WHO Surgical Site Infection Prevention Guidelines

Web Appendix 6

Summary of a systematic review on mechanical bowel preparation and the use of oral antibiotics

1. Introduction

The optimal preparation of the bowel of patients undergoing colorectal surgery has been a subject of debate for many years. The main focus has been on whether or not mechanical cleansing of the bowel should be part of the standard preoperative regimen. Mechanical bowel preparation (MBP) involves the preoperative administration of substances to induce voiding of the intestinal and colonic contents. The most commonly used cathartics for MPB are polyethylene glycol and sodium phosphate. It was assumed that cleaning the colon of its contents was necessary for a safe operation and could lower the risk of surgical site infection (SSI) by decreasing the intraluminal fecal mass and theoretically decreasing the bacterial load in the intestinal lumen. Furthermore, it was believed that it could prevent the possible mechanical disruption of a constructed anastomosis by the passage of hard faeces. Finally, MBP was perceived to improve handling of the bowel intraoperatively.

Another aspect of preoperative bowel preparation that has evolved over the last decades concerns the administration of oral antibiotics. Orally administered antibiotics have been used since the 1930s with the aim to decrease the intraluminal bacterial load. However, these drugs had typically poor absorption, achieved high intraluminal concentrations and had activity against (anaerobic and aerobic) species within the colon. The addition of oral antibiotics that selectively target potentially pathogenic microorganisms originating from the digestive tract, predominantly gram-negative bacteria, *Staphylococcus aureus* and yeasts, is known also as "selective digestive decontamination". This term originates from intensive care medicine and usually refers to a regime of tobramycin, amphotericin and polymyxin combined with a course of an intravenous antibiotic, often cefotaxime. Originating from the belief that oral antibiotics would work only when the bowel had been cleansed of its contents, a regime of oral antibiotics was frequently combined with MBP.

Several organizations have issued recommendations regarding preoperative MBP and the administration of oral antibiotics. Most recommend to use MBP for colorectal procedures, but only combined with oral antibiotics. The United Kingdom (UK) National Institute for Health and Care Excellence (NICE) guidelines recommend not to use MBP routinely to reduce the risk of SSI *(1)*. The SSI prevention guidelines issued in 1999 by the United States (US) Centers for Disease Control and Prevention recommend MBP before elective colorectal operations in combination with the administration of non-absorbable oral antimicrobial agents in divided doses on the day before the operation *(2)*. The most recent guideline on this topic was issued by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) and recommends using a combination of parenteral antimicrobial agents and oral antimicrobials to reduce the risk of SSI following colorectal procedures. It is emphasized that MBP without oral antimicrobials does not decrease the risk of SSI *(3)*.

The purpose of this systematic review is to assess the available evidence on the effectiveness of preoperative oral antibiotics and MBP for the prevention of SSI.

2. PICO question

Is MBP combined with or without oral antibiotics effective for the prevention of SSI in colorectal surgery?

- **P**opulation: inpatients and outpatients of any age undergoing elective colorectal surgery
- **I**ntervention: (1) MBP combined with oral antibiotics
  (2) MBP alone
- **C**omparator: (1) MBP and standard intravenous antibiotic prophylaxis only
  (2) standard intravenous antibiotic prophylaxis only
- **O**utcomes: SSI, SSI-attributed mortality, anastomotic leakage

3. Methods

The following databases were searched: Medline (Ovid); Excerpta Medica Database (EMBASE); Cumulative Index to Nursing and Allied Health Literature (CINAHL); the Cochrane Central Register of Controlled Trials (CENTRAL); and WHO regional medical databases. The time limit for the review was between 1 January 1990 and 17 January 2014. Language was restricted to English, French and Spanish. A comprehensive list of search terms was used, including Medical Subject Headings (MeSH) (Appendix 1).

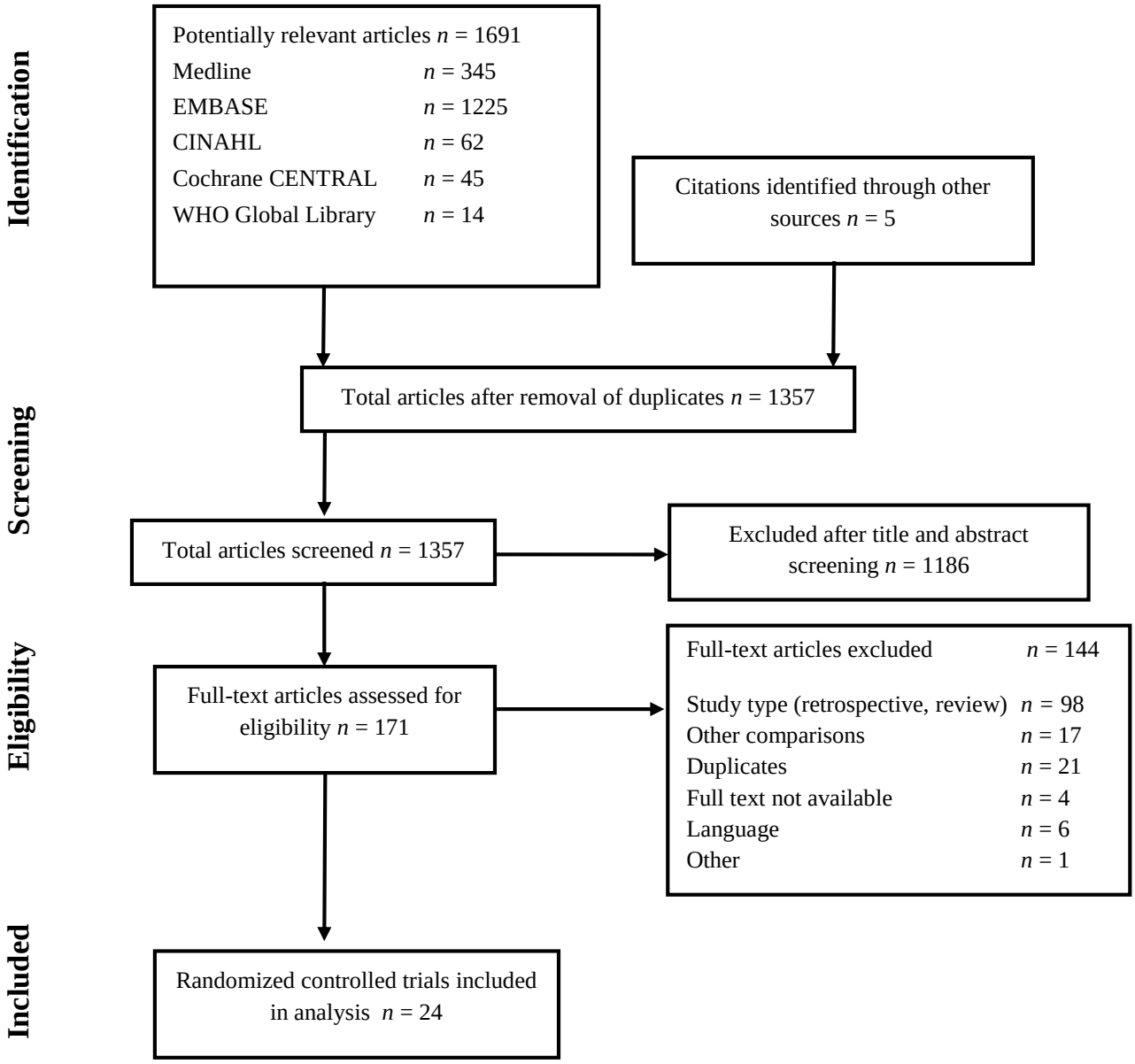
Two independent reviewers screened the titles and abstracts of retrieved references for potentially relevant studies. The full text of all potentially eligible articles was obtained and then reviewed independently by two reviewers for eligibility based on inclusion criteria. Duplicate studies were excluded.

