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Bowel Preparation for Elective Colorectal Procedures: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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Abbreviations

ABX	Antibiotic prophylaxis
ACS	American College of Surgeons
APR	Abdominoperineal resection
ASCRS	American Society of Colon and Rectal Surgeons
ASHP	American Society of Hospital Pharmacists
CD	Crohn's disease
CI	Confidence interval
CRC	Colorectal cancer
CXM	Cefuroxime and metronidazole
IDSA	Infectious Diseases Society of Health-System Pharmacists
IV	Intravenous antibiotic prophylaxis
MBP	Mechanical bowel preparation
NR	Not reported
OR	Odds ratio
PO	Oral antibiotic prophylaxis
RCT	Randomized controlled trial
RR	Risk ratio
SAGES	Society of American Gastrointestinal and Endoscopic Surgeons
SD	Standard deviation
SHEA	Society for Healthcare Epidemiology of America
SIS	Surgical Infection Society
SSI	Surgical site infection
SWI	Surgical wound infection
TSM	Trimethoprim-sulfamethoxazole and Metronidazole
UC	Ulcerative colitis
WHO	World Health Organization

Context and Policy Issues

The risk of abdominal surgical site infection after surgery on the large intestine without antibiotics is significant, with one estimate indicating that the incidence is approximately 40%.[1] The possible downstream effects of surgical site infections include prolonged hospital stay, increased hospital readmission, and mortality.[1] The use of perioperative parenteral antibiotics (e.g., second-generation cephalosporins with aerobic and anaerobic coverage administered intravenously) is well-established and commonly recommended in colorectal surgical guidelines.[2] Recommendations on the use of mechanical bowel preparation and oral antibiotic prophylaxis for colorectal surgery are also found in recent guidelines for colorectal surgery, but there has been historical debate on the optimal approach; specifically, the value of including oral antibiotics and/or mechanical bowel preparations as part of the standard preoperative regimen for elective colorectal procedures.

At least one frequently-cited 2013 surgical guideline[3] and a 2011 systematic review[4] have recommended against the routine use of mechanical bowel preparation in colonic surgery due to lack of clear benefit as compared to no mechanical bowel preparation; the distress that mechanical bowel preparation administration may cause patients, and; the potential adverse effects on postoperative complications (e.g., fluid status and the consequent need for additional, downstream intervention). Similarly, evidence-based recommendations produced by the Canadian Society of Colon and Rectal Surgeons in 2010 reported finding sufficient evidence to recommend against the routine use of mechanical bowel preparation in elective colorectal procedures.[5]

Oral antibiotics may also be used prior to colorectal surgery with the intent to reduce postoperative surgical site infection.[2] Orally administered drugs such as neomycin and kanamycin have been used in this context because they have good activity against colonic bacterial species and can achieve high intraluminal concentration with minimal systemic absorption.[6,7] However, a recent CADTH report investigating the role of orally-administered neomycin in patients undergoing elective colorectal procedures identified no evidence to inform its use.[8]

While there is evidence to suggest that mechanical bowel preparation should not be used in isolation,[9] there is renewed interest in determining the value of adding oral antibiotics to the preoperative regimen for elective colorectal procedures. For instance, a recent retrospective database analysis has suggested that there may be an important role for the combination of mechanical bowel preparation and oral antibiotics in reducing postoperative surgical site infections in elective colorectal surgery.[10] Thus, this report aims to review relevant evidence addressing the clinical effectiveness, cost-effectiveness, and evidence-based guidelines for the use of standard, parenteral antibiotic prophylaxis with or without mechanical bowel preparation versus intravenous plus oral antibiotic prophylaxis with or without mechanical bowel preparation for patients undergoing elective colorectal procedures.

Research Questions

1. What is the comparative clinical effectiveness of parenteral prophylaxis versus parenteral prophylaxis plus oral antibiotics, with or without mechanical bowel preparation, as part of preparation for elective colorectal procedures?
2. What is the cost-effectiveness of parenteral prophylaxis versus parenteral prophylaxis plus oral antibiotics, with or without mechanical bowel preparation, as part of preparation for elective colorectal procedures?
3. What are evidence-based guidelines informing the use of parenteral prophylaxis versus parenteral prophylaxis plus oral antibiotics, with or without mechanical bowel preparation, as part of preparation for elective colorectal procedures?

Key Findings

Three systematic reviews and five randomized controlled trials were identified describing the clinical effectiveness of antibiotic prophylaxis as part of bowel preparation for elective colorectal procedures. No evidence describing cost-effectiveness was identified and seven evidence-based guidelines were found to be eligible for this review. Most studies reporting on clinical effectiveness investigated surgical site infections in patients receiving combined intravenous and oral antibiotic prophylaxis versus intravenous antibiotic prophylaxis only

(most often with mechanical bowel preparation). Three systematic reviews of good quality and four randomized controlled trials of variable quality reported statistically significant improvements in surgical site infections for patients receiving combined intravenous and oral antibiotic prophylaxis as compared to patients receiving intravenous antibiotic prophylaxis only. Whereas rates of incisional surgical site infections were generally found to also be reduced in patients receiving combined intravenous and oral antibiotic prophylaxis as compared to patients receiving intravenous antibiotic prophylaxis only, differences were not generally observed in organ/space infections. Across three studies reporting on adverse effects, there were few statistically differences observed between groups. Guidelines generally favoured the use of intravenous and oral antibiotics (either alone or combined), with some recommending the use of mechanical bowel preparation in combination with intravenous and/or oral antibiotics, and others recommending that mechanical bowel preparation not be used at all. The authors of most included sources either concluded or recommended that combination oral and intravenous antibiotic prophylaxis be used for reducing surgical site infection in patients undergoing elective colorectal procedures.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Medline and Embase, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2013 and June 13, 2018.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first phase of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for eligibility. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients preparing to undergo elective colorectal procedures (e.g., planned procedures such as hemicolectomy, sigmoid colectomy, anterior resection)
Intervention	Parenteral prophylaxis (i.e., intravenous antibiotics) with or without mechanical bowel preparation
Comparator	Parenteral prophylaxis plus oral antibiotics (e.g., neomycin and metronidazole, kanamycin, or any viable alternatives for use in a Canadian context) with or without mechanical bowel preparation
Outcomes	Q1: Comparative clinical effectiveness i.e., benefits (e.g., decreased postop infection) or harms (e.g. infection, anastomotic leak, intra-abdominal infections, ileus, repeat procedure, readmission) Q2: Cost-effectiveness Q3: Evidence-based guidelines
Study Designs	Health Technology Assessments, Systematic Reviews or Meta-Analyses , randomized controlled studies, evidence based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, were duplicate publications, were primary studies included within systematic reviews eligible for the current review, or were published prior to 2013. Guidelines with an unclear method for developing recommendations and guidance were also excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using AMSTAR 2;[11] randomized controlled trials were critically appraised using the Down's and Black checklist,[12] and; guidelines were assessed with the AGREE II instrument.[13] Summary scores were not calculated for the included studies — rather, a description of the strengths and limitations of each included study were narratively summarized.

Summary of Evidence

Quantity of Research Available

A total of 422 citations were identified in the literature search. Following screening of titles and abstracts, 387 citations were excluded and 35 potentially relevant reports from the electronic search were retrieved for full-text review. Five potentially relevant publications were retrieved from the grey literature search for full text review. Of the 40 potentially relevant articles, 25 sources were excluded for various reasons, and 15 publications were eligible for inclusion within this report. These comprised three systematic reviews, five RCTs, and seven evidence-based guidelines. Appendix 1 presents the PRISMA[14] flowchart of the study selection.

Additional references of potential interest are provided in Appendix 6.

Summary of Study Characteristics

Of the 15 publications included in this review, eight addressed clinical effectiveness and seven addressed guidance and recommendations of relevance to bowel preparation for elective colorectal procedures. No eligible studies were identified addressing cost-effectiveness.

