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SYSTEMATIC REVIEW

Has network meta-analysis resolved the controversies related to bowel preparation in elective colorectal surgery?

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Abstract

Aim: There are discrepancies in the guidelines on preparation for colorectal surgery. While intravenous antibiotics (IV) are usually administered, the use of mechanical bowel preparation (MBP) and/or oral antibiotics (OA) is controversial. A recent network meta-analysis (NMA) demonstrated that the addition of OA reduced incisional surgical site infections (iSSIs) by more than 50%. We aimed to perform a NMA including only the highest quality randomized clinical trials (RCTs) in order to determine the ranking of different treatment strategies and assess these RCTs for methodological problems that may affect the conclusions of the NMAs.

Method: A NMA was performed according to PRISMA guidelines. RCTs of adult patients undergoing elective colorectal surgery with appropriate antibiotic cover and with at least 250 participants recruited, clear definition of endpoints and duration of follow-up extending beyond discharge from hospital were included. The search included Medline, Embase, Cochrane and SCOPUS databases. Primary outcomes were iSSI and anastomotic leak (AL). Statistical analysis was performed in Stata v.15.1 using frequentist routines.

Results: Ten RCTs including 5107 patients were identified. Treatments compared IV (2218 patients), IV + OA (460 patients), MBP + IV (1405 patients), MBP + IV + OA (538 patients) and OA (486 patients). The likelihood of iSSI was significantly lower for IV + OA (rank 1) and MBP + IVA + OA (rank 2), reducing iSSIs by more than 50%. There were no differences between treatments for AL. Methodological issues included differences in definition, assessment and frequency of primary endpoint infections and the limited number of participants included in some treatment options.

Conclusion: While this NMA supports the addition of OA to IV to reduce iSSI it also highlights unanswered questions and the need for well-designed pragmatic RCTs.

INTRODUCTION

Anastomotic leak (AL) and incisional surgical site infection (iSSI) continue to be frustratingly prevalent complications in elective colorectal surgery [1], resulting in significant morbidity for patients and cost to health care providers. Ongoing research focusing on the prevention of these complications has not yet resulted in a consensus on the importance of different bowel preparation regimens. This is reflected in differences in practices and guidelines in America [2] and Europe [3] and of international societies such as the ERAS Society [4].

One method for assessing outcomes where there are differences in practice is large database reviews. Studies reviewing the American

College of Surgeons National Surgical Quality Improvement Program (NSQIP) database report that the addition of oral antibiotics (OA) significantly reduces iSSI, AL, ileus and hospital stay [5–7]. While these results reflect real life practice, they also raise questions. What is the quality of evidence in databases compared with randomized clinical trials (RCTs)? In terms of controlling for differences in risk factors, American Society of Anesthesiologists grade, disseminated cancer, laparoscopic surgery and other risk factors favour the OA group [5, 6]. Accurately adjusting for these as well as other potential differences is difficult. Also, no data are available on the adequacy of the combined antibiotic cover against aerobic and anaerobic bacteria between the groups being compared.

Another method is to systematically assess high-quality studies, in this case RCTs, by using meta-analysis or network meta-analysis (NMA). Meta-analyses compare two options using pairwise comparisons. These have demonstrated no important differences between mechanical bowel preparation (MBP) and MBP with intravenous antibiotics (MBP + IV) and intravenous antibiotics alone (IV). In contrast, other meta-analyses have shown advantages for IV + OA compared with IV [8–10]. Unfortunately, many included RCTs compare IV regimens that provide incomplete aerobic and anaerobic cover with IV + OA regimens providing good aerobic and anaerobic antibiotic cover, making it unclear if this difference is due to better antibiotic cover or the additional use of OA.

NMA has the advantage of integrating data assessing multiple options into a network where direct evidence from head-to-head comparisons and indirect evidence of comparisons linked within the network are assessed. A NMA of RCTs comparing methods of bowel preparation that only included RCTs with good aerobic and anaerobic cover in all groups being compared has recently been published [11]. This demonstrated that the addition of OA to IV reduced the incidence of iSSI by more than 50%. This was the case both with and without the use of MBP. There were no differences in AL or in other clinical outcomes. Has this NMA resolved the controversy, or are additional studies still required?

Systematic reviews depend on the quality of the included studies and the methodological quality of the review [1]. While many quality issues are recognized and assessed in the Cochrane Collaboration's risk of bias tool, others are less well-recognized. For example, meta-analyses combining small studies with different methods for diagnosing endpoints and inadequate blinding have reported results which conflict with subsequent, high-quality RCTs. Examples in the colorectal literature include meta-analyses looking at the use of wound protectors to prevent iSSI [12, 13] and prophylactic mesh placement to prevent parastomal hernias [14, 15]. We therefore wanted to assess the impact of 'lower quality' studies on our NMA results by performing a NMA including only the highest quality studies, in-line with predefined criteria. We will then examine the limitations of these NMAs to identify any outstanding questions about bowel preparation in elective colorectal surgery.

What does this paper add to the literature?

Assessment of the highest quality randomized clinical trials (RCTs) in a network meta-analysis confirmed that combining oral and intravenous antibiotics reduced incisional surgical site infections by more than 50%. There were significant methodological issues related to definition, assessment and frequency of endpoint infections, and the limited sample size. Further pragmatic RCTs assessing the impact of adding oral antibiotics should be performed.