The two reviewers extracted data in a predefined evidence table (Appendix 2) and critically appraised the retrieved studies. Quality was assessed using the Cochrane Collaboration tool to assess the risk of bias of randomized controlled studies (RCTs) *(4)* (Appendix 3). Any disagreements were resolved through discussion or after consultation with the senior author, when necessary.

Meta-analyses of available comparisons were performed using Review Manager version 5.3 as appropriate *(5)* (Appendix 4). Adjusted odds ratios (OR) with 95% confidence intervals (CI) were extracted and pooled for each comparison with a random effects model. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology *(6)* (GRADE Pro software) *(7)* was used to assess the quality of the body of retrieved evidence (Appendix 5).

4. **Study selection**

Flow chart of the study selection process



5. Summary of the findings and quality of the evidence

A total of 24 RCTs *(8-31)* were identified either comparing MBP vs. no MBP or a combined intervention of MBP and oral antibiotics vs. MBP and no oral antibiotics. Most studies assessed the outcome of anastomotic leakage, while all assessed SSIs. Included patients were adults undergoing colorectal surgical procedures. No study was available in the paediatric population. All patients received antibiotic prophylaxis prior to surgery, both in the intervention and control groups.

According to the interventions, we were able to make the following **comparisons:**

1. MBP and oral antibiotics vs. MBP and no oral antibiotics
2. MBP vs. no MBP

1. Among the 11 RCTs *(13, 15, 16, 18, 19, 21, 24, 25, 27-29)* comparing MBP combined with oral antibiotics vs. MBP and no oral antibiotics, 6 trials *(13, 15, 18, 24, 27, 28)* showed no statistically significant difference in the SSI rate between the 2 groups. Five RCTs *(16, 19, 21, 25, 29)* showed a decrease of the SSI rate in patients undergoing MBP combined with oral antibiotics prior to the operation. In 8 trials, oral aminoglycosides were combined with anaerobic coverage (metronidazole *(13, 19, 21, 25, 28)* or erythromycin *(16, 18, 27)*) and 3 studies *(15, 24, 29)* applied a gram-negative coverage only. In these 8 RCTs *(13, 16, 18, 19, 21, 25, 27, 28)*, a combination of non-absorbable and absorbable antibiotics were administered, whereas 2 studies *(15, 24)* applied non-absorbable and one study *(29)* absorbable antibiotics only.

   A meta-analysis of the 11 trials (Appendix 4, comparison 1a) showed that preoperative oral antibiotics combined with MBP reduce the SSI rate when compared to MBP only (OR: 0.56; 95% CI: 0.37–0.83). There was no difference in the occurrence of anastomotic leakage (OR: 0.64; 95% CI: 0.33–1.22; Appendix 4, comparison 1b).

   The quality of the evidence for this comparison was moderate due to the risk of bias (Appendix 5).

   Two trials *(27, 29)* reported specifically on SSI-attributable mortality. Both studies reported a lower mortality rate when oral antibiotics were administered, although they failed to report a test for statistical significance.

2. Thirteen trials comparing MBP vs. no MBP were identified. Of these, 12 trials *(9-12, 14, 17, 20, 22, 23, 26, 30, 31)* showed no statistically significant difference in the SSI rate between performing a preoperative MBP vs. not doing so. One study *(8)* showed a decrease of SSI when MBP was performed prior to the operation. Polyethylene glycol and/or sodium phosphate were the predominant agents of choice for MBP, although the protocols differed between the studies in terms of dosage and/or timing of the application. In 2 studies *(10, 31)*, patients undergoing rectal surgery were additionally given a single enema in both the intervention and the control group.

   A meta-analysis of the 13 trials (Appendix 4, comparison 2a) showed that preoperative MBP has neither benefit nor harm in reducing the SSI rate when compared to not carrying out a MBP at all (OR: 1.31; 95% CI: 1.00–1.72). In addition, a separate meta-analysis based on these studies (Appendix 4, comparison 2b) showed no difference in the occurrence of anastomotic leakage with or without MBP (OR: 1.03; 95% CI: 0.73–1.44).

The quality of the evidence for this comparison was moderate due to the risk of bias (Appendix 5).

Three trials reported specifically on SSI-attributable mortality *(11, 22, 31)*. None of the 3 studies reported on a statistical difference in the mortality rate.

In conclusion, the available evidence can be summarized as follows.

- **MBP and oral antibiotics versus MBP and no oral antibiotics** (Appendix 4, comparison 1a)
  Overall, a moderate quality of evidence shows that preoperative oral antibiotics combined with MBP reduce the SSI rate when compared to MBP only.

- **Preoperative MBP versus no MBP** (Appendix 4, comparison 2a)
  Overall, a moderate quality of evidence shows that preoperative MBP has no benefit in reducing the SSI rate when compared to not carrying out MBP at all.

  There was a heterogeneity regarding the protocols across the included studies. Polyethylene glycol and/or sodium phosphate were the agents of choice for MBP in most studies. The protocols differed between the trials in terms of dosage and/or timing of the application and fasting. Apart from the MBP regimen, the oral antibiotics and the drug of choice for intravenous antibiotic prophylaxis varied across the studies. In 8 trials, oral aminoglycosides were combined with anaerobic coverage (metronidazole *(13, 19, 21, 25, 28)* or erythromycin *(16, 18, 27)*) and 3 studies *(15, 24, 29)* applied a gram-negative coverage only. In the studies included for the comparison of MBP vs. no MBP, all patients received intravenous antibiotic prophylaxis according to the local protocol. In 2 of these studies, oral antibiotics were given also as part of a standard procedure to patients in both study groups. Most studies had a considerable risk of bias, particularly related to blinding of outcome assessors.

6. Other factors considered in the review of studies

The systematic review team identified the following other factors to be considered.

Potential harms

Overall, the meta-analyses results show that the use of antibiotics combined with MBP for preoperative bowel preparation reduces the incidence of SSI, which can be an expensive and complicated condition to treat. However, there are concerns about inducing potential antibiotic resistance and adverse events related to the oral antibiotics used (for example, high risk of idiosyncratic reaction with erythromycin). These harms could be even more important if the oral antibiotics are continued postoperatively as this intervention is restricted to the preoperative period only. Patient discomfort, electrolyte abnormalities and possible severe dehydration at the time of anaesthesia and incision are further concerns potentially associated with the use of MBP.

Values and preferences

Six studies comparing MBP combined with oral antibiotics *vs.* MBP alone reported on patient discomfort. One study *(15)* found a higher incidence of diarrhoea when oral antibiotics were administered. Another study *(13)* assessed patient tolerance with 3 different oral antibiotic regimes. Patients reported more gastrointestinal symptoms (that is, nausea and vomiting) at the time of preoperative preparation when given 3 doses of oral antibiotics compared to no oral antibiotics or one dose only. The remaining 4 studies *(18, 19, 21, 25)* found no differences in terms of adverse events such as nausea, vomiting, diarrhoea and abdominal pain related to the addition of oral antibiotics.