Study Design

Three of the eight studies addressing clinical effectiveness were systematic reviews (SRs) published between 2014 and 2016,[1,15,16] and included between seven[15] and 27[1] relevant primary studies reporting on between 1,769[15] and 59,323[16] patients. There was considerable overlap between the SRs, with multiple primary studies being included in more than one included SR. This overlap is detailed in Appendix 5. The other five studies addressing clinical effectiveness were randomized controlled trials (RCTs) published between 2015 and 2017, and evaluating between 190[17] and 1,073[18] patients.[17-21] Notably, one of the five RCTs employed a non-inferiority design.[21]

Seven eligible guidelines produced by a variety of both national and international developers were identified.[2,9,22-26] The guidelines were produced by multiple groups; several developed by a single group or entity, and several developed jointly by two or more groups or entities. Guidelines developed by a single group included those from the American College of Surgeons and Surgical Infection Society;[22] American Society of Colon and

Rectal Surgeons;[24] the American Pediatric Surgical Association,[25] and; the World Health Organization.[9] Jointly-produced guidelines included those developed by the American Society of Colon and Rectal Surgeons and the Society of American Gastrointestinal and Endoscopic Surgeons;[26] the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), the Surgical Infection Society (SIS), and the Society for Healthcare Epidemiology of America (SHEA),[2] and; the Association of Surgeons of Great Britain and Ireland and The Association of Coloproctology of Great Britain and Ireland.[23] There was variability observed in the extent to which guidelines explicitly relied on an rigorous evidence collection and synthesis process; whereas some guidelines reported a systematic review,[2,9,23,25,26] others were unclear as to the methods used to collect, synthesize and/or incorporate evidence.[22,24]

Country of Origin

The SRs were published by authors from China[15] and the UK.[1,16] The RCTs were conducted in China,[17] Japan[19,20] and Sweden.[18] Guidelines were produced by groups from the USA,[2,22,24-26] UK,[23] and the international World Health Organization (WHO).[9]

Patient Population

Two SRs explicitly investigated outcomes in patients undergoing elective colorectal surgery,[15,16] whereas one SR considered outcomes in patients undergoing both elective and emergency colorectal surgery.[1] Two RCTs investigated outcomes in patients undergoing elective laparoscopic colorectal surgery for colorectal cancers;[20,21] one RCT investigated patients undergoing elective colorectal surgery for multiple indications;[17] one RCT investigated patients undergoing elective colorectal surgery for unspecified indication(s);[18] and one RCT investigated patients with Crohn's disease undergoing intestinal resection.[19]

Two guidelines were intended for application to patients undergoing colorectal surgery,[25,26] — one specific to children[25] and the other not explicit about a particular age range.[26] Three guidelines were intended for application to patients undergoing a variety of types of surgeries (with specific subsections addressing colorectal surgeries);[2,9,22] one guideline was intended for application to patients undergoing surgery for sigmoid diverticulitis[24] and; another was specific to the prevention and management of anastomotic leakage resulting from colorectal surgery.[23]

Interventions and Comparators

The eight studies addressing clinical effectiveness reported on a variety of comparisons between oral and intravenous antibiotics, with all but two[1,18] explicitly reporting on the use of mechanical bowel preparation as part of the preparatory regimen.[15-17,19-21] Comparisons of oral and intravenous antibiotic prophylaxis included: oral-only versus intravenous-only [1,16,18] oral plus intravenous versus intravenous-only, and;[15-17,19-21] oral plus intravenous versus oral-only.[16]

The seven guidelines presented recommendations and guidance specific to the use of oral antibiotics and mechanical bowel preparation,[9,22,24-26] as well as oral plus intravenous antibiotics and mechanical bowel preparation,[22] and; oral and intravenous antibiotics.[2,23]

Outcomes

Surgical site infection was described as an outcome of interest in all eight of the included studies reporting on clinical effectiveness,[1,15-21] with many also describing specific types of

infection by location (e.g., incisional, organ/space, superficial, deep).[15,17-21] Three of the included RCTs also reported on adverse effects, including anastomotic leakage, intra-abdominal abscess, post-operative complications, septicemia, pneumonia, urinary tract infection, post-operative antibiotic administration, post-operative hospital stay, and number of health care encounters for surgical site infection.[17,18,21]

Similarly, the seven included guidelines focused on surgical site infection with other outcomes of interest including complications, morbidity, anastomotic leakage, *C difficile,* ileus, abscess, length of hospital stay and readmission to hospital.[2,9,22-26]

Additional details regarding the characteristics of included sources are provided in Appendix 2.

Summary of Critical Appraisal

Systematic Reviews

Assessment of the three SRs included in this review using the AMSTAR II instrument[11] indicated that the reviews were generally well-conducted and well-reported, with a few demonstrated limitations. In terms of strengths, all three SRs made reference to an a priori design, reported a comprehensive search, study selection and data abstraction conducted by two independent reviewers, and provided a detailed list of included studies as well as a description of study characteristics. In addition, all three SRs conducted critical appraisal of included primary studies, incorporated these findings into their interpretation and conclusions, and performed appropriate quantitative syntheses. However, while one SR explicitly provided a list of excluded studies,[1] two did not.[15,16] Further, whereas two SRs addressed publication status,[1,15] one did not, [16] leaving uncertainty with regard to the latter SR as to whether its included studies are representative of the entire body of both published and unpublished evidence. Finally, none of the three SRs explicitly addressed publication bias,[1,15,16] which is an important factor in understanding the extent to which findings from included, published studies could over-represent any observed effect.

Randomized Controlled Trials

Clarity of reporting is critical to a transparent assessment of the strengths and limitations of primary studies included in any review. Study reporting was clear for most criteria across the five RCTs included in this review, with hypotheses, objectives, main outcomes, patient characteristics, interventions, random variability, adverse events and probability values clearly described.[17-21] However, whereas four of the five RCTs also described the distribution of principal confounders, one did not.[18] On the other hand, none of the included RCTs described the characteristics of patients lost to follow-up (though, one of these did report that no patients were lost to follow-up[21]). Because some information was lacking from the reports of the studies included in this review, the quality of their reporting could not be assessed completely.

Likewise, it was not possible to assess any of the items addressing external validity for the five included RCTs, as details about the representativeness of subjects asked to participate; patients who consented to participate, and; the interventions administered, were either not reported or not reported in sufficient detail to assess.[17-21] Because external validity could not be ascertained for the RCTs, it remains unclear whether their findings can appropriately be applied to other, similar patients. In addition to external validity, an understanding of internal validity in general, including risk of bias and confounding in particular, is critical to informing the interpretation of a study. In this review, the risks of bias

and confounding observed across the five RCTs was found to vary i.e., while all of the trials presented detailed descriptions of appropriate outcome measures; recruited patients from the same population and time period; suggested compliance with the interventions; used ostensibly appropriate statistical tests; presented detailed descriptions of appropriate outcome measures, and; demonstrated no evidence of unplanned analyses, none of the five RCTs were able to blind patients to the assigned interventions.[17-21] And whereas four of the five RCTs reported blinded outcome assessment,[17-19,21] it was unclear whether outcome assessment was blind for the remaining RCT.[20] Similarly, while four of the RCTs reported concealment of the randomized assignment,[17,18,20,21] one trial did not clearly describe whether randomization was concealed.[19] Further, it was unclear whether three of the RCTs adequately adjusted for variable follow-up duration.[17,19,20] Lastly, methods for handling patient loss to follow-up was unclear in three of the RCTs.[18-20]

Finally, a power calculation is a critical component when considering the adequacy of sample size used in a study — which is a fundamental consideration in weighing the importance of its findings and conclusions, as it serves as an indicator of the probability of avoiding a Type II error (i.e., finding an apparent effect among the sampled patients in a study where no effect actually exists).In this review, all five RCTs reported sufficient study power and addressed conflicts of interest,[17-21] which may increase confidence in their reported findings.