METHOD

We performed a systematic review of RCTs comparing methods of bowel preparation in elective colorectal surgery. This included the use of IV, OA, MBP, enema (E) and combinations of these. The use of E with MBP was counted as part of the MBP. Studies had to compare at least two bowel preparation options. Outcomes assessed were iSSI and AL. AL was defined as clinical disruption of the anastomosis. A radiological diagnosis of AL without a clinical problem, or a space SSI without a clinical AL, were not counted. An iSSI required a wound problem consistent with the Centers for Disease Control (CDC) definitions of superficial incisional or deep incisional SSI.

Predefined criteria for selecting the 'best quality studies' were RCTs, good aerobic and anaerobic cover in all groups being compared, at least 250 participants recruited, clear definitions of the endpoints, and the duration of endpoint follow-up extending to after discharge from hospital. Exclusion criteria included studies which were not RCTs, were in paediatric patients, where results for different bowel preparation interventions were combined [16] and where the 'best study' criteria were not met. Effective aerobic cover was defined in line with Clinical and Laboratory Standards Institute guidelines [11], and effective anaerobic cover was defined as a MIC90 <16 for the majority of anaerobic pathogens and/or an overall resistance to anaerobic bacteria of less than 20%. Direct comparisons of all colorectal resections, all left-sided colon resections and all colon resections were included.

Medline, Embase, the Cochrane Library (CENTRAL) and SCOPUS databases and trial registries (clinicaltrials.gov and WHO International Clinical Trials Registry) were searched. The bibliographies of included studies, clinical practice guidelines and systematic reviews were hand searched for other relevant articles. There were no limitations on language or publication period. Two researchers independently screened all citations, reviewed identified abstracts for eligibility, extracted data and summarized the methodological quality of studies using the Cochrane Collaboration's risk of bias tool for RCTs. Discrepancies were resolved by the senior author. Corresponding authors were contacted to clarify information as required.

Network diagrams illustrated the direct comparisons between the bowel preparation treatments. Random effects NMA was performed, including direct and indirect comparisons, to determine the pooled relative effect of each treatment compared with every other treatment for the outcomes of interest. Analyses were performed using a frequentist framework in Stata v.15.1 [17]. Categorical data were summarized as odds ratios (95% confidence intervals) and

presented in league tables. The relative ranking of different bowel preparations was estimated for each outcome using the distribution of ranking probabilities and surface under cumulative ranking curves [18]. Between-study heterogeneity was evaluated using the tau-square statistic and each model was assessed for global and local inconsistency. A more detailed description of the methods including the search strategy and statistics is published elsewhere [11].

RESULTS

From 6834 titles, 472 abstracts and 175 identified studies, 10 eligible RCTs including 5107 patients were identified. Identified bowel preparation options were: MBP + IV six studies, IV with no bowel preparation with or without E (IV) eight studies, IV and OA with or without E (IV + OA) two studies, MBP with IV with good aerobic and anaerobic cover and additional OA (MBP + IV + OA) three studies, and OA with no bowel preparation with or without E (OA) one study.

The PRISMA flow chart is summarized in Figure 1. The network is illustrated in Figure 2, and the details of the included RCTs are presented in Table 1.

Even in the 'best studies', quality issues were identified. For iSSI, there were differences in the definition, assessment, follow-up and frequency of infection. Definitions were according to CDC guidelines on four occasions and were individually defined on six occasions; in two, erythema was sufficient and in four, discharge from the wound was required. iSSI was the primary endpoint on four occasions, was possibly the primary endpoint on three occasions and was not the primary endpoint on three occasions. Duration of follow-up was until 2 weeks after discharge on one occasion, up to 4 weeks (1 month or 30 days) after surgery on six occasions and for longer on three occasions. Only one RCT detailed the effort made to diagnose an iSSI. With respect to frequency of iSSI, in four RCTs the rates of iSSI and AL were similar for at least one of the bowel preparation options. The rate of iSSI varied from 1.9% to 14.3%. This varied from 3.6% to 14.3% for MBP + IV from 2.3% to 14% for IV and from 2.5% to 7% for MBP + IV + OA. In three studies there was assessor blinding, in four studies details were unclear and three studies were 'open label' or unblinded. Similar observations were made for AL (Table 1).

All patients were assessed for iSSI and AL. Analysis of iSSI demonstrated consistency between direct and indirect measurements ($\chi^2 = 1.03$, $p = 0.59$), local consistency with all loops having an inconsistency factor (IF) < 1.0 and no evidence of publication bias (Figure S1). The best ranking (Figure 3) was achieved with IV + OA (71% probability of being the best treatment) followed by MBP + IV + OA (71% probability of being the second-best treatment). In order of ranking, these were followed by IV, MBP + IV and OA. Patients treated with either IV + OA or MBP + IV + OA had significantly fewer iSSIs when compared with any of the other treatment options ($p < 0.001$; Table 2; Figure 4). MBP + IV had significantly fewer associated iSSIs than OA ($p = 0.045$). There was no significant difference between IV + OA (460 patients) and MBP + IV + OA (538 patients).