Among the studies comparing MBP with no MBP, 4 reported on patient discomfort. Barrera and colleagues *(8)* reported that half of all patients (50%) receiving MBP reported fair or poor tolerance. Main causes were related to symptoms of nausea (56%), vomiting (23%) and cramping abdominal pain (15%). In another study *(9)* including 89 patients with MBP, 17% complained of nausea or vomiting, 18% of abdominal pain and 28% about abdominal bloating. These disorders led to a stop of preoperative MBP in 11% of cases. In one study *(10)*, MBP was associated with discomfort in 22% of patients, including difficulty in drinking the preparation, nausea, vomiting and abdominal pain. Zmora and colleagues *(31)* found that diarrhoea in the early postoperative period was more common in the MBP compared to the non-MBP group and this difference reached statistical significance.

7. **Key uncertainties and future research priorities**

The systematic review team identified the following key uncertainties and future research priorities. Based on available evidence, no recommendation on the preferred type and dose of oral antibiotics can be made. Further research is needed on the effects of using oral antibiotics without MBP for the reduction of SSI rates, particularly well-designed RCTs comparing oral antibiotics and standard intravenous prophylactic antibiotics vs. standard intravenous prophylactic antibiotics only. A few studies evaluated the role of these interventions for patients undergoing laparoscopic procedures, but this merits further research and more studies are needed to draw firm conclusions. Some observational studies of mixed populations undergoing open and laparoscopic procedures suggested benefits from MBP across all groups. A RCT was recently published on this topic, but it could not be included in the systematic review due to the time limits of study inclusion. This study showed a significant reduction of SSI in laparoscopic patients receiving oral antibiotics in addition to MBP and standard intravenous antibiotic prophylaxis *(32)*.

APPENDICES

Appendix 1: Search terms

Medline (via OVID)
1. colorectal surgery/ or (colorectal surger* or colon surg* or rectal surger* or proctolog* or proctocolonic surg* or intestine surger*).ti,ab,kw.
2. exp anti-bacterial Aagents/ or antibiotic prophylaxis/ or antibiotic*.ti,ab,kw.
3. surgical wound infection/ or (surgical site infection* or SSI or SSIs or surgical wound infection* or surgical infection* or post-operative wound infection* or postoperative wound infection*).ti,ab,kw.
6. wound infection.mp. or exp wound infection/
7. exp infection control/ or exp decontamination/ or exp bacterial infections/ or exp gastrointestinal tract/ or exp digestive system/ or exp intensive care units/ or exp sulfones/ or exp anti-bacterial agents/ or exp cross infection/ or SDD.mp. or exp toxoplasmosis, animal/
8. decontamination.mp. or exp decontamination/
9. exp laxatives/ or (laxative* or laxantia* or purgative or cathartic agent or cathartic*).ti,ab,kw. or (bowel preparat* or intestine preparat* or colon preparat*).ti,ab,kw.
10. oral drug administration/ or oral*.ti,ab,kw.
11. 2 and 10
12. 7 or 8 or 9 or 11
13. 3 or 6
14. 1 and 12 and 13
15. limit 14 to yr="1990 -Current"

EMBASE
1. exp wound infection/
2. exp colorectal surgery/ or exp colon surgery/ or intestine surgery/ or (colorectal surger* or colon surg* or rectal surger* or proctolog* or proctocolonic surg* or intestine surger*).ti,ab,kw.
3. exp antibiotic agent/ or antibiotic prophylaxis/ or antibiotic*.ti,ab,kw.
4. surgical infection/ or (surgical site infection* or SSI or SSIs or surgical wound infection* or surgical infection* or post-operative wound infection* or postoperative wound infection*).ti,ab,kw.
5. 2 and 3 and 4
6. limit 5 to yr="1990 - 2014"
7. 1 or 4
8. 2 and 3 and 7
9. exp bacterial infection/ or exp colistin/ or exp cefotaxime/ or exp intensive care/ or exp digestive system/ or exp intensive care unit/ or exp amphotericin B/ or exp tobramycin/ or exp antibiotic agent/ or sdd.mp. or exp sulfone/
10. decontaminat*.mp.
11. oral drug administration/ or oral*.ti,ab,kw.
12. 3 and 11
13. 9 or 10 or 12
14. 2 and 7 and 13

15. exp laxative/ or (laxative* or laxantia* or purgative or cathartic agent or cathartic*).ti,ab,kw. or (bowel preparat* or intestine preparat* or colon preparat*).ti,ab,kw.
16. 9 or 10 or 12 or 15
17. 2 and 7 and 16
18. limit 17 to yr="1990 -Current"

CINAHL
1. (MH "wound infection")
2. (MH "surgical wound infection")
3. ("wound infection")
4. (MH “colorectal surgery”)
5. (“colon surgery”)
6. (“rectal surgery”)
7. (MH "mechanical bowel preparation")
8. ("colon preparation")
9. ("intestinal preparation")
10. (MH “administration, oral”)
11. (MH “antibiotics”)
12. 1 or 2 or 3
13. 4 or 5 or 6
14. 7 or 8 or 9
15. 10 and 11
16. 14 or 15
17. 12 and 13 and 16

Cochrane CENTRAL
1. wound infection:ti,ab,kw
2. surgical wound infection:ti,ab,kw
3. colorectal surgery:ti,ab,kw
4. selective digestive decontamination:ti,ab,kw
5. “oral antibiotic”:ti,ab,kw
6. mechanical bowel preparation:ti,ab,kw
7. 1 or 2
8. 4 or 5 or 6
9. 7 and 3 and 8

WHO regional medical databases
1. (ssi)
2. (surgical site infection)
3. (surgical site infections)
4. (Wound infection)
5. (Wound infections)
6. (postoperative wound infection)
7. (digestive decontamination)

8. (oral antibiotics)
9. (sdd)
10. (mechanical bowel)
11. (bowel preparation)
12. (colorectal surgery)
13. (colon surgery)
14. 1 or 2 or 3 or 4 or 5 or 6
15. 7 or 8 or 9
16. 10 or 11
17. 12 or 13
18. 15 or 16
19. 14 and 17 and 18

African Index Medicus
1. infection [key word]
2. surgical [key word]
3. surgery [key word]
4. 2 or 3
5. 1 and 4