Guidelines

For the seven guidelines included in this review, six domains were considered as part of the assessment using the AGREE II instrument:[13] scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability and editorial independence. Scope and purpose were generally well described, with all but two of the guidelines clearly reporting on these items.[9,22,24-26] Of the remaining two guidelines, two failed to explicitly state the health questions being addressed[2,23] and one also failed to explicitly describe the objectives of the guideline.[23] Stakeholder involvement was described variably across the guidelines, with one reporting clearly on the composition of the guideline development group, the intended target users and efforts to engage with the target population to solicit their views and preferences,[9] whereas the remaining six guidelines only reported some of these criteria explicitly.[2,22-26] Clarity of presentation was thorough in five of the seven guidelines,[9,22,24-26] whereas two of the guidelines did not present easily identifiable recommendations,[2,23] and one failed to make explicit recommendations altogether and did not explicitly present different options for the prevention of anastomotic leakage.[23] Similarly, rigour of development as reported by the seven included guidelines varied, with two guidelines reporting most criteria to warrant a rigorous process,[9,25] and the remaining five demonstrating some evidence of a rigorous development process combined with some important criteria left undescribed.[2,22-24,26] The applicability of the guidelines included in this review was generally not reported in detail, with only one reporting on any items of relevance.[9] Similarly, whereas two guidelines were transparent about editorial independence,[9,26] most of the included guidelines either failed to report on their funding source(s) and/or reported at least some support from private industry.[2,22-25]

Additional details regarding the strengths and limitations of included sources are provided in Appendix 3.

Summary of Findings

Clinical Effectiveness of Bowel Preparation for Elective Colorectal Surgery

Surgical Site Infection (SSI) — Oral-only (PO) versus Intravenous-only (IV) Antibiotics

Three studies reported data on SSIs in patients receiving oral versus intravenous antibiotics — with or without mechanical bowel preparation (MBP) — two SRs[1,16] and one RCT[18] Whereas Koullouros and colleagues reported a significant improvement in SSIs in patients receiving either PO as opposed to IV (both with MBP) in a meta-analysis of 11 RCTs (odds ratio [OR] 1.82; 95% confidence interval [CI] 1.28 to 2.58; $P < 0.0008$),[16] Nelson and colleagues reported no difference in surgical wound infections (SWI) in patients receiving either PO or IV (receipt of MBP was not described) in a meta-analysis of three RCTs (RR 2.31; 95% CI 0.60 to 8.83; $P = 0.22$).[1] Hjalmarrson and colleagues investigated incisional and organ/space SSIs at 28 weeks post-surgery and reported a significant improvement in patients receiving PO as compared to IV ($P = 0.02$), but no difference in organ/space SSIs.[18]

Surgical Site Infection (SSI) — Oral-plus-Intravenous versus Intravenous-only Antibiotics

All but one of the studies addressing clinical effectiveness reported on SSIs in patients receiving either IV-only or IV plus PO (with or without MBP) i.e., all three SRs [15,16] [1] and four of the five eligible RCTs.[17,19-21] There was agreement across six of these seven studies, reporting a significant improvement in total SSIs among patients receiving combination PO plus IV as compared to IV-only antibiotics. [15,16] [1,17,19,20] The statistical significance of these findings were further investigated using subgroup and sensitivity analyses by Chen and colleagues, and were found to be robust to both: (i) stratification by type of surgery (i.e., colorectal cancer or ulcerative colitis) and (ii) limitation to only those four of seven included RCTs that employed the use of adequate randomization, concealment and/or blinding procedures.[15] Conversely, the RCT employing a non-inferiority design reported no statistically significant difference in the odds of SSI for either group of patients, concluding that IV-only was non-inferior to IV plus PO.[21]

In five studies reporting on incisional SSIs, one SR[15] and two RCTs[17,19] reported a statistically significant improvement in patients receiving combination IV plus PO as compared to IV-only prophylaxis. Two other RCTs also reported on incisional SSIs, with Hata and colleagues reporting separately on deep and superficial incisional SSIs and finding no statistical difference between groups receiving IV-only versus IV plus PO prophylaxis.[20] Similarly, the non-inferiority RCT reported by Ikeda and colleagues found no statistical difference in overall incisional SSIs, or in perineal and abdominal incisional SSIs.[21]

Organ/space SSIs were reported in five eligible studies; one SR[15] and four RCTs.[17,19-21] Four of these five studies reported no statistically significant difference in organ/space SSIs in patients receiving IV-only as compared with IV plus PO prophylaxis.[15,19-21] The remaining RCT reported a significant improvement in patients receiving combined IV plus PO prophylaxis versus IV-only (i.e., 4/95 versus 0/95 patients; $P = 0.04$).[17]

Surgical Site Infection (SSI) — Oral-plus-Intravenous versus Oral-only Antibiotics

Two SRs reported on comparisons of patients receiving PO-only compared to those receiving PO plus IV antibiotic prophylaxis (with or without MBP).[1,16] Again, there was

agreement between the findings of these meta-analyses, with both studies reporting significantly fewer SSIs in patients receiving combined PO plus IV as compared to patients receiving only IV prophylaxis.[1,16] Notably, these SRs demonstrated considerable overlap in their included studies (see Appendix 5)

Adverse Effects — Oral-only versus Intravenous-only Antibiotics

Hjalmarrson and colleagues found no statistically significant differences in any adverse effects between patients receiving PO as compared to IV.[18]

Adverse Effects — Oral-plus-Intravenous versus Intravenous-only Antibiotics

Three RCTs describing comparisons of IV versus IV plus PO (both interventions including MBP) reported on adverse effects.[17,20,21] Two of these trials found no statistically significant difference in any adverse effects investigated, and; of nine adverse effects reported on by Anjum and colleagues, a statistically significant difference was observed only in hospital readmissions, where four occurred in the IV-only arm and zero occurred in the IV plus PO arm of the study (P = 0.04).[17]

Cost-Effectiveness of Bowel Preparation for Elective Colorectal Surgery

No evidence describing cost-effectiveness of various approaches to bowel preparation for elective colorectal surgery was identified.

Guidelines Informing the Use of Bowel Preparation for Elective Colorectal Surgery

Four guidelines recommend the use of oral antibiotics with mechanical bowel preparation before colorectal surgery.[2,9,22] Three of these guidelines also recommend intravenous antibiotic prophylaxis in the context of colorectal surgery.[2,22,26] One guideline suggests that MBP is not required, but that oral antibiotics are recommended in the context of colon resection for sigmoid diverticulitis.[24] Two guidelines explicitly recommend against the use of MBP without oral antibiotics.[9,25] One guideline made specific recommendations on oral antibiotic drug selection.[2] First-choice antibiotics according to this guideline should be oral neomycin sulfate plus oral erythromycin base or oral neomycin sulfate plus oral metoronidazole.[2] One guideline explicitly stated that no recommendation could be made regarding the use of MBP plus oral antibiotics in children because most of the available data have been generated from studies of adults.[25] Two guidelines made no explicit recommendations on preoperative intravenous antibiotic use,[24,26] whereas four guidelines made explicit recommendations about intravenous antibiotics — all of which either assumed and/or favoured their use.[2,9,22,25] One source did not make any explicit recommendations, but presented their findings as considerations, reporting that 26% of experts included in their Delphi process favoured the use of preoperative IV antibiotic prophylaxis, and 74% favoured the use of oral antibiotics.[23]

Appendix 4 presents a table of the main study findings, author conclusions and evidence/recommendations for of the included studies and guidelines summarized here.