Analysis of AL demonstrated consistency between direct and indirect measurements ($\chi^2 = 0.71$, $p = 0.70$), local consistency with all loops having an IF < 1.0 and no evidence of publication bias (Figure S2). The best ranking was achieved with IV + OA (77% probability of being the best treatment), followed by MBP + IV + OA (58% probability of being the second-best treatment) (Figure S3). While the odds of AL were lower in IV + OA and MBP + IV + OA, this did not reach statistical significance (Table 2; Figure 5).

DISCUSSION

The main findings for 'the ten best studies' were very similar to our larger NMA which included 35 RCTs [11]. In both NMAs, IV + OA and MBP + IV + OA were significantly better than other options, reducing iSSI by more than 50%. There were no significant differences in AL. Our current analyses, which only includes high-quality RCTs, with good statistical consistency and no publication bias, suggest that the addition of OA to IV, both with and without MBP, should become standard practice in elective colorectal surgery. However, a more careful analysis demonstrates methodological problems with even the best RCTs, as well as limitations within the NMAs, which require further examination.

Incisional SSI within 30 days is one of eight clinical indicators for measuring quality, safety and improvement in perioperative care [19]. In this NMA, the frequency of iSSI ranged from 1.9% to 14.3%, with a concerning three- to four-fold variation for the same method of bowel preparation. One of the domains in the PRECIS-2 toolkit is the intensity and measurement of follow-up, including both the duration and frequency of measurement. When diagnosing iSSI an important factor is the ability of patients to report back to the medical team (incorporating the patient's perspective). The majority of iSSIs develop after discharge from hospital [20, 21], with 50%–80% of iSSIs being identified by the 16th postoperative day [22–24]. While RCTs in this NMA followed patients for approximately 30 days or more, infections developing postdischarge may be overlooked without a targeted identification strategy. Diagnosis of iSSI is also more frequent when patients are formally contacted after discharge [13, 25]. For example, when followed up by phone interview 30 days after surgery, 57% of iSSIs had started after hospital discharge [26] and even more iSSIs were identified when using a validated, patient-centred questionnaire 4 weeks after discharge [27]. The Bluebelle study developed a wound scoring questionnaire for iSSI with an area under the receiver operating characteristic curve of 0.9056 (0.82–0.98) when assessed against CDC criteria [28]. The ROSSINI study, with an iSSI rate of 25% after open abdominal surgery, included the clinical training of wound assessors, clinical reviews at days 7 and 30 and a patient self-reported questionnaire to identify iSSI. This high level of scrutiny is likely to identify an iSSI rate of greater than 10%–15% in studies combining elective laparoscopic and open colorectal surgery.

Another domain in the PRECIS-2 toolkit is the importance of primary outcome. It is especially important to distinguish between