ti: title; ab: abstract; kw: key word

Appendix 2: Evidence table

Appendix 2a: Studies on MBP and oral antibiotics vs. MBP and no oral antibiotics

Author, year, reference	Design, setting, population	Type of surgery	SSI /anastomotic leakage definition	Preoperative intravenous antibiotics and/or MBP	Intervention/ oral antibiotics	Microbiological coverage of the antibiotics gram-negative+ anaerobic yes/no	Absorbable or non-absorbable	Results
Espin-Basany, 2005 *(13)*	RCT single centre	Elective colorectal surgery.	Modified CDC guidelines (Horan et al 1992) No definition for anastomotic leakage.	MBP (sodium phosphate) and IV cefoxitin.	A) Neomycin 1 g and metronidazole 1g in 3 dd on day before surgery. B) Neomycin 1g and metronidazole 1g 1 dd on day before surgery. C) No oral antibiotics.	Yes	Neomycin: non-absorbable Metronidazole: absorbable	A) 100 patients SSI: 7/100; 2/100 with anastomotic leakage B) 100 patients SSI: 8/100; 2/100 with anastomotic leakage C) 100 patients SSI: 6/100; 3/100 with anastomotic leakage
Horie, 2007 *(15)*	RCT single centre	Elective surgery for colorectal cancer.	"Wound infection was indicated by presence of pus or discharge resulting in a positive bacteriological culture." No definition for anastomotic leakage.	MBP (polyethylene glycol) and 1 g cefotiam IV.	A) Kanamycin 1.5 g during 3 days before surgery. B) No oral antibiotics.	No Only gram-negative	Non- absorbable	A) 46 patients SSI: 10/46; 7/46 with anastomotic leakage B) 45 patients SSI: 5/45; 4/45 with anastomotic leakage
Ishida, 2001 *(16)*	RCT single centre	Elective colorectal surgery.	CDC guidelines "Anastomotic dehiscence was confirmed by clinical and/or radiographic examinations."	MBP (polyethylene glycol) and IV cefotiam 1g before and after surgery.	A) Kanamycin 500g and erythromycin 400 mg in 2 dd on 2 days before surgery. B) No oral antibiotics.	Kanamycin: gram-negative Erythromycin: minimal anaerobic activity	Kanamycin: non-absorbable Erythromycin: absorbable	A) 72 patients SSI: 8/72 (11.1%); 1/72 with anastomotic leakage B) 71 patients SSI: 17/71 (23.9%); 2/71 with anastomotic leakage
Kobayashi, 2007 *(18)*	RCT, multicentre, adult patients (>20 years of age)	Elective surgery for colorectal cancer.	CDC guidelines	MBP (2 l polyethylene glycol) and 1 g cefmetazole IV (prolonged if necessary).	A) Kanamycin 1g and erythromycin 400 mg in 3 dd on day before surgery. B) No oral antibiotics.	Kanamycin: gram-negative Erythromycin: minimal anaerobic activity	Kanamycin: non-absorbable Erythromycin: absorbable	A) 242 patients, SSI: 17/242 (7.0%) B) 242 patients SSI: 26/242 (10.7%)

Lewis, 2002 *(19)*	RCT single centre	Elective colon surgery.	CDC guidelines No definition for anastomotic leakage.	MBP (sodium phosphate) and intravenous amikacin and metronidazole.	A) Neomycin 1g and metronidazole 1 g in 2dd on day before surgery. B) Placebo	Yes	Neomycin: non-absorbable Metronidazole: absorbable	A) 104 patients SSI: 5/104; 3/104 with anastomotic leakage B) 104 patients SSI: 17/104; 1/104 with anastomotic leakage
Oshima, 2013 *(21)*	RCT single centre	Open restorative procto-colectomy with IPAA for ulcerative colitis.	According to the Japanese National Nosocomial Infections Surveillance system	MBP (1.8 L of magnesium citrate solution) and IV prophylaxis with second generation cephalosporin for 24 hours.	A) Kanamycin 500mg and metronidazole 1 mg in 3 dd on day before surgery. B) No oral antibiotics.	Yes	Kanamycin: non-absorbable Metronidazole: absorbable	A) 97 patients SSI: 6/97 (6.2%) B) 98 patients, SSI : 22/98 (22.4%)
Roos, 2011 *(24)*	RCT multicentre	Elective resection of the digestive tract with a primary anastomosis, with or without a diverting ileostomy or closure of a temporary colostomy.	"The clinical signs of a wound infection are purulent discharge, redness, swelling, tenderness and local warmth. The clinical diagnosis is confirmed by the isolation of ≥3+ or $\geq 10^5$ microorganisms and ≥++ leukocytes in the purulent discharge of the wound." Dehiscence of anastomosis identified by relaparotomy or computed tomography, and intra-abdominal abscess without obvious dehiscence."	MBP for colonic surgery 1500 mg cefuroxime and 500 mg metronidazole for 24 hours, at 8-hour intervals, starting 30 minutes before surgery.	A) Polymyxin B sulphate 100 mg, tobramycin 80 mg and amphotericin B 500 mg, in 4 dd from two days before surgery. B) Placebo	No anaerobic activity	Non-absorbable	A) 143 patients SSI: 10/143 (7.0%); 9/143 with anastomotic leakage B) 146 patients SSI: 19/146 (13.0%); 22/146 with anastomotic leakage

Sadahiro, 2014 *(25)*	RCT adult patients	Elective surgery for colon cancer.	"Within 30 days. Incisional SSI; infection with a discharge or the presence of gross pus or purulent exudates in the surgical wound. Organ/space SSI: infection in the organs/tissues in the area in which surgery was performed." No definition for anastomotic leakage.	MBP (10 ml of sodium picosulfate two days before surgery and 2 litres of polyethylene glycol–electrolyte sodium on day of surgery) IV prophylaxis with 1 g flomoxef.	A) Kanamycin 500 mg and metronidazole 500 mg in 3 dd on day of surgery. B) No oral antibiotics.	Yes	Kanamycin: non-absorbable Metronidazole: absorbable	A) 99 patients SSI: 10/99 (10.1%; 6 incisional and 4 organ/space), 1/99 with anastomotic leakage B) 95 patients SSI: 22/95 (23.2%; 17 incisional and 5 organ/space); 7/95 with anastomotic leakage
Stellato, 1990 *(27)*	RCT single centre	Elective colorectal surgery	"Evaluations of temperature and pulse, progress notes, results of postoperative culture."	MBP (magnesium citrate and sodium bi-phosphate/sodium phosphate enema) and IV prophylaxis 2 g cefoxitin.	A) Neomycin 1 g and erythromycin 1 g in 3 dd on day before surgery. B) No oral antibiotics.	Neomycin: gram-negative Erythromycin: minimal anaerobic activity	Neomycin: non-absorbable Erythromycin: absorbable	A) 51 patients, SSI: 6/51 (11.8%); 1/51 with anastomotic leakage B) 51 patients SSI: 2/51 (3.9%); 3/51 with anastomotic leakage
Takesue, 2000 *(28)*	RCT multicentre	Elective colorectal surgery	"Presence of pus or discharge resulting in a positive bacteriological culture. "Anastomotic dehiscence was confirmed by clinical and radiographic examination."	MBP (polyethylene glycol) and 1 g cefmetazole IV	A) Kanamycin 500 mg and metronidazole 500 mg in 3 dd on day of surgery. B) No oral antibiotics.	Yes	Kanamycin: non-absorbable Metronidazole: absorbable	A) 38 patients SSI: 2/38 (5.3%); 2/38 with anastomotic leakage B) 45 patients SSI: 4/45 (8.8%); 2/45 with anastomotic leakage
Taylor, 1994 *(29)*	RCT multicentre, adult patients	Elective colorectal surgery	"Based on clinical criteria with microbiologic confirmation whenever it was available."	MBP (sodium picosulfate) and piperacillin 4 g IV	A) Ciprofloxacin 500 mg in 2 dd on day before surgery. B) No oral antibiotics.	No anaerobic activity	Absorbable	A) 159 patients, SSI: 18/159 (11%) B) 168 patients SSI: 39/168 (23%) NB: patients with anastomotic leakage were withdrawn from the analysis

MBP: mechanical bowel preparation; dd: divided dose; SSI: surgical site infection; RCT: randomized controlled trial; CDC: Centers for Disease Control and Prevention; IV: intravenous; IPAA: ileal pouch-anal anastomosis.