Limitations

There were some important limitations with the evidence identified in this review describing antibiotic use during bowel preparation for elective colorectal procedures. First, the type of surgery being investigated was not always made explicit e.g., elective surgery versus emergency surgery; whether specific types of surgery were necessarily elective colorectal procedures, etc. The SRs included in this review generally used rigorous methods to meta-

analyze many of the same studies; nonetheless, their descriptions of the interventions were similarly not always clear or consistent i.e., whereas two SRs were clear about the use of MBP,[15,16] the largest SR included in this review was not.[1] This leaves some uncertainty as to the direct comparability of the interventions being described across the three SRs. Similarly, reporting of the use of IV antibiotics was not always explicit e.g., in one RCT, no explicit mention of the use of IV antibiotic prophylaxis is reported, but a statement is made concerning "standard procedures" (p. 606) being used in addition to antibiotic prophylaxis (though, these procedures are not delineated).[18] As well, guidelines were likewise not always explicit in providing guidance or recommendations concerning IV antibiotic prophylaxis.

While the findings with regard to SSI were consistent across the studies addressing the comparative clinical effectiveness of IV plus PO versus IV-only antibiotics, one RCT concluded that IV-only antibiotic prophylaxis was non-inferior to IV plus PO antibiotics. This discordant finding relative to those of the other studies included in this review could be the result of various factors, including sample size, clinical context, or study design i.e., demonstrating non-inferiority is a very different — and more complex — endeavor than the more common superiority approach,[27] and seeks, by definition, a fundamentally different outcome, making comparison with findings from superiority trials necessarily less straightforward.

The lack of evidence addressing cost-effectiveness is a notable gap in the evidence base addressing bowel preparation for elective colorectal procedures. Due to this lack of data, the current review is limited from the presentation or interpretation of any evidence informing this consideration.

The guidelines included in this review were not always developed specifically in the context of colorectal surgery, and so, some of the evidence and recommendations were limited in the scope of their relevance. Likewise, some guidelines and recommendations emphasized the utility (or disutility) of MBP as compared to focusing on antibiotic use, and so bore less relevance to the current review. Importantly, none of the primary studies, guidance and recommendations identified were conducted or developed within or for a Canadian context, potentially limiting their generalizability.

As with all reviews of published evidence, the quality of the primary sources included is an important factor contributing to the limitations of the review. In this review, the SRs were generally well-conducted with few limitations, whereas the RCTs and guidelines were of variable quality, demonstrating both strengths and weaknesses. It is important that these quality considerations are incorporated into the interpretation of the findings summarized and presented herein.

Conclusions and Implications for Decision or Policy Making

This review identified three SRs, five RCTs, and seven evidence-based guidelines addressing the clinical effectiveness or guidance and recommendations concerning bowel preparation in elective colorectal procedures. Most of the evidence describing clinical effectiveness focused on SSIs from colorectal surgery in patients receiving IV plus oral antibiotic prophylaxis s as compared to patients receiving IV-only, and reported a benefit of the former, combined intervention. In addition, adverse effects did not demonstrably differ between these groups. Considered together, the authors and the conclusions of the studies and the included in this review generally supported the use of combined IV plus PO antibiotic prophylaxis to reduce overall SSIs in patients undergoing elective colorectal

surgery. Similarly, guidelines included in this review generally favoured the use of either, or both, IV and PO antibiotics; whereas the use of MBP was neither uniformly addressed nor recommended.

The use of oral antibiotics as part of the preoperative regimen for elective colorectal surgery has likewise been found to be of benefit in related studies as well; recent cohort analyses of the addition of PO antibiotic to MBP support its use in reducing SSIs.[28-30] Similarly, recent review articles echo the benefit of oral antibiotic use as added prophylaxis in elective colorectal procedures;[31] even to the extent that some authors have questioned the value of any further research on the subject, suggesting the importance of implementation as a current focus of research and practice.[32]

Given that the availability of specific antibiotics may be limited in a given health care jurisdiction, future research of value in the Canadian context may investigate the relative benefit of types of commercially available oral antibiotics. Oral antibiotics reported in the included primary studies for this review were kanamycin, levofloxacin, trimethoprim-sulfamethoxazole and metronidazole, and; those of potential relevance mentioned in the included guidelines for this review were tobramycin, amphotericin and/or polymyxin, and; clindamycin or metronidazole (both with aminoglycoside, aztreonam, and/or a fluoroquinolone). While the availability and use of these drugs in Canada was not described in the included studies of this report, they may suggest alternatives in cases of limited availability in the Canadian context. Future research may also focus on the cost-effectiveness of the addition of oral antibiotics in elective colorectal procedures, as well as the comparative clinical and cost-effectiveness of various oral antibiotics. These data may better inform any resource and/or budgetary considerations that will impact decisions concerning the implementation of oral antibiotic use in elective colorectal procedures.

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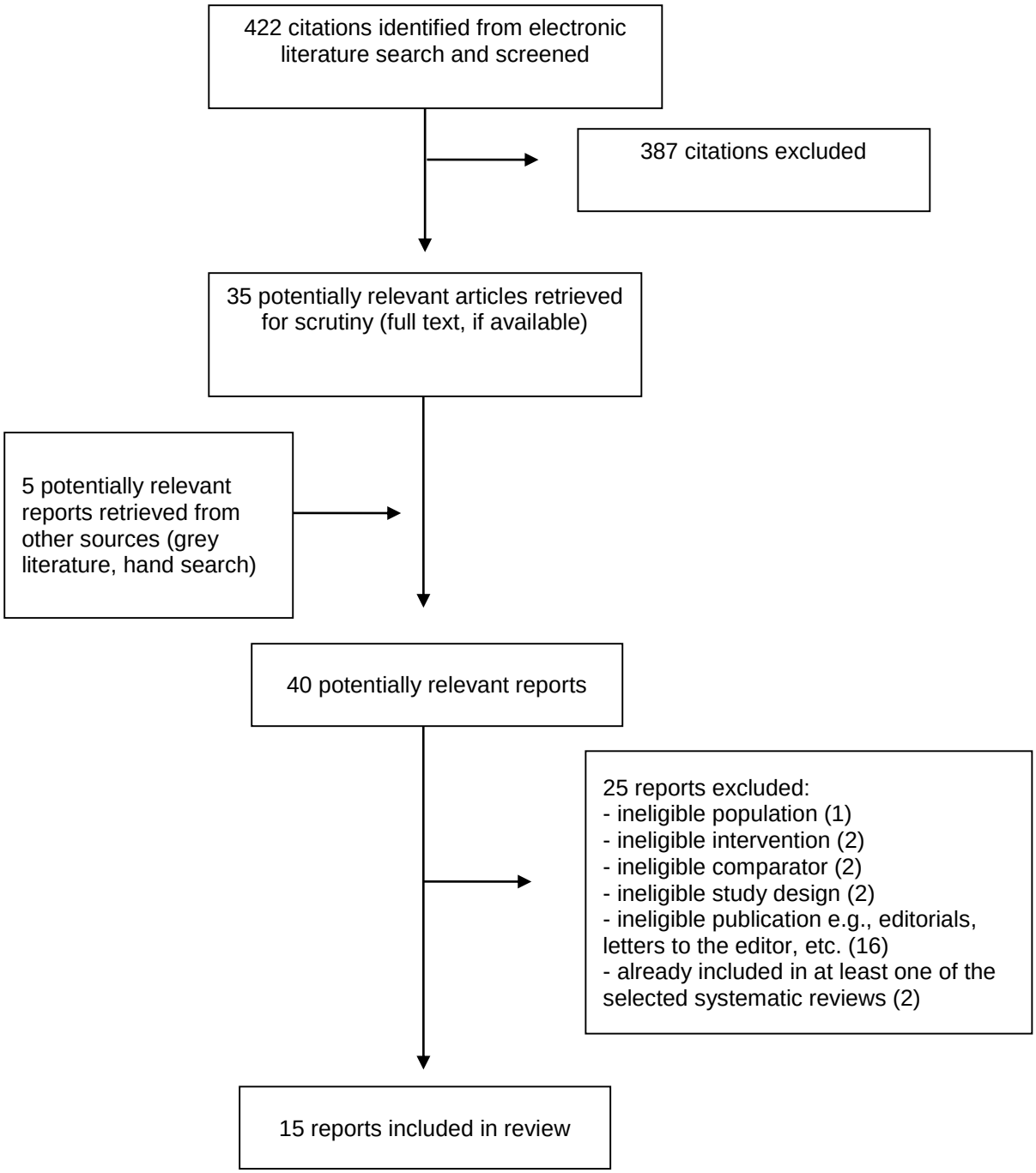
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

