are a lack of RCTs that focus on OAB alone in the absence of MBP, small numbers in the OAB alone groups and selection bias in the cohort studies. In the largest and most recent meta-analysis [42], SSI rates were compared between patients having MOAB and OAB alone. Four studies were included in this analysis, 2 RCTs (n=709) and 2 cohort studies (n=22774), with no difference in the incidence of SSI between these groups overall or when the RCTs and cohort studies were considered separately. So, the use of OAB alone does seem to reduce SSI by at least an equivalent level to MOAB. This is reinforced by a further comparison considering OAB alone versus no preparation in 2 cohort studies including 16,390 patients with SSI reduced in the OAB group (RR 0.56. 95% CI 0.38-0.83, P=0.004). In the Netherlands, a cohort study assessing OAB alone as standard of care over time was able to demonstrate a 6.2% reduction in deep SSI and/or mortality, which equated to a 42% risk reduction [88]. The authors question the benefit of MBP in addition to OAB and are running the PreCaution study to assess whether use of OAB alone is sufficient [89].

There is little level 1 evidence for OAB alone, so should we wait to change practice until ongoing RCTs report? The first level 1 evidence including a no bowel preparation arm is the report of the MOBILE study [45]. Patients undergoing colonic, but not rectal, surgery were randomised 1:1 to MOAB or no bowel preparation. Of the 417 patients randomised, there was no difference in the

primary endpoint of SSI at 30 days postoperatively (7% vs 11%, odds ratio 1.65 (95% CI 0.80-3.40, p=0.17). In the MOBILE study, low SSI rates may have been due to a high proportion of laparoscopic resections, high case exclusion rate, and more than 50% of resections being right-sided, with the suggestion that the low SSI rates may have meant it was underpowered [90, 91]. However, this study does not address the issue of whether OAB alone reduce SSI. This is being examined in several large, well-powered, ongoing RCTs. The PreCaution [89], COMBINE [92] and SELDDEC trials include both colon and rectal resections, the REaCT-NSQIP and COLONPREP trials examine colonic resection alone. These large trials will provide further evidence about the role of OAB alone. However, the inclusion of both colon and rectal resections together introduces heterogeneity and possible difficulty with interpretation as OAB alone may be preferred in colonic surgery and MOAB in rectal surgery [93]. However, the use of MOAB in rectal surgery will be addressed by the PREPACOL2 study. There is also a concern that these trials will end up being underpowered as they assume SSI rates in the control arms in the region of 15% and aim to show a 40-50% reduction in primary outcome with the intervention. As SSI rates fall more widely, due to better awareness and control of SSI risk factors, the statistical assumptions on which the power calculations are based will be challenged. The relative benefit on SSI of MOAB or OAB alone, if proven, may only be small within the context of well-implemented SSI reduction bundles.

The choice of antibiotics to be employed for MOAB or OAB prophylaxis is unclear. Huge numbers of antibiotics and antibiotic combinations have been employed in clinical trials. The Cochrane review of antimicrobial prophylaxis in colorectal surgery identified 68 different antibiotics in the 260 trials included. The use of multiple different drugs, regimes, and site of application, including intraluminal [94], make it impossible to conclude if any regime is better or worse than any other. It does, though, appear clear that combination aerobic and anaerobic cover is important. Concerns about excessive and widespread use of antibiotics leading to antibiotic resistance have led to programmes such as 'Start Smart and then Focus' within the UK [95]. Despite guidelines, national surveys show that adherence to surgical prophylaxis is poor, both in timing and duration [96].

As well as concerns for antibiotic stewardship, the widespread reintroduction of MOAB or OAB alone in elective colorectal surgery may have unintended consequences on the human microbiome, although this may be offset by a subsequent reduction in the use of broad spectrum antibiotic courses to treat SSI. The human large bowel microbiota comprises a consortium of many hundreds of bacterial species that carry out an array of enzymatic reactions, many distinct but essential to human genome encoded activities. In essence therefore, humans possess an 'extended genome' of hundreds of millions of microbial genes located in the intestine, known as 'the microbiome' [97]. The microbiome is highly individualized and niche specific, which may in itself explain much of the conflicting data from both MBP and MOAB trials. We have limited mechanistic data to explain how MOAB actually reduce SSI rates, as almost all prospective trials have completely failed to account for the microbiome and its functions. Recent data suggests that the commensal bacterium *Enterococcus faecalis* contributes to the pathogenesis of anastomotic leak through its capacity to degrade collagen and to activate tissue matrix metalloproteinase 9 (MMP9) in host intestinal tissues [98]. The conclusion of this work does not support the wholesale destruction of the gut microbiome, but rather a precision guided approach that knocks down specific strains or their functions at the site of surgical pathology.