Appendix 2b: Studies on MBP vs. no MBP

Author, year, reference	Design, setting, population	Type of surgery	SSI /anastomotic leakage definition	Preoperative prophylactic antibiotics	Intervention	Results
Barrera, 2012 *(8)*	RCT single centre	Elective colorectal surgery	Unknown ("both superficial and deep")	Cefazoline 1 g and metronidazole 500 mg IV	A) Sodium phosphate B) No MBP	A) 60 patients SSI: 4/60 (6.7%); 4/60 with anastomotic leakage B) 62 patients SSI: 12/62 (19.4%); 2/62 with anastomotic leakage
Bretagnol, 2010 *(9)*	RCT multicentre, adult patients	Sphincter-saving rectal resection for cancer	"Wound abscess" (unknown definition) Clinical anastomotic leakage defined as symptoms related to leakage were noted (i.e. gas, pus, or faecal discharge from the drain, peritonitis, discharge of pus per rectum).	IV Ceftriaxone 1 g and metronidazole 500 mg	A) Senna on day before surgery and 1 litre of povidone-iodine enema (night before and morning of surgery) B) No MBP	A) 89 patients SSI: 3/89 (3%); 6/89 with anastomotic leakage B) 89 patients SSI: 1/89 (1%); 14/89 with anastomotic leakage
Bucher, 2005 *(10)*	RCT dual centre, adult patients	Elective left-sided colorectal resection with primary anastomosis.	"Wound requiring partial or complete opening for drainage of a purulent collection, or erythema requiring initiation of antibiotic treatment." "Anastomotic dehiscence was defined by the demonstration of extraluminal leakage of contrast by imaging or was documented during reoperation."	Metronidazole and ceftriaxone IV	A) Polyethylene glycol (3 litres) on the day before surgery B) No MBP (one saline enema was given to patients undergoing rectal resection in both groups)	A) 78 patients SSI: 10/78 (13%); 5/78 with anastomotic leakage B) 75 patients SSI: 3/75 (4%); 1/75 with anastomotic leakage
Burke, 1994 *(11)*	RCT single centre	Elective left colonic or rectal resection.	Unknown "Anastomotic dehiscence was diagnosed clinically and suspected if there was deterioration in the general condition, abdominal distension, diarrhoea, or blond clot passed per anum, or signs of peritonitis. If necessary, leakage was confirmed radiologically using a water-soluble enema."	Ceftriaxone 1 g and metronidazole 500 mg IV	A) Sodium picosulphate 10 mg in 2 dd on the day before surgery B) No MBP	A) 82 patients SSI: 4/82 (4.9%); 3/82 with anastomotic leakage B) 87 patients SSI; 3/87 (3.4%); 4/87 with anastomotic leakage
Contant, 2007 *(12)*	RCT multicentre	Elective colorectal surgery.	"Wound infection was regarded as mild if it manifested only with erythema or discharge of seroma, and severe if it was characterised by discharge of pus, wound necrosis, or wound dehiscence." Anastomotic leakage: "Clinical suspicion based on persistent fever, abdominal pain, local or generalized peritonitis, or leucocytosis was followed by contrast radiography, CT	IV: Cefuroxim and metronidazole, cefazoline and metronidazole, cefamandole and metronidazole, gentamycin and metronidazole, amoxicillin-clavulanate or others	A) Polyethylene glycol (2-4 litres) and bisacodyl or sodium phosphate solution (at two hospitals). B) No MBP	A) 670 patients SSI: 90/670 (13.4%); 32/670 with anastomotic leakage B) 684 patients SSI: 96/684 (14.0%); 37/684 with anastomotic leakage

			scan, or laparotomy to substantiate the diagnosis."			
Fa-Si-Oen, 2005 *(14)*	RCT, multicentre	Elective colon surgery.	"Clinically significant infection of the skin for which the wound had to be evacuated." "Anastomotic leakage was defined as major when leakage was clinically significant leading to a relaparotomy and minor when leakage was subclinical, verified by radiographic examination, and treated conservatively."	IV: Cefazoline 2 g and metronidazole 1.5 g or gentamicin 240 mg and metronidazole 1.5 g	A) Polyethylene glycol 4L B) No MBP	A) 125 patients SSI: 9/125 (7.2%); 7/125 with anastomotic leakage B) 125 patients SSI: 7/125 (5.6%); 6/125 with anastomotic leakage
Jung, 2007 *(17)*	RCT multicentre, adult patients	Elective open colon surgery involving an anastomosis.	"Superficial infection needing surgical intervention in the wound." "Anastomotic leak verified at surgery or contrast radiography."	Oral sulfamethoxazole-trimethoprim and metronidazole in 46%, intravenous cephalosporin and metronidazole in 33%, and doxycycline and metronidazole in 14%	A) Polyethylene glycol or sodium phosphate B) No MBP	A) 686 patients SSI: 54/686 (7.9%); 13/686 with anastomotic leakage B) 657 patients SSI: 42/657 (6.4%); 17/657 with anastomotic leakage
Miettinen, 2000 *(20)*	RCT dual centre	Elective colorectal surgery.	"Presence of pus or discharge with positive bacteriologic culture." "Rupture of the anastomosis was detected by radiologic imaging using water-soluble contrast enema done on clinical grounds."	IV ceftriaxone 2 g and metronidazole 1 g	A) Polyethylene glycol electrolyte solution on day before surgery (until clear fluid was evacuated) B) No MBP	A) 138 patients SSI: 5/138 (4%); 5/138 with anastomotic leakage B) 129 patients SSI: 3/129 (2%); 3/129 anastomotic leakage
Pena-Soria, 2008 *(22)*	RCT single centre	Elective colon or proximal rectal resection with a primary anastomosis.	CDC guidelines "Anastomotic failure was diagnosed if there was a fecal fistula, an anastomotic dehiscence was identified at re-operation or during post mortem, and/or if clinical suspicion was confirmed by a radiological test (CT)."	Gentamicin 80 mg and metronidazole 500 mg IV	A) Oral polyethylene glycol B) No MBP	A) 65 patients SSI: 19/65 (29.2%); 4/65 with anastomotic leakage B) 64 patients SSI: 11/64 (17.2%); 3/64 with anastomotic leakage
Ram, 2005 *(23)*	RCT single centre	Elective colorectal surgery.	"The presence of pus or discharge resulting in a culture positive for bacteria." "Anastomotic dehiscence was detected by radiologic imaging using water-soluble contrast."	Metronidazole 500 mg and ceftriaxone 1g IV	A) Monobasic sodium phosphate 2.4 g and dibasic sodium phosphate 0.9 g B) No MBP	A) 164 patients SSI: 16/164 (9.8%); 1/164 with anastomotic leakage B) 165 patients SSI: 10/165 (6.1%); 2/165 with anastomotic leakage
Santos, 1994 *(26)*	RCT single centre	Elective colorectal surgery.	"Presence of pus or discharge resulting in a positive bacteriological culture." "Anastomotic dehiscence was confirmed on clinical, radiographic or intraoperative examination."	Cephalothin 2 g in 2 dd (followed by 1 g at 6 and 12 hours) and metronidazole 1g IV (followed by 500 mg at 8 and 16 hours)	A) Mineral oil, agar and phenolphthalein 15 ml in 3 dd for 5 days before surgery, enema in 1dd for 2 days before surgery and mannitol 1 L on the day before surgery B) No MBP	A) 72 patients SSI: 17/72 (24%); 7/72 with anastomotic leakage B) 77 patients SSI: 9/77 (12%); 4/77 with anastomotic leakage