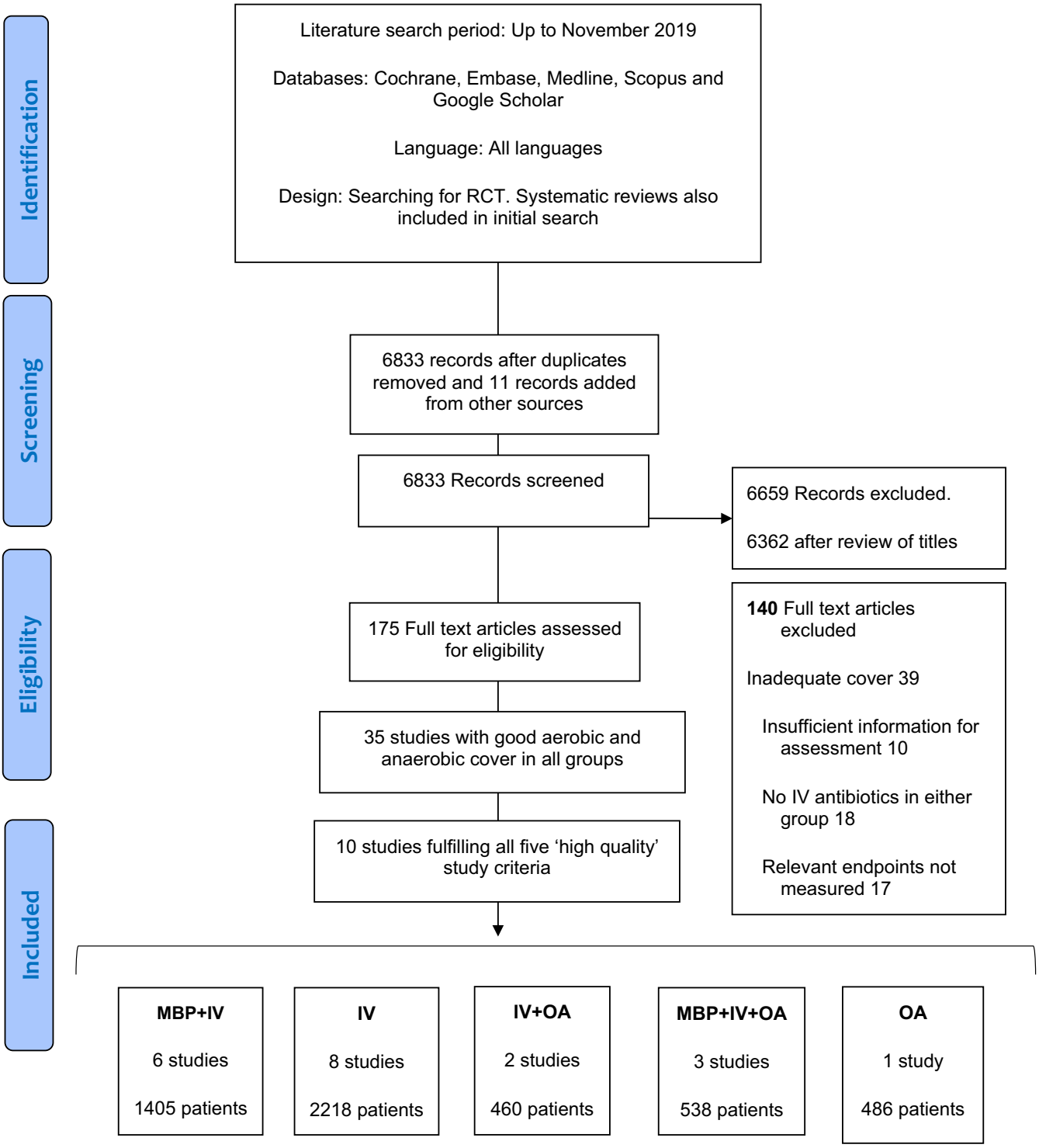

FIGURE 1 Prisma flow diagram for data collection. IV, intravenous antibiotics; MBP, mechanical bowel preparation; OA, oral antibiotics; RCT, randomized clinical trial

primary and secondary endpoints when performing meta-analyses. Matthews et al. [29] demonstrated that iSSI rates were 12.6% when studied as the primary endpoint and 5.1% as a secondary endpoint. In this NMA, iSSI was the primary endpoint on four occasions, was unclear on three occasions and was a secondary endpoint on three occasions. While this introduces heterogeneity, we do note that there were similar rates of iSSI in all categories, including two of the three secondary endpoint studies which identified iSSI rates of more than 10%. Another issue is the potential impact of lack of blinding on iSSI results. A review of blinding in surgical RCTs comparing laparoscopic and open surgery showed a significant reduction in the differences in length of stay and complications when participant or assessor blinding was achieved [30]. While patient blinding is not possible with MBP, assessor blinding

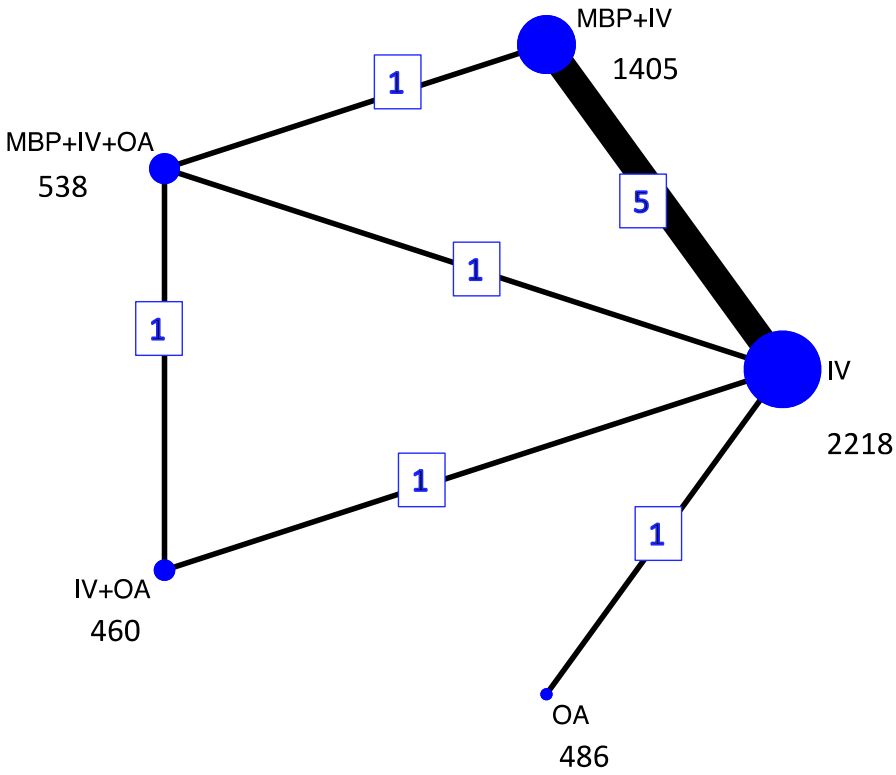

FIGURE 2 Network plot of direct comparisons for surgical site infection. The size of the individual nodes represents the number of patients studied for each bowel preparation option, and the thickness of the lines is proportional to the number of studies directly comparing the different nodes. IV, intravenous antibiotics; MBP, mechanical bowel preparation; OA, oral antibiotics

can still be achieved. In this NMA, assessor blinding was confirmed in only three RCTs. It is difficult to control for the cumulative impact of small differences introduced by variations in definitions, primary endpoints and follow-up, only a proportion of iSSIs being identified, and a lack of blinding. However, this combination does increase the risk of inaccuracy, such as exaggerated differences between treatments.