Author, year, country	Number and type of included studies, Total N, indication	Subgroup of comparison relevant to this review	Intervention description	Comparator description	Main outcomes of interest
Chen (2016)[15] **China**	7 RCTs (N=1,769), elective colorectal surgery	Same as total population	MBP+PO+IV	MBP+IV	Surgical site infection; incisional infection; organ/space infection
Koullouros (2016)[16] **UK**	23 RCTs and 8 cohort studies (N=59,323), elective colorectal surgery	Same as total population	(i) PO+MBP (ii) PO+IV+MBP (iii) PO+MBP	(i) IV+MBP (ii) IV+MBP (iii) IV+PO+MBP	Surgical site infection
Nelson (2014)[1] **UK**	260 RCTs describing 43,451 adults with colorectal surgery	27 RCTs (n=5,046) adults with colorectal surgery	PO+IV (MBP use not explicitly reported)	IV (MBP use not explicitly reported)	Rate of surgical wound infection

IV= intravenous antibiotic prophylaxis; MBP=mechanical bowel preparation; n/a=not applicable; NR=not reported; PO= oral antibiotic prophylaxis; RCT = randomized controlled trial

Table 3: Characteristics of Included Randomized Controlled Trials

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Population Characteristics
Anjum (2017)[17] **China**	Open-label RCT, blinded outcome assessors, single center, N=190	Adults undergoing elective colorectal surgery for multiple indications	MBP + metronidazole PO and levofloxacin PO + metronidazole IV and 2nd generation cephalosporin IV *vs.* MBP + metronidazole IV and 2nd generation cephalosporin IV	Surgical site infection (superficial, deep, organ/space), adverse effects
Uchino (2017)[19] **Japan**	Open-label RCT, blinded outcome assessors, single center, N=335	Patients with Crohn's disease undergoing intestinal resection	MBP + kanamycin PO and metronidazole PO + floxomef IV *vs.* MBP + floxomef IV	Surgical site infection, (incisional, organ/space)

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Population Characteristics
Hata (2016)[20] **Japan**	Open-label RCT, 5 centers, N=579	Adults undergoing elective laparoscopic colorectal surgery for colorectal cancer or adenoma	MBP + kanamycin PO and metronidazole PO + cefmetazole IV *vs.* MBP + cefmetazole IV	Surgical site infection (incisional, organ/space, superficial, deep), enteritis, other infections
Ikeda(2016)[21] **Japan**	Open-label RCT, blinded outcome assessors, single center, N=515 Non-inferiority design	Adults undergoing elective laparoscopic colorectal surgery for colorectal cancer	MBP + kanamycin PO and metronidazole PO + cefmetazole IV *vs.* MBP + cefmetazole IV	Surgical site infection, incisional site infection, organ/space infection, anastomotic leakage, intra-abdominal abscess, post-op complications
Hjalmarsson[18] (2015) **Sweden**	Open-label RCT, blinded outcome assessors, multi-centre, N=1,073 (randomized)	Patients undergoing elective colorectal resection for unspecified indication(s)	TSM PO *vs.* CXM IV	Surgical site infection (rate, type), anastomotic leakage, septicemia, pneumonia, urinary tract infection, post-operative antibiotic administration, post-operative hospital stay, health care encounters for SSI

CSM = Cefuroxime and metronidazole; IV= intravenous antibiotic prophylaxis; MBP=mechanical bowel preparation; n/a=not applicable; NR=not reported; PO= oral antibiotic prophylaxis; RCT = randomized controlled trial; SSI= Surgical site infection; TSM = trimethoprim-sulfamethoxazole and metronidazole

Table 4: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Recommendations Development and Evaluation	Guideline Validation
American Society of Colon and Rectal Surgeons (ASCRS) & Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) 2017[26]					
Surgeons, healthcare workers, patients	Addition of PO antibiotic to MBP before colorectal surgery,	Surgical site infection, complications, overall morbidity, anastomotic leakage	Systematic literature search, meta-analysis where needed	Quality assessment of the literature	NR
World Health Organization (WHO) Global Guidelines for the Prevention of Surgical Site Infection. 2016[9]					
Surgical team (surgeons, nurses, technical support staff, anaesthetists)	The use of MBP with/without oral antibiotics before elective colorectal surgery;	Surgical site infection, anastomotic leakage	Systematic literature search, meta-analysis where needed	Quality assessment of the literature	Contains an evaluation plan.

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Recommendations Development and Evaluation	Guideline Validation
	IV antibiotics before surgery(type of surgery not specified)				
American College of Surgeons (ACS) and Surgical Infection Society Surgical Site Infection Guidelines Update 2016[22]					
Surgeons and surgical staff	The use of MBP with/without oral antibiotics before elective colorectal surgery; IV antibiotics	Surgical site infection, anastomotic leakage, *C difficile,* ileus, length of hospital stay, readmission	For this update, there was a focus on "recent literature" (methods not described)	Internal and external experts consulted together "to reach consensus agreement on the final guidelines"	NR
Prevention, Diagnosis and Management of Anastomotic Leakage (ASGBI and ACGBI) 2016[23]					
NR	Multiple interventions, including IV antibiotics, MBP and oral antibiotics	Prevention, diagnosis and management of anastomotic leakage	Systematic review	Delphi process drawing from systematic review evidence	Three-round Delphi process
ASCRS Practice Parameters for the Treatment of Sigmoid Diverticulitis 2014[24]					
Surgeons, healthcare workers, patients	The use of MBP with/without oral antibiotics before elective colorectal surgery	Surgical site infection, anastomotic leakage, *C difficile,* ileus, length of hospital stay, readmission	Authors performed literature search.	Quality assessment of the literature	NR
Prevention of infectious complications after elective colorectal surgery in children (APSA) 2014[25]					
Pediatric surgeons and surgical staff	The use of MBP with/without oral antibiotics before elective colorectal surgery; IV antibiotics	Surgical site infection, anastomotic leakage, abscess, *C difficile,*	Systematic literature search	Quality assessment of the literature	NR
Clinical practice guidelines for antimicrobial prophylaxis in surgery (ASHP, IDSA, SIS, SHEA). 2013[2]					
Surgeons, pharmacists, surgical staff	Oral antibiotics before colorectal surgery (with MBP); IV antibiotics	Surgical site infection, infectious complications,	Systematic literature search	Quality assessment of the literature	NR

*All guidelines considered multiple interventions and practices; only the intervention of interest is listed here.