Young Tabusso, 2002 *(30)*	RCT single centre	Elective surgery for colorectal cancer.	Unknown "Anastomotic dehiscence was evidenced by the discharge of intestinal contents through the drainage system and those who had abdominopelvic infection: peritonitis, abscess or purulent drainage with positive culture,"	"Antibiotics prophylaxis with anaerobic Gram-negative coverage"	A) Mannitol or polyethylene glycol on the day before surgery B) No MBP	A) 24 patients SSI: 2/24 (8.3%); 5/24 with anastomotic leakage B) 23 patients SSI: 0/23 (0%); 0/23 with anastomotic leakage
Zmora, 2003 *(31)*	RCT dual centre	Elective colon and rectal surgery with primary anastomosis.	"Wound requiring partial or complete opening for drainage of purulent collection, or erythema requiring initiation of antibiotic treatment," "Anastomotic leak was identified if demonstrated by imaging or documented in surgery, or if fecal drainage was evident through a peri-anastomotic drain,"	1 g neomycin and 1 g erythromycin in 3 dd orally on the day before surgery and 500 mg metronidazole, 240 mg gentamicin, and 1 g ampicillin IV	A) Polyethylene glycol (1 gallon) on day before surgery B) No MBP (one phosphate enema was given to patients undergoing rectal surgery in both groups)	A) 187 patients SSI: 12/187 (6.4%); 7/187 with anastomotic leakage B) 193 patients SSI: 11/193 (5.7%); 4/193 with anastomotic leakage Mortality: 4 deaths, none was attributed to surgical infectious complications

MBP: mechanical bowel preparation; dd: divided dose; SSI: surgical site infection; RCT; randomized clinical trial; CDC: Centers for Disease Control and Prevention; IV: intravenous, CT: computed tomography

Appendix 3: Risk of bias assessment of the included studies

Appendix 3a: Studies on MBP and oral antibiotics vs. MBP and no oral antibiotics

Author, year, reference	Sequence generation	Allocation concealment	Participants blinded	Care providers blinded	Outcome assessors blinded	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Espin-Basany, 2005 *(13)*	Unclear	Unclear	High risk	Unclear	Low risk	Low risk	Low risk	-
Horie, 2007 *(15)*	Low risk	Low risk	High risk	Unclear	Unclear	Low risk	Low risk	-
Ishida, 2001 *(16)*	Low risk	Low risk	High risk	Low risk	Unclear	Low risk	Low risk	-
Kobayashi, 2007 *(18)*	Low risk	Low risk	High risk	Unclear	Unclear	Low risk	Low risk	-
Lewis, 2002 *(19)*	Unclear	Unclear	High risk	Unclear	Unclear	Low risk	Low risk	-
Oshima, 2013 *(21)*	Unclear	Unclear	High risk	Unclear	Unclear	Low risk	Low risk	-
Roos, 2011 *(24)*	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	-
Sadahiro, 2014 *(25)*	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	-
Stellato, 1990 *(27)*	Low risk	Low risk	High risk	Unclear	Unclear	Low risk	Low risk	-
Takesue, 2000 *(28)*	Unclear	Unclear	High risk	Unclear	Unclear	Low risk	Low risk	-
Taylor, 1994 *(29)*	Low risk	Low risk	High risk	Unclear	Unclear	Low risk	Low risk	-

MBP: mechanical bowel preparation

Appendix 3b: Studies on MBP vs. no MBP

Author, year, reference	Sequence generation	Allocation concealment	Participants blinded	Care providers blinded	Outcome assessors blinded	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Barrera, 2012 *(8)*	Low risk	Low risk	High risk	High risk	Unclear	Low risk	Low risk	-
Bretagnol, 2010 *(9)*	Low risk	Low risk	High risk	Low risk	Unclear	Low risk	Low risk	-
Bucher, 2005 *(10)*	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk	-
Burke, 1994 *(11)*	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Low risk	-
Contant, 2007 *(12)*	Low risk	Low risk	High risk	High risk	High risk	Low risk	Low risk	-
Fa-Si-Oen, 2005 *(14)*	Low risk	Low risk	High risk	High risk	Unclear	Low risk	Low risk	-
Jung, 2007 *(17)*	Low risk	Low risk	High risk	High risk	Unclear	Low risk	Low risk	-
Miettinen, 2000 *(20)*	Low risk	Low risk	High risk	High risk	Unclear	Low risk	Low risk	-
Pena-Soria, 2008 *(22)*	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	-
Ram, 2005 *(23)*	High risk	High risk	High risk	High risk	Unclear	Low risk	Low risk	-
Santos, 1994 *(26)*	Low risk	Unclear	High risk	High risk	Unclear	Low risk	Low risk	-
Young Tabusso, 2002 *(30)*	Unclear	Unclear	High risk	High risk	Unclear	Unclear	Unclear	-
Zmora, 2003 *(31)*	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Low risk	-

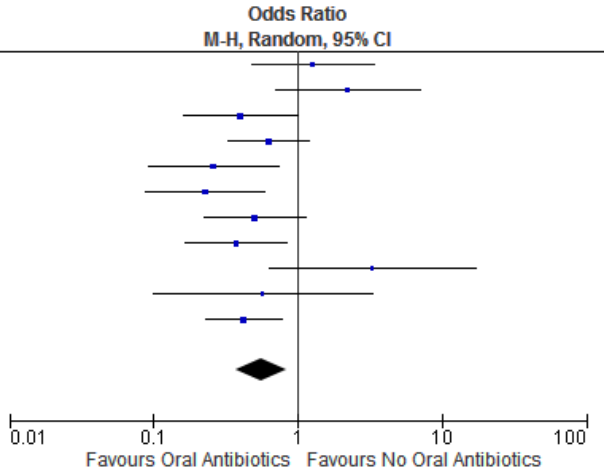
MBP: mechanical bowel preparation

Appendix 4: Comparisons

Comparison 1a: MBP and oral antibiotics vs. MBP and no oral antibiotics, outcome SSI

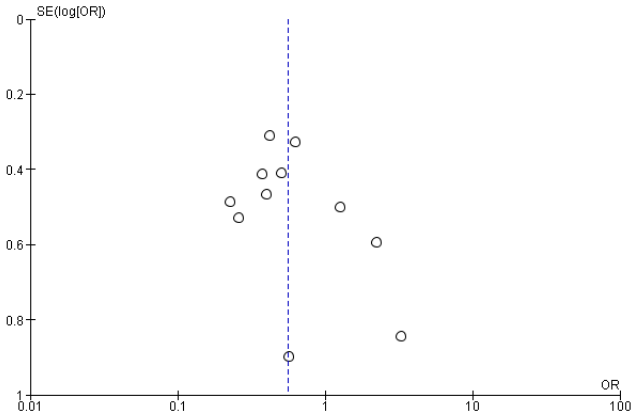
Study or Subgroup	Oral Antibiotics Events	Oral Antibiotics Total	No Oral Antibiotics Events	No Oral Antibiotics Total	Weight	Odds Ratio M-H, Random, 95% CI
Espin-Basany 2005	15	200	6	100	9.0%	1.27 [0.48, 3.38]
Horie 2007	10	46	5	45	7.3%	2.22 [0.69, 7.12]
Ishida 2001	8	72	17	71	9.6%	0.40 [0.16, 0.99]
Kobayashi 2007	17	242	26	242	12.9%	0.63 [0.33, 1.19]
Lewis 2002	5	104	17	104	8.4%	0.26 [0.09, 0.73]
Oshima 2013	6	97	22	98	9.2%	0.23 [0.09, 0.59]
Roos 2011	10	143	19	146	10.8%	0.50 [0.23, 1.12]
Sadahiro 2014	10	99	22	95	10.8%	0.37 [0.17, 0.84]
Stellato 1990	6	51	2	51	4.5%	3.27 [0.63, 17.02]
Takesue 2000	2	38	4	45	4.1%	0.57 [0.10, 3.29]
Taylor 1994	18	159	39	168	13.3%	0.42 [0.23, 0.78]
Total (95% CI)		**1251**		**1165**	**100.0%**	**0.56 [0.37, 0.83]**
Total events	107		179			