In this NMA, when we compare IV + OA or MBP + IV + OA with IV or MBP + IV, there was an approximate four-fold reduction in iSSI. Are these results pathophysiologically credible? When OA were introduced, RCTs in the 1970s comparing MBP with OA against MBP alone (with no IV being used) demonstrated a reduction in iSSIs from 42% to 17% [31] and from 31% to 9% [32]. When using effective IV [33] we would expect the impact of adding OA to IV to be less. It is therefore likely that the advantages of adding OA in our NMA are exaggerated. In terms of pathophysiology, MBP + IV + OA reduces bacterial colonization within the colon [34]. The mechanism of using IV + OA without MBP is not due to this mechanism and is likely to be more nuanced. This may involve host–gut flora interactions and changes in the microbiome including adjustments in levels of commensal and pathogenic bacteria. Avoiding the detrimental impact of MBP on the microbiome (which includes reducing *Bifidobacterium* and *Lactobacillus* [35]) and on the colonic mucosa [36] may be an important factor. Understanding the physiology will aid our understanding of the benefits of IV + OA without MBP. This will also help with clinical decision-making as correct conclusions are most likely when clinical outcomes, pathophysiology and statistical results are consistent with each other, as illustrated in the differences in meta-analyses assessing the impact of single- and double-ring wound protectors on iSSI [12, 37].

The main weakness of our larger NMA is the limited number of RCTs and patients included in some treatment options. Similarly, in this NMA of high-quality studies approximately 500 patients were included in the IV + OA, MBP + IV + OA and OA only groups. The limitation is demonstrated by a sample size of 434 patients being required in each group to demonstrate a reduction in a clinical outcome from 10% to 5% with 80% power, assuming a well-designed RCT with 1:1 randomization. There also needs to be caution interpreting results when a treatment examined by few studies is ranked at either extreme of the network. For example, IV + OA (two RCTs) performed as the best option for iSSI, and OA alone (one RCT) as the worst option. The relatively limited data in the IV + OA group was expected, as this has only been assessed in a few studies. However, with the long history of using MBP + IV + OA and the amount of literature discussing this, the limited number of patients in the MBP + IV + OA group (in both our previous larger NMA and in this NMA) was less than expected and is the main reason for controversy around the advantages of MBP + IV + OA. Another limitation of our NMAs was insufficient numbers of RCTs reporting results separately for colon and rectal surgery. For example, most of the IV + OA cases underwent colon surgery, and this option has not been adequately assessed in rectal surgery. Other potential limitations of our main NMA, including issues of study complexity, the antibiotic cover of included studies and the impact of changes in practice over time have been discussed previously [11].

For some, the results of our NMAs incorporating all RCTs with good antibiotic cover, combined with the international literature [38–45], will provide sufficient information to routinely add OA to IV, with or without MBP, in preparation for colorectal surgery. However, in this discussion we have highlighted problems with

TABLE 1 Summary table of included studies

Study	Country	Sample size	Mean age (years)	Sex (%F)	Group and number	IV antibiotics	Oral antibiotics	MBP	Definition of iSSI
Abis (2019) [41][a]	Netherlands	455	67.8	72	MBP + IV + OA (155)	1 g cefazolin, 0.5 g metronidazole	0.5 g ampotericin B, 100 mg colistin sulphate, 80 mg tobramycin	MBP Given	According to CDC guidelines
					MBP + IV (161)	1 g cefazolin, 0.5 g metronidazole		MBP given	
Contant (2007) [50]	Netherlands	1354	67	50	MBP + IV (670)	Broad-spectrum anaerobic options and metronidazole		Hospital protocol	Mild-erythema or discharge of seroma
					IV (684)	Broad-spectrum anaerobic options and metronidazole			Severe- discharge of pus, necrosis or wound dehiscence
Espin Basany (2020) [40]	Spain	536	71	45	IV (269)	1.5 g cefuroxime and 1 g metronidazole			According to CDC guidelines
					IV + OA (267)	1.5 g cefuroxime and 1 g metronidazole	Ciprofloxacin 750 mg ×4 and metronidazole 250 mg ×9		
Fa-Si-Oen (2005) [51]	Netherlands	250	70	54	MBP + IV (125)	Cefazolin or gentamicin and 1.5 g metronidazole		4 l PEG	Clinically significant infection of the skin requiring wound evacuation
					IV (125)	Cefazolin or gentamicin and 1.5 g metronidazole			
Hjalmarsson (2015) [52]	Sweden	985	70	47	OA (486)		Cotrimoxazole and 1.2 g metronidazole		According to CDC guidelines
					IV (499)	1.5 g cefuroxime, 1.5 g metronidazole			
Koskenvuo (2019) [53]	Finland	396	70.1	49	MPB + IV + OA (196)	1.5 g cefuroxime, 0.5 g metronidazole	2 g neomycin, 2 g metronidazole	2 l PEG	According to CDC guidelines
					IV (200)	1.5 g cefuroxime, 0.5 g metronidazole		2 l PEG	
Miettinen (2000) [54]	Finland	267	63	51	MBP + IV (138)	2 g ceftriaxone, 1 g metronidazole		PEG	Presence of pus or discharge with microbiological culture
					IV (129)	2 g ceftriaxone, 1 g metronidazole			
Platell (2006) [48]	Australia	294	66	65	MBP + IV (147)	Timentin or gentamicin and 0.5 g metronidazole		3 l PEG	Discharge with microbiological confirmation
					IV + E (147)	Timentin or gentamicin and 0.5 g metronidazole		Phosphate E	
Ram (2005) [55]	Israel	329	68	39	MBP + IV (164)	1 g ceftriaxone, 0.5 g metronidazole		3.3 g Na phosphate	Discharge with microbiological confirmation
					IV (165)	1 g ceftriaxone, 0.5 g metronidazole			
Zmora (2003) [44]	Israel	380	68	48	MBP + IV + OA (187)	Broad-spectrum aerobic and anaerobic	Neomycin and erythromycin ×3	4.5 l PEG	Erythema needing antibiotics or requiring opening of wound
					IV + OA (193)	Broad-spectrum aerobic and anaerobic	Neomycin and erythromycin ×3		

Abbreviations: AL, anastomotic leak; CDC, Centers for Disease Control; IV, intravenous antibiotics; MBP, mechanical bowel preparation; NS, not stated; OA, oral antibiotics; PEG, polyethylene glycol; WI, wound infection.