ACS = American College of Surgeons; ASCRS = American Society of Colon and Rectal Surgeons; ASHP = American Society of Hospital Pharmacists; IDSA = Infectious Diseases Society of Health-System Pharmacists; IV = intravenous; MBP = mechanical bowel preparation; NR = not reported; SHEA = Society for Healthcare Epidemiology of America; SIS = Surgical Infection Society; SAGES = Society of American Gastrointestinal and Endoscopic Surgeons; WHO = World Health Organization

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of Systematic Reviews using AMSTAR II[11]

Strengths	Limitations
Chen (2016)[15]	
• An *a priori* design was evident • Duplicate study selection and data abstraction occurred • A comprehensive literature search was performed • Publication status was considered • A list of included studies was provided • Study characteristics were described • Scientific quality of included studies was assessed and documented • Scientific quality of included studies was appropriately incorporated into the interpretation and conclusions • Methods for quantitative syntheses were appropriate	• A list of excluded studies was not provided • Publication bias was not reported
Koullouros (2016)[16]	
• An *a priori* design was evident • Duplicate study selection and data abstraction occurred • A comprehensive literature search was performed • A list of included studies was provided • Study characteristics were described • Scientific quality of included studies was assessed and documented • Scientific quality of included studies was appropriately incorporated into the interpretation and conclusions • Methods for quantitative syntheses were appropriate	• Consideration of publication status was unclear • A list of excluded studies was not provided • Publication bias was not reported
Nelson (2015)[1]	
• An *a priori* design was evident • Duplicate study selection and data abstraction occurred • A comprehensive literature search was performed • Publication status was considered • A list of included and excluded studies was provided • Study characteristics were described • Scientific quality of included studies was assessed and documented • Scientific quality of included studies was appropriately incorporated into the interpretation and conclusions • Methods for quantitative syntheses were appropriate	• Publication bias was not reported

Table 6: Strengths and Limitations of Randomized Controlled Trials using Down's and Black Checklist[12]

Strengths	Limitations
Anjum (2017)[17]	
Reporting • The hypothesis, objective, main outcomes, patient characteristics, interventions, distributions of principal confounders, estimates of random variability, adverse events and probability values were clearly reported. **Internal validity** • Outcome assessors were blinded to the interventions received • Statistical tests were appropriate • Compliance with interventions was reliable • Main outcome measures were valid and reliable • Patients from both intervention groups were recruited from the same population and during the same time period • Subjects were randomized to treatment • Random assignment was concealed • Analyses included adjustment for confounding • Patient loss to follow-up was accounted for **Power** • The study was sufficiently powered **Conflict of interest** • Conflict of interest was sufficiently addressed	**Reporting** • Characteristics of patients lost to follow-up were not clearly reported **External validity** • Representativeness of eligible patients, study participants, staff, context and facilities were unclear **Internal validity** • Patients were not blinded to the intervention received • Unclear whether analyses were adjusted for variable follow-up duration
Uchino (2017)[19]	
Reporting • The hypothesis, objective, main outcomes, patient characteristics, interventions, distributions of principal confounders, estimates of random variability, adverse events and probability values were clearly reported. **Internal validity** • Outcome assessors were blinded to the interventions received • Statistical tests were appropriate • Compliance with interventions was reliable • Main outcome measures were valid and reliable • Patients from both intervention groups were recruited from the same population and during the same time period • Subjects were randomized to treatment • Analyses included adjustment for confounding **Power** • The study was sufficiently powered	**Reporting** • Characteristics of patients lost to follow-up were not clearly reported **External validity** • Representativeness of eligible patients, study participants, staff, context and facilities were unclear **Internal validity** • Patients were not blinded to the intervention received • Unclear whether analyses were adjusted for variable follow-up duration • Unclear whether random assignment was concealed • Unclear whether patient loss to follow-up was accounted for

Strengths	Limitations
Conflict of interest • Conflict of interest was sufficiently addressed	
Hata (2016)[20]	
Reporting • The hypothesis, objective, main outcomes, patient characteristics, interventions, distributions of principal confounders, estimates of random variability, adverse events and probability values were clearly reported. **Internal validity** • Statistical tests were appropriate • Compliance with interventions was reliable • Main outcome measures were valid and reliable • Patients from both intervention groups were recruited from the same population and during the same time period • Subjects were randomized to treatment • Random assignment was concealed • Analyses included adjustment for confounding **Power** • The study was sufficiently powered **Conflict of interest** • Conflict of interest was sufficiently addressed	**Reporting** • Characteristics of patients lost to follow-up were not reported **External validity** • Representativeness of eligible patients, study participants, staff, context and facilities were unclear **Internal validity** • Patients were not blinded to the intervention received • Outcome assessors were not blinded to the interventions received • Unclear whether analyses were adjusted for variable follow-up duration • Unclear whether patient loss to follow-up was accounted for
Ikeda(2016)[21]	
Reporting • The hypothesis, objective, main outcomes, patient characteristics, interventions, distributions of principal confounders, estimates of random variability, adverse events and probability values were clearly reported. **Internal validity** • Outcome assessors were blinded to the interventions received • Statistical tests were appropriate • Compliance with interventions was reliable • Main outcome measures were valid and reliable • Patients from both intervention groups were recruited from the same population and during the same time period • Subjects were randomized to treatment • Random assignment was concealed • Analyses included adjustment for confounding **Power** • The study was sufficiently powered **Conflict of interest** • Conflict of interest was sufficiently addressed •	**External validity** • Representativeness of eligible patients, study participants, staff, context and facilities were unclear **Internal validity** • Patients were not blinded to the intervention received

Strengths	Limitations
Hjalmarsson (2015)[18]	
Reporting • The hypothesis, objective, main outcomes, patient characteristics, interventions, estimates of random variability, adverse events and probability values were clearly reported. **Internal validity** • Outcome assessors were blinded to the interventions received • Statistical tests were appropriate • Compliance with interventions was reliable • Main outcome measures were valid and reliable • Patients from both intervention groups were recruited from the same population and during the same time period • Subjects were randomized to treatment • Random assignment was concealed **Power** • The study was sufficiently powered **Conflict of interest** • Conflict of interest was sufficiently addressed	**Reporting** • Distributions of principal confounders not reported • Characteristics of patients lost to follow-up were not reported **External validity** • Representativeness of eligible patients, study participants, staff, context and facilities were unclear **Internal validity** • Patients were not blinded to the intervention received • Patient loss to follow up was reported but not otherwise accounted for • Analyses did not include adjustment for confounding

Table 7: Strengths and Limitations of Guidelines using AGREE 2[13]

Strengths	Limitations
American Society of Colon and Rectal Surgeons (ASCRS) & Society of American Gastrointestinal and Endoscopic Surgeons(SAGES) 2017[26]	
Scope and Purpose • The objectives were described. • The health questions were described. • Target populations were described. **Stakeholder Involvement** • The guideline was developed by individuals with relevant professional backgrounds. • Target users were described. **Rigour of development** • Systematic methods were used to search for evidence. • Strengths and limitations of the evidence were described. • Health benefits, side effects and risks were considered in formulating the recommendations. • Experts were involved in its development. • Appears to be updated regularly • The link between recommendations and the supporting evidence was explicit.	Stakeholder Involvement • Unclear if user feedback and patient feedback is solicited. **Rigour of development** • Criteria for selecting the evidence were not fully described in the guideline but are available in the attached online supplement. • Methods for formulating the recommendations were not clearly described, but authors stated that a process has been developed. **Applicability** • The guideline did not describe facilitators of and barriers to its application. • The guideline did not appear to advise on how the recommendations can be put into practice. • The potential resource implications of applying the recommendations were not explicitly considered for our comparison of interest (PO antibiotics).

Strengths	Limitations
Clarity of Presentation • The recommendations are specific and unambiguous. • The different options for management of the health issue are briefly presented. • Key recommendations are easily identifiable. **Editorial Independence** • This guideline was funded by the ASCRS and SAGES. Some authors reported paid roles from private companies.	
World Health Organization (WHO) Global Guidelines for the Prevention of Surgical Site Infection 2016[9]	
Scope and Purpose • The objectives were described. • The health questions were described. • Target populations were described. **Stakeholder Involvement** • The guideline was developed by individuals with relevant professional backgrounds. • Target users were described. • WHO appears to be interested in feedback through regional evaluations. **Rigour of development** • Systematic methods were used to search for evidence. • Strengths and limitations of the evidence were described. • Health benefits, side effects and risks were considered in formulating the recommendations. • Experts were involved in its development. • Updates to guidance are considered every 5 years. • The link between recommendations and the supporting evidence was explicit. • Methods for formulating the recommendations were clearly described **Clarity of Presentation** • The recommendations are specific and unambiguous. • The different options for management of the health issue are briefly presented. • Key recommendations are easily identifiable. **Applicability** • The guideline states that a separate implementation plan will be developed • The potential resource implications of applying the recommendations were considered (page 79) **Editorial Independence** • This guideline was funded mostly by WHO and some authors reported receiving monies from companies for work not related to this guideline.	**Rigour of development** • Criteria for selecting the evidence were not fully described in the guideline but are available in online appendices. **Applicability** • The guideline did not describe facilitators of and barriers to its application.