Heterogeneity: Tau² = 0.22; Chi² = 20.35, df = 10 (P = 0.03); I² = 51%
Test for overall effect: Z = 2.85 (P = 0.004)



MBP: mechanical bowel preparation; SSI: surgical site infection; M-H: Mantel-Haenszel (test**);** CI: confidence interval

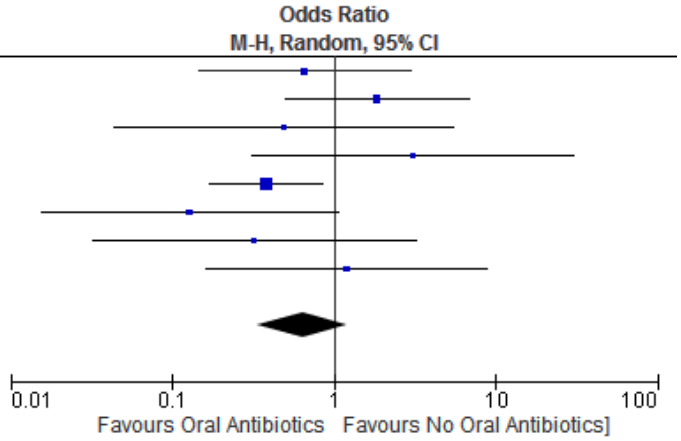
Funnel plot of comparison 1a:



Comparison 1b: MBP and oral antibiotics vs. MBP and no oral antibiotics, outcome anastomotic leakage

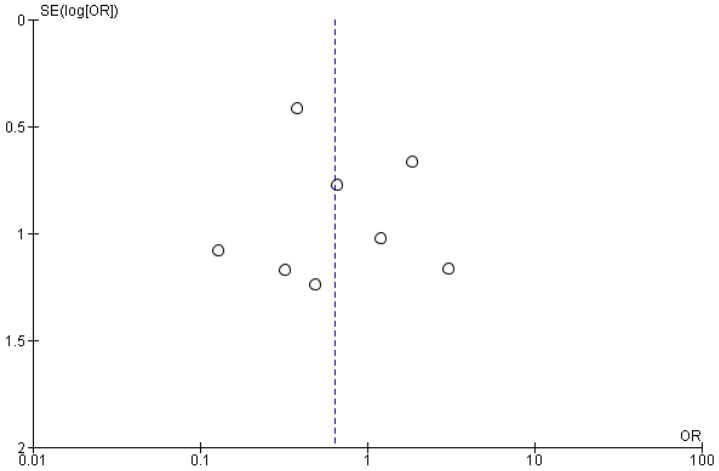
Study or Subgroup	Oral Antibiotics Events	Total	No Oral Antibiotics Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Espin-Basany 2005	4	200	3	100	14.0%	0.66 [0.14, 3.01]
Horie 2007	7	46	4	45	17.5%	1.84 [0.50, 6.78]
Ishida 2001	1	72	2	71	6.4%	0.49 [0.04, 5.48]
Lewis 2002	3	104	1	104	7.1%	3.06 [0.31, 29.90]
Roos 2011	9	143	22	146	31.0%	0.38 [0.17, 0.85]
Sadahiro 2014	1	99	7	95	8.1%	0.13 [0.02, 1.06]
Stellato 1990	1	51	3	51	7.0%	0.32 [0.03, 3.18]
Takesue 2000	2	38	2	45	8.9%	1.19 [0.16, 8.91]
Total (95% CI)		**753**		**657**	**100.0%**	**0.64 [0.33, 1.22]**
Total events	28		44			

Heterogeneity: Tau² = 0.18; Chi² = 8.87, df = 7 (P = 0.26); I² = 21%
Test for overall effect: Z = 1.36 (P = 0.17)



MBP: mechanical bowel preparation; M-H: Mantel-Haenszel (test); CI: confidence interval

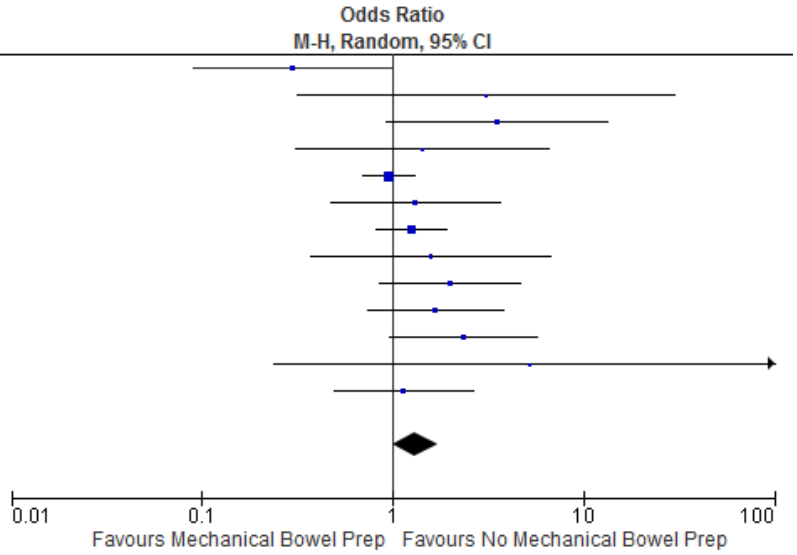
Funnel plot of comparison 1b:



Comparison 2a: MBP vs. no MBP, outcome SSI

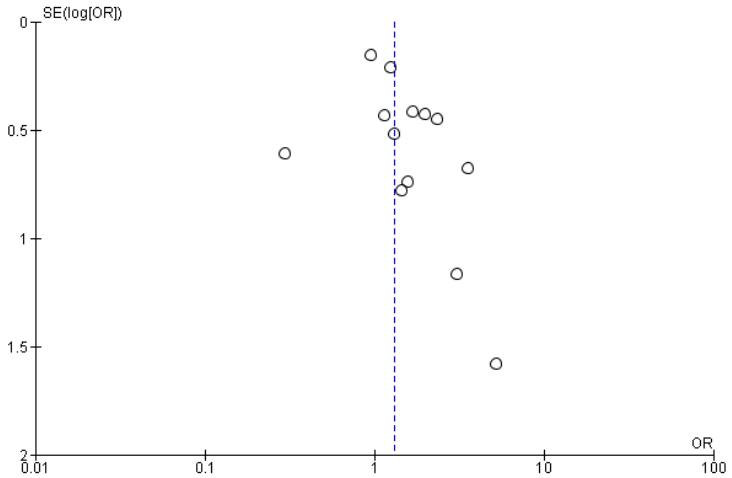
Study or Subgroup	Mechanical Bowel Prep Events	Total	No Mechanical Bowel Prep Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Barrera 2012	4	60	12	62	4.6%	0.30 [0.09, 0.98]
Bretagnol 2010	3	89	1	89	1.4%	3.07 [0.31, 30.09]
Bucher 2005	10	78	3	75	3.8%	3.53 [0.93, 13.37]
Burke 1994	4	82	3	87	3.0%	1.44 [0.31, 6.62]
Contant 2007	90	670	96	684	24.9%	0.95 [0.70, 1.30]
Fa-Si-Oen 2005	9	125	7	125	6.0%	1.31 [0.47, 3.63]
Jung 2007	54	686	42	657	19.7%	1.25 [0.82, 1.90]
Miettinen 2000	5	138	3	129	3.2%	1.58 [0.37, 6.74]
Pena-Soria 2008	19	65	11	64	8.2%	1.99 [0.86, 4.61]
Ram 2005	16	164	10	165	8.5%	1.68 [0.74, 3.81]
Santos 1994	17	72	9	77	7.6%	2.34 [0.97, 5.65]
Young Tabusso 2002	2	24	0	23	0.8%	5.22 [0.24, 114.87]
Zmora 2003	12	187	11	193	8.2%	1.13 [0.49, 2.64]
Total (95% CI)		**2440**		**2430**	**100.0%**	**1.31 [1.00, 1.72]**
Total events	245		208			