[a]Details provided by corresponding author.

iSSI primary endpoint?	Definition of AL	AL primary endpoint?	Time for diagnosis	Blinding	No. of iSSIs	No. of ALs	Issues with paper
No	Clinical suspicion and requiring a radiological or surgical intervention	Yes	Within 30 days	Open label	4/155 (2.5%)	12/155 (7.7%)	No blinding Similar infection rates for iSSI and AL Only left-sided groups included because of transitivity assumption for AL
					20/161 (12.4%)	19/161 (11.8%)	
No	Clinical suspicion confirmation by radiology or surgery	Yes	Up to 2/52 postdischarge	Unblinded	90/670 (13.4%)	32/670 (4.8%)	Unblinded but similar infection rates in both groups
					96/684 (14.0%)	37/684 (5.4%)	
Yes	Not clearly stated, although investigations with CT and surgery discussed	No	4/52 postdischarge	Assessor blinded	22/269 (8.2%)	0/269 (0%)	
					5/267 (1.9%)	0/267 (0%)	
Yes	Clinical diagnosis. Major if laparotomy, minor if radiological intervention	Yes	Up to 3 months	Unclear	9/125 (7.2%)	7/125 (5.6%)	Blinding not clear, but similar infection rates in both groups Wound and AL rates similar
					7/125 (5.6%)	6/125 (4.8%)	
Yes	Clinically confirmed anastomotic insufficiency	No	Assessed daily for 28 days	Assessor blinded	34/486 (7.0%)	17/486 (3.5%)	Wound and AL rates similar in IV group
					18/499 (3.6%)	17/499 (3.4%)	
Yes	Clinical suspicion and confirmation of anastomotic dehiscence within 30 days after surgery	No	30 days	Assessor blinding	13/196 (7%)	7/196 (3.6%)	
					21/200 (10.5%)	8/200 (4.0%)	
NS, but first listed	Brief description. Implies clinical suspicion confirmed by radiology	NS, third outcome listed	1–2 months	Unclear	5/138 (3.6%)	5/138 (3.6%)	Blinding unclear Wound infection and AL infection rates similar in both groups
					3/129 (2.3%)	3/129 (2.3%)	
No	Clinical suspicion confirmed with radiology or surgery	Yes	30 days	Unclear	21/147 (14.3%)	7/147 (4.8%)	Blinding unclear but similar infection rates in both groups
					19/147 (13.3%)	3/147 (2.0%)	
NS, but first listed	Clinical suspicion confirmed with radiology (water-soluble contrast)	NS, fourth (last) listed	1, 3 and 6 weeks postdischarge	Not stated	10/165 (6.1%)	2/165 (1.2%)	Blinding unclear
					16/164 (9.8%)	1/164 (0.6%)	
Infectious complications, including WI	Clinical suspicion confirmed by imaging or surgery or faecal material in drain	Infectious complications including AL	Up to 1 month	Unblinded	12/187 (6.4%)	7/187 (3.7%)	No blinding but similar infection rates in both groups
					11/193 (6.0%)	4/193 (2.1%)	