Strengths	Limitations
American College of Surgeons (ACS) and Surgical Infection Society *Update* 2016[22]	
Scope and Purpose • The objectives were described. • The health questions were described. • Target populations were described. **Stakeholder Involvement** • The guideline was developed by individuals with relevant professional backgrounds. **Rigour of development** • Health benefits, side effects and risks were considered in formulating the recommendations. • Experts were involved in its development. • Update policy exists (this is an update) • The link between recommendations and the supporting evidence was explicit. **Clarity of Presentation** • The recommendations are specific and unambiguous. • The different options for management of the health issue are briefly presented. • Key recommendations are easily identifiable.	**Stakeholder Involvement** • Target users were not well described. • Unclear from this update how user feedback is solicited **Rigour of development** • No mention of systematic methods used to search for evidence for this update. • Strengths and limitations of the evidence were not well described. • Criteria for selecting the evidence were not fully described in the guideline. • Methods for formulating the recommendations were not clearly described. **Applicability** • The guideline does not provide advice on how the recommendations can be put into practice. • The potential resource implications of applying the recommendations were not considered. **Editorial Independence** • Funding unclear. Some authors received monies from pharmaceutical companies for consulting. **Applicability** • The guideline did not describe facilitators of and barriers to its application.
Prevention, Diagnosis and Management of Anastomotic Leakage (ASGBI and ACGBI) 2016[23]	
Scope and Purpose • Target population was implicitly described. **Stakeholder Involvement** • Views and preferences of the target population were sought **Rigour of development** • Systematic methods were used to search for evidence • Strengths and limitations of evidence are described • Methods for formulating evidence are described • Health benefits, side effects and risks were considered in formulating the recommendations. • The link between recommendations and the supporting evidence was explicit.	**Scope and Purpose** • The objectives were not explicitly stated. • The health questions were not explicitly stated. **Stakeholder Involvement** • Composition of the guideline development group was not explicitly described **Rigour of development** • Criteria for selecting evidence is not explicitly described within the guidance document • No evidence that the guidance was externally reviewed • No procedure for updating the guidance is reported **Clarity of Presentation** • Guidance is provided but recommendations are not stated explicitly • Different options for management of the health issue are not explicitly presented. • Key recommendations are not easily identifiable. **Applicability** • Barriers and facilitators to the application of guidance are not

Strengths	Limitations
	explicitly presented. • The guideline does not provide advice on how the recommendations can be put into practice and does not present monitoring/audit criteria. • The potential resource implications of applying the recommendations were not described. **Editorial Independence** • The funding body or source of support is not reported • Competing interests are not reported
ASCRS Practice Parameters for the Treatment of Sigmoid Diverticulitis 2014[24]	
Scope and Purpose • The objectives were described. • The health questions were described. • Target populations were described. **Stakeholder Involvement** • The guideline was developed by individuals with relevant professional backgrounds. • Target users were not well described. **Rigour of development** • Health benefits, side effects and risks were considered in formulating the recommendations. • Experts were involved in its development. • Update policy exists (previous version was 2006) • The link between recommendations and the supporting evidence was explicit. **Clarity of Presentation** • The recommendations are specific and unambiguous. • The different options for management of the health issue are briefly presented. • Key recommendations are easily identifiable.	**Stakeholder Involvement** • Unclear whether user feedback is solicited **Rigour of development** • Literature methods not well described (no search strategy provided) • Strengths and limitations of the evidence were not well described. • Criteria for selecting the evidence were not fully described in the guideline. • Methods for formulating the recommendations were not clearly described. **Applicability** • The guideline does not provide advice on how the recommendations can be put into practice. • The potential resource implications of applying the recommendations were not considered. **Editorial Independence** • Funding unclear. There was no conflict of interest statement. **Applicability** • The guideline did not describe facilitators of and barriers to its application.
American Pediatric Surgical Association (APSA) Prevention of infectious complications after elective colorectal surgery in Children. 2014[25]	
Scope and Purpose • The objectives were described. • The health questions were described. • Target populations were described. **Stakeholder Involvement** • The guideline was developed by individuals with relevant professional backgrounds. • Target users were described. **Rigour of development** • Systematic methods were used to search for evidence (but search strategy not provided).	**Stakeholder Involvement** • Unclear if user feedback and patient feedback is solicited. **Rigour of development** • Methods for formulating the recommendations not clear. • Schedule for updating guidelines is not clear **Applicability** • The guideline did not describe facilitators of and barriers to its application. • The guideline did not advise on how the recommendations can be put into practice. • The potential resource implications of applying the

Strengths	Limitations
• Criteria for selecting the evidence were described • Strengths and limitations of the evidence were described. • Health benefits, side effects and risks were considered in formulating the recommendations. • Experts were involved in its development. • The link between recommendations and the supporting evidence was explicit. **Clarity of Presentation** • The recommendations are specific and unambiguous. • The different options for management of the health issue are briefly presented. • Key recommendations are easily identifiable.	recommendations were not explicitly considered for our comparison of interest (PO antibiotics). **Editorial Independence** • Funding unclear. There was no conflict of interest statement.
Clinical practice guidelines for antimicrobial prophylaxis in surgery (ASHP, IDSA, SIS, SHEA). 2013[2]	
Scope and Purpose • The objectives were described. • Target populations were described. **Stakeholder Involvement** • The guideline was developed by individuals with relevant professional backgrounds. • Target users were described. **Rigour of development** • Systematic methods were used to search for evidence (but search strategy not provided). • Criteria for selecting the evidence were described • Health benefits, side effects and risks were considered in formulating the recommendations. • Experts were involved in its development. • The link between recommendations and the supporting evidence was explicit. **Clarity of Presentation** • The recommendations are specific and unambiguous. • The different options for management of the health issue are briefly presented.	**Scope and Purpose** • The health questions were not explicitly stated. **Stakeholder Involvement** • Unclear if user feedback and patient feedback is solicited. **Rigour of development** • Methods for formulating the recommendations not clear. • Schedule for updating guidelines is not clear • Some discussion about level of evidence for the recommendations, but many studies were cited without adjacent statements regarding the level of evidence. **Clarity of Presentation** • Key recommendations were not easily identifiable. **Applicability** • The guideline did not describe facilitators of and barriers to its application. • The guideline did not advise on how the recommendations can be put into practice. • The potential resource implications of applying the recommendations were not explicitly considered for our comparison of interest (PO antibiotics). **Editorial Independence** • Funding was from several universities. Several authors reported consulting fees from pharmaceutical companies.