Heterogeneity: Tau² = 0.05; Chi² = 15.94, df = 12 (P = 0.19); I² = 25%
Test for overall effect: Z = 1.93 (P = 0.05)



MBP: mechanical bowel preparation; SSI: surgical site infection; Mantel-Haenszel **(**test); CI: confidence interval

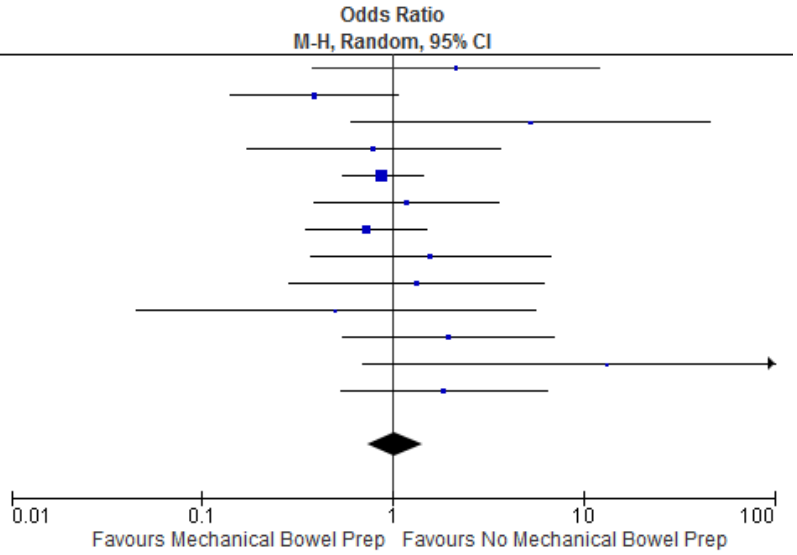
Funnel plot of comparison 2a:



Comparison 2b: MBP vs. no MBP, outcome anastomotic leakage

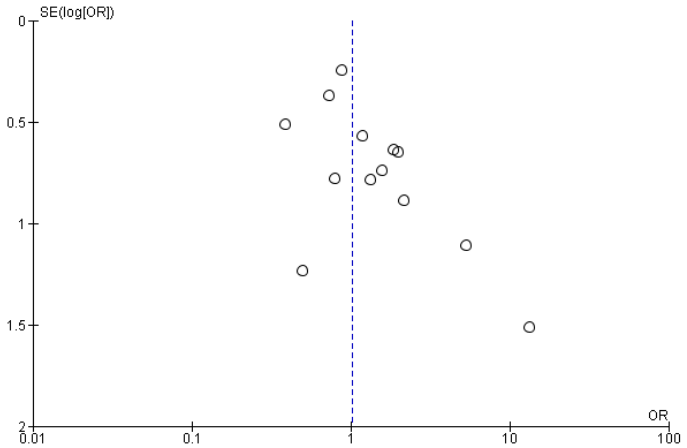
Study or Subgroup	Mechanical Bowel Prep Events	Total	No Mechanical Bowel Prep Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Barrera 2012	4	60	2	62	3.6%	2.14 [0.38, 12.16]
Bretagnol 2010	6	89	14	89	9.8%	0.39 [0.14, 1.06]
Bucher 2005	5	78	1	78	2.3%	5.27 [0.60, 46.23]
Burke 1994	3	82	4	87	4.6%	0.79 [0.17, 3.63]
Contant 2007	32	670	37	684	29.2%	0.88 [0.54, 1.43]
Fa-Si-Oen 2005	7	125	6	125	8.1%	1.18 [0.38, 3.61]
Jung 2007	13	686	17	657	16.6%	0.73 [0.35, 1.51]
Miettinen 2000	5	138	3	129	5.0%	1.58 [0.37, 6.74]
Pena-Soria 2008	4	65	3	64	4.5%	1.33 [0.29, 6.21]
Ram 2005	1	164	2	165	1.9%	0.50 [0.04, 5.57]
Santos 1994	7	72	4	77	6.4%	1.97 [0.55, 7.02]
Young Tabusso 2002	5	24	0	23	1.3%	13.26 [0.69, 254.97]
Zmora 2003	7	187	4	193	6.7%	1.84 [0.53, 6.38]
Total (95% CI)		**2440**		**2433**	**100.0%**	**1.03 [0.73, 1.44]**
Total events	99		97			

Heterogeneity: Tau² = 0.04; Chi² = 13.42, df = 12 (P = 0.34); I² = 11%
Test for overall effect: Z = 0.14 (P = 0.89)



MBP: mechanical bowel preparation; SSI: surgical site infection; Mantel-Haenszel **(**test); CI: confidence interval

Funnel plot of comparison 2b:



Appendix 5: Grade tables

Comparison 1a: MBP and oral antibiotics *vs.* MBP and no oral antibiotics

Quality assessment							№ of patients		Effect		Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mechanical bowel prep with oral antibiotics**	**Mechanical bowel prep without oral antibiotics**	**Relative (95% CI)**	**Absolute (95% CI)**	
Surgical site infection											
11	RCTs	serious [1]	not serious	not serious	not serious	none	107/1251 (8.6%)	179/1165 (15.4%)	**OR: 0.56** (0.37 to 0.38)	**61 fewer per 1.000** (from 89 fewer to 91 fewer)	⊖⊖⊖◯ MODERATE

1. Risk of detection bias

MBP: mechanical bowel preparation; RCT: randomized controlled trial; CI confidence interval; OR: odds ratio

Comparison 2a: MBP *vs*. no MBP

Quality assessment							№ of patients		Effect		Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**With mechanical bowel prep**	**Without mechanical bowel prep**	**Relative (95% CI)**	**Absolute (95% CI)**	
Surgical site infection											
13	RCTs	serious [1]	not serious	not serious	not serious	none	245/2440 (10.0%)	208/2430 (8.6%)	**OR: 1.31** (1.00 to 1.72)	**24 more per 1.000** (from 1 fewer to 53 more)	⊕⊕⊕◯ MODERATE

1. Risk of detection bias

MBP: mechanical bowel preparation; RCT: randomized controlled trial; CI: confidence interval; OR: odds ratio

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