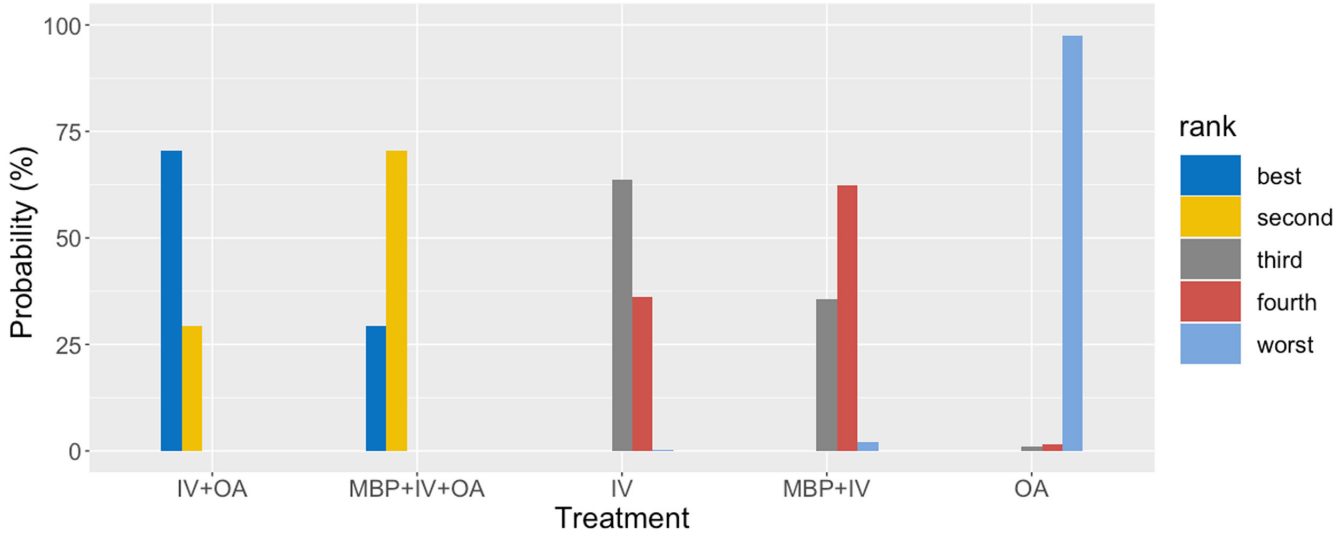

FIGURE 3 Rankogram for incisional surgical site infection. The rankogram shows the probability of each preparation option being ranked best to worst. For example, IV + OA has a 70.6% probability of being ranked best, 29.4% probability of being ranked second and a <1% probability for the other options. In comparison, IV has a 63.6% probability of being ranked third, a 36.2% probability of being ranked fourth and <1% probability for the other options. IV, intravenous antibiotics; MBP, mechanical bowel preparation; OA, oral antibiotics

TABLE 2 Odds ratios (95% CI) for comparisons of treatments for incisional surgical site infection and anastomotic leak[a]

	IV	OA	IV + OA	MBP + IV + OA	MBP + IV
Incisional surgical site infection					
IV		2.01 (1.12,3.61)	0.23 (0.11,0.49)	0.27 (0.14,0.54)	1.05 (0.82,1.34)
OA	0.50 (0.28,0.89)		0.11 (0.04,0.30)	0.14 (0.05,0.34)	0.52 (0.28,0.98)
IV + OA	4.37 (2.05,9.31)	8.79 (3.38,22.87)		1.19 (0.59,2.41)	4.58 (2.10,9.97)
IV + MBP + OA	3.68 (1.84,7.35)	7.39 (2.98,18.31)	0.84 (0.42,1.70)		3.85 (1.91,7.78)
MBP + IV	0.95 (0.74,1.22)	1.92 (1.02,3.63)	0.22 (0.10,0.48)	0.26 (0.13,0.52)	
Anastomotic leak					
IV		1.03 (0.52,2.04)	0.41 (0.11,1.54)	0.69 (0.36,1.32)	0.92 (0.63,1.35)
OA	0.97 (0.49,1.93)		0.40 (0.09,1.77)	0.67 (0.26,1.72)	0.90 (0.41,1.97)
IV + OA	2.44 (0.65,9.20)	2.51 (0.56,11.16)		1.68 (0.51,5.51)	2.25 (0.60,8.42)
IV + MBP + OA	1.45 (0.76,2.79)	1.49 (0.58,3.85)	0.60 (0.18,1.96)		1.34 (0.72,2.50)
MBP + IV	1.08 (0.74,1.59)	1.11 (0.51,2.44)	0.44 (0.12,1.66)	0.74 (0.40,1.39)	

[a]OR > 1: the outcome is more likely after treatment in the corresponding cell in the top row when compared with treatment indicated in the corresponding cell in the left column. OR < 1: the outcome is less likely after treatment in the corresponding cell in the top row when compared with treatment indicated in the corresponding cell in the left column.

limited sample size for some bowel preparation options, including both IV + OA and MBP + IV + OA, 'greater than expected' differences in iSSI when OA are added to IV and methodological problems with the frequency of diagnosis of iSSI and lack of assessor blinding. In this context, the NMA should be viewed as an opportunity to design and implement large, rigorous studies to test the main findings [1]. It is important that such studies are pragmatic [46], designed to answer current questions, and not repeating the limitations of previous RCTs. Studies need to be powered to assess for differences in iSSI and AL as primary endpoints, have a clearly agreed method for diagnosing iSSI (consistent with the ROSSINI study or including another validated, patient-focused questionnaire), include blinding of assessors and include an assessment of the impact of IV + OA on the microbiome. For iSSI, RCTs examining the role of IV + OA and MBP + IVA + OA in both colon and rectal surgery [47] are indicated. For AL, larger RCTs assessing the impact of combining OA with IV, with good antibiotic cover in all groups, will clarify if OA significantly reduces rates of AL or not. The severity of AL [48] should also be assessed. Research should also assess the impact of OA with or without MBP on the microbiome, including on commensal and pathogenic bacteria, and the preferential colonization of collagenase-producing bacteria such as *Pseudomonas aeruginosa*