ACS= American College of Surgeons; ASCRS=American Society of Colon and Rectal Surgeons; ASHP= American Society of Hospital Pharmacists; IDSA= Infectious Diseases Society of Health-System Pharmacists; MBP= mechanical bowel preparation; PO=Per os (i.e., oral antibiotics); SHEA= Society for Healthcare Epidemiology of America; SIS= Surgical Infection Society; SAGES= Society of American Gastrointestinal and Endoscopic Surgeons; WHO=World Health Organization

Appendix 4: Main Study Findings and Authors' Conclusions

Table 8: Summary of Findings for Included Systematic Reviews

Main Study Findings	Authors' Conclusion
Chen (2016)[15]	

SSIs
• **Total (7 studies), n**
  ○ MBP+IV (n=884)
  ▪ 141
  ○ MBP+IV+PO (n=885)
  ▪ 64
  ○ Statistical difference between groups
  ▪ RR (95% CI)
  • 0.45 (0.34 to 0.60)
  ▪ *P* < 0.00001
 	
• **Incisional (6 studies), n**
  ○ MBP+IV (n=710)
  ▪ 86
  ○ MBP+IV+PO (n=714)
  ▪ 33
  ○ Statistical difference between groups
  ▪ RR (95% CI)
  • 0.38 (0.26 to 0.56)
  ▪ *P* < 0.00001
 	
• **Organ/space (5 studies), n**
  ○ MBP+IV (n=606)
  ▪ 29
  ○ MBP+IV+PO (n=610)
  ▪ 25
  ○ Statistical difference between groups
  ▪ RR (95% CI)
  • 0.85 (0.51 to 1.44)
  ▪ *P* = 0.56
 	
Subgroup analyses
• **SSI following colorectal cancer surgery (2 studies), n**
  ○ MBP+IV (n=199)
  ▪ 29
  ○ MBP+IV+PO (n=198)
  ▪ 14
  ○ Statistical difference between groups
  ▪ RR (95% CI)
  • 0.47 (0.26 to 0.86)
  ▪ *P* < 0.01
 	
• **SSI following ulcerative colitis surgery (2 studies), n**
  ○ MBP+IV (n=168)
  ▪ 42
  ○ MBP+IV+PO (n=169)
  ▪ 9
  ○ Statistical difference between groups
  ▪ RR (95% CI)
	"Our meta-analysis revealed that oral systemic antibiotics and MBP significantly reduced incisional SSI compared with systemic antibiotics alone and MBP. This effect holds true regardless of CRC or UC surgery. However, no significant difference was detected in the rate of organ/space SSI." (p.76)

Main Study Findings	Authors' Conclusion
• 0.21 (0.11 to 0.42) ▪ *P* < 0.0001 **Sensitivity analyses** • **Total SSIs (4 studies that used true randomization and allocation concealment), n** ○ MBP+IV (n=512) ▪ NR ○ MBP+IV+PO (n=517) ▪ NR ○ Statistical difference between groups ▪ OR (95% CI) • 0.48 (0.34 to 0.69) ▪ *P* < 0.0001 • **Total SSIs (2 studies that used true randomization, allocation concealment and blinding), n** ○ MBP+IV (n=199) ▪ NR ○ MBP+IV+PO (n=203) ▪ NR ○ Statistical difference between groups ▪ OR (95% CI) • 0.37 (0.21 to 0.66) ▪ *P* < 0.0006 • **Incisional SSIs (4 studies that used true randomization and allocation concealment), n** ○ MBP+IV (n=512) ▪ NR ○ MBP+IV+PO (n=517) ▪ NR ○ Statistical difference between groups ▪ OR (95% CI) • 0.36 (0.23 to 0.58) ▪ *P* < 0.0001 • **Incisional SSIs (2 studies that used true randomization, allocation concealment and blinding), n** ○ MBP+IV (n=199) ▪ NR ○ MBP+IV+PO (n=203) ▪ NR ○ Statistical difference between groups ▪ OR (95% CI) • 0.32 (0.17 to 0.61) ▪ *P* < 0.0005 • **Organ/space SSIs (3 studies that used true randomization and allocation concealment), n** ○ MBP+IV (n=408) ▪ NR ○ MBP+IV+PO (n=413) ▪ NR ○ Statistical difference between groups	

Main Study Findings	Authors' Conclusion
▪ OR (95% CI) • 0.82 (0.45 to 1.47) ▪ *P* = 0.50	
Koullouros (2016)[16]	
SSIs (reported in RCTs) • **PO+MBP vs. IV+MBP (11 RCTs), n** ○ IV+MBP (n=624) ▪ 58 ○ PO+MBP (n=592) ▪ 92 ○ Statistical difference between groups ▪ OR (95% CI) • 1.82 (1.28 to 2.58) ▪ *P* < 0.0008 • **PO+IV+MBP vs. IV+MBP (12 RCTs), n** ○ IV+MBP (n=1678) ▪ 234 ○ PO+IV+MBP (n=1159) ▪ 81 ○ Statistical difference between groups ▪ OR (95% CI) • 0.44 (0.33 to 0.58) ▪ *P* < 0.00001 • **PO+MBP vs. PO+IV+MBP (3 RCTs), n** ○ PO+MBP (n=714) ▪ 33 ○ PO+IV+MBP (n=706) ▪ 58 ○ Statistical difference between groups ▪ OR (95% CI) • 1.87 (1.20 to 2.92) ▪ *P* < 0.005 **SSIs (reported in cohort studies)** • **IV vs. PO+IV (6 studies), n** ○ IV (n=13697) ▪ 1718 ○ PO+IV (n=3584) ▪ 231 ○ Statistical difference between groups ▪ RR (95% CI) • 0.52 (0.46 to 0.59) ▪ *P* < 0.00001 • **IV+MBP vs. PO+IV+MBP (5 studies), n** ○ PO+IV+MBP (n=16010) ▪ 2006 ○ IV+MBP (n=11090) ▪ 697 ○ Statistical difference between groups	*"The addition of oral antibiotics to systemic antibiotics could potentially reduce the risk of SSIs in elective colorectal surgery. Additionally, MBP does not seem to provide a clear benefit with regard to SSI prevention. However, there is a need for a large-scale multicentre RCT to further define the role of oral antibiotics in colorectal surgery due to several limitations of the available data from the existing literature."* (p.15)

Main Study Findings	Authors' Conclusion
▪ RR (95% CI) • 0.48 (0.44 to 0.52) ▪ *P* < 0. 00001	
Nelson (2015)[1]	
SWIs • **PO vs. IV (3 RCTs), n** ○ IV (n=118) ▪ 6 ○ PO (n=119) ▪ 18 ○ Statistical difference between groups ▪ RR (95% CI) • 2.31 (0.60 to 8.83) ▪ *P* = 0.22 • **PO+IV vs. IV (15 RCTs), n** ○ PO+IV (n=1456) ▪ 100 ○ IV (n=1473) ▪ 188 ○ Statistical difference between groups ▪ RR (95% CI) • 0.55 (0.43 to 0.71) ▪ *P* < 0.00001 • **PO vs. PO+IV (9 RCTs), n** ○ PO (n=937) ▪ 74 ○ PO+IV (n=943) ▪ 39 ○ Statistical difference between groups ▪ RR (95% CI) • 0.52 (0.35 to 0.76) ▪ *P* < 0.00073	*"This review has found high quality evidence that antibiotics covering aerobic and anaerobic bacteria delivered orally or intravenously (or both) prior to elective colorectal surgery reduce the risk of surgical wound infection….antibiotics delivered within this framework can reduce the risk of postoperative surgical wound infection by as much as 75%. It is not known whether oral antibiotics would still have these effects when the colon is not empty. This aspect of antibiotic dosing has not been tested. Further research is required to establish the optimal timing and duration of dosing, and the frequency of longer-term adverse effects such as Clostridium difficile pseudomembranous colitis."* (p.2)

CI = Confidence interval; CRC = Colorectal cancer; IV = Intravenous; MBP = Mechanical bowel preparation; n = Number; NR = Not reported; OR = Odds ratio; PO = Per os (i.e., by mouth); RCT = Randomized controlled trial; RR = Risk ratio; SSI = Surgical site infection; SWI = Surgical wound infection; UC = Ulcerative colitis

Table 9: Summary of Findings for Included Randomized Controlled Trials

Main Study Findings	Authors' Conclusion
Anjum (2017)[17]	
SSI • **Overall, n (%)** ○