Antibiotics have a dramatic and long standing impact on both the structure and function of the gut microbiome, that lasts well beyond the surgical intervention [99]. By fundamentally altering (perhaps permanently) the gut microbiome with MOAB or OAB in the context of surgery it is possible that we are inadvertently modifying patient response to adjuvant therapy [100] and drug metabolism [101-103], adversely influencing their risk of non-communicable disease, drug toxicity, or even irrevocably altering gut function that may have a deleterious impact on QoL. Currently, none of these endpoints are measured in MOABP trials. While massive destruction of a complex and delicate ecosystem vital for human health and recovery from surgery should not be undertaken without careful consideration as it may have unpredictable consequences that lead to patient harm, it needs to be balanced against the reduced use of broad spectrum therapeutic antibiotics to treat SSI. Moving forwards, choice of bowel preparation must adopt a personalised strategy that promotes the beneficial behaviours of an individual's commensal organisms and suppresses pathobionts that drive surgical complications [90, 104].

Conclusion

There is strong evidence that SSI reduction bundles are effective and should be used routinely in the elective colorectal surgery pathway. Colorectal units should monitor SSI rates and implementation of SSI bundles should be audited while aspiring to the low SSI rates known to be achievable from published work.

There is a large and increasing body of evidence showing that MOAB is associated with reduced SSI and other postoperative complications but the quality of this evidence and its subsequent weighting is debated. It is possible that any observed effect on reduced SSI rates may be due simply to the use of OAB alone rather than MOAB. It is conceivable that, in time, OAB may be preferred in colonic surgery and MOAB in rectal resections. Informing patients of the possible benefits and risks and involving them in shared decision-making to use OAB or MOAB is recommended as best current practice due to the considerable uncertainty that persists.

Emerging research focusing on the microbiome is likely to guide more personalised and specific bowel preparation regimes which will target both reduction of AL and SSI. It is imperative that clinicians contribute to ongoing research and offer their patients the opportunity to participate in high quality research studies designed to fill the existing knowledge gaps.

Whilst there is much that is still unknown, the use of MOAB appears to be safe and could reasonably be used as part of an audited SSI reduction bundle, with the caveat that its use may need to be adjusted as results of ongoing high quality research emerge.

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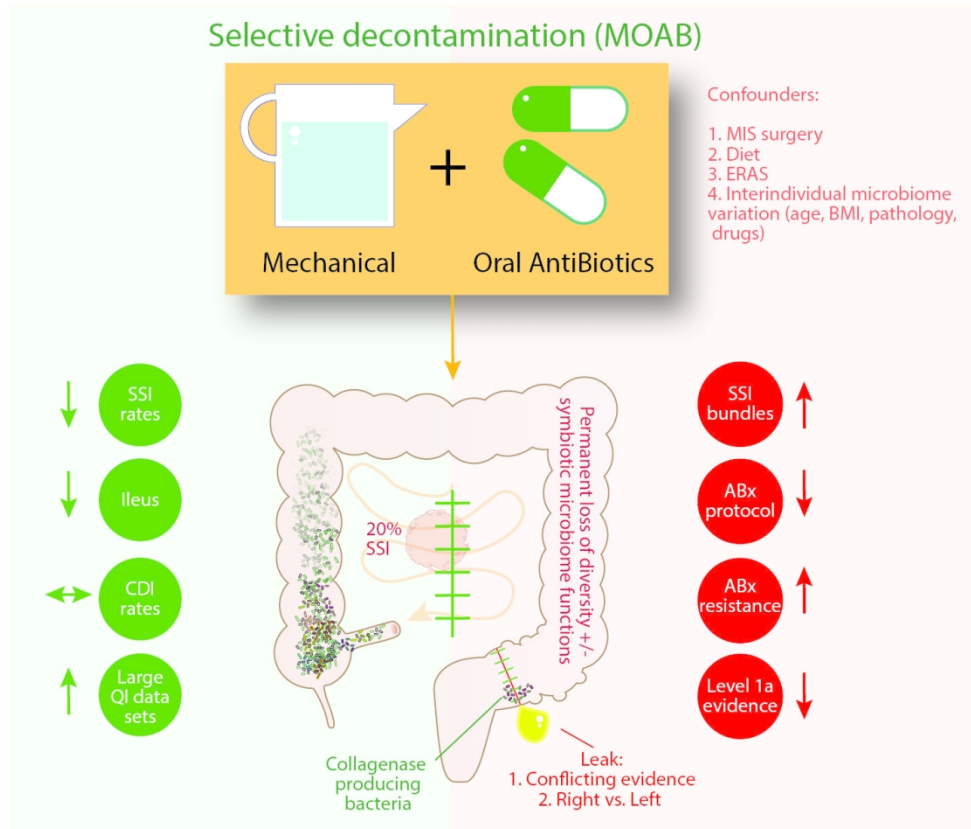
Arguments for and against the use of mechanical bowel preparation and oral antibiotics in elective colorectal resection

MOAB, mechanical bowel preparation and oral antibiotics; MIS, minimally invasive surgery; ERAS, enhanced recovery after surgery; BMI, body mass index; SSI, surgical site infection; ABx, antibiotics; CDI, Clostridium difficile infection; QI, quality improvement

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