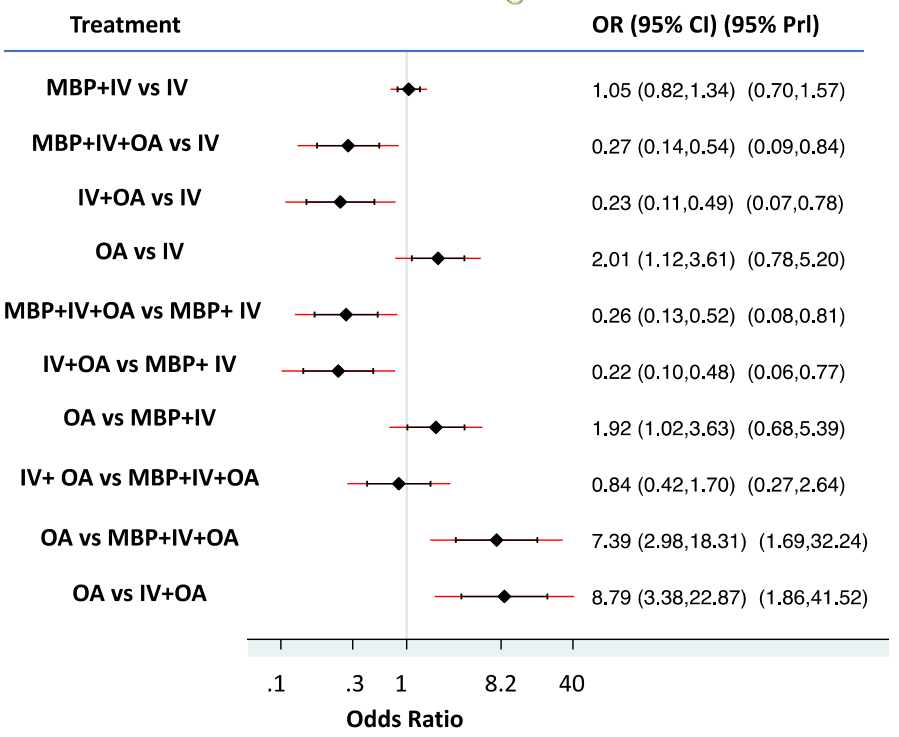

FIGURE 4 Forest plot comparing odds ratios (ORs) for treatments and their effect on the occurrence of incisional surgical site infection (iSSI). OR > 1: iSSI is more likely after treatment listed on the left when compared with treatment indicated on the right. OR < 1: iSSI is more likely after treatment listed on the right when compared with treatment indicated on the left. CI, confidence interval; IV, intravenous antibiotics; MBP, mechanical bowel preparation; OA, oral antibiotics; Prl, predicted interval

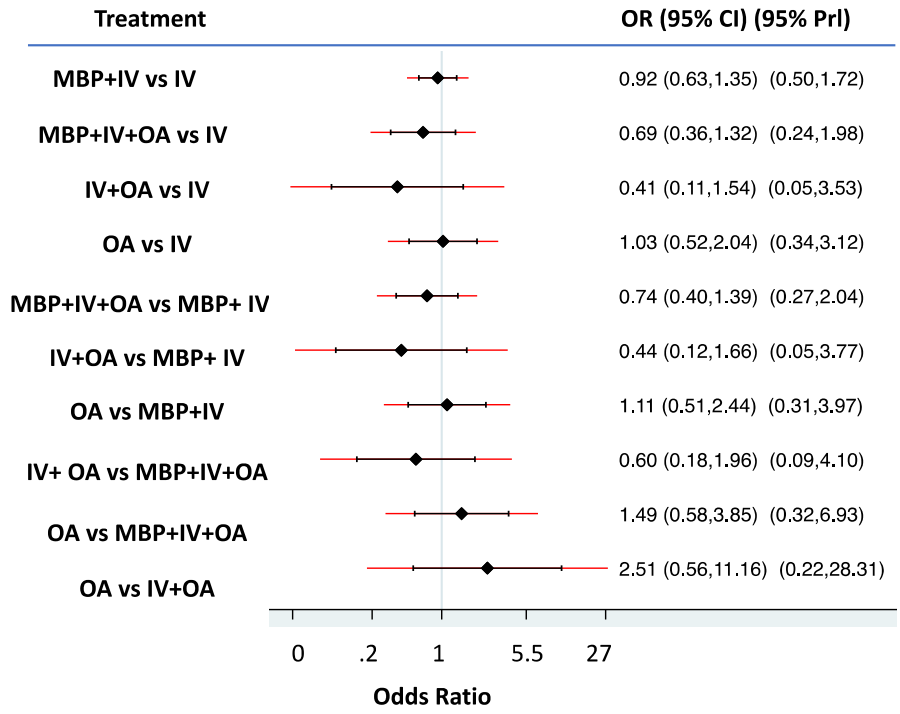

FIGURE 5 Forest plot comparing odds ratios for treatments and their effect on the occurrence of anastomotic leak. OR > 1: iSSI is more likely after treatment listed on the left when compared with treatment indicated on the right. OR < 1: iSSI is more likely after treatment listed on the right when compared with treatment indicated on the left. CI, confidence interval; IV, intravenous antibiotics; MBP, mechanical bowel preparation; OA, oral antibiotics; Prl, predicted interval

and *Enterococcus faecalis* [49]. In contrast, sufficient data exist comparing MBP + IV and intravenous antibiotics alone, and no further studies comparing these options are necessary.

In conclusion, in this NMA including only high-quality RCTs, some treatment options were underpowered and methodological issues were still present. To address ongoing questions, large, well-designed and pragmatic studies, as described above, assessing the impact of additional OA in colon and rectal surgery are required.

AUTHOR CONTRIBUTIONS

John C. Woodfield: Conceptualization, methodology, data review, writing (original draft and review). Kari Clifford: Methodology, data collection, data analysis and visualisation, writing (review). Barry Schmidt: Methodology, data collection. Mark Thompson-Fawcett: Supervision, writing (original draft and review).

CONFLICT OF INTEREST

We declare no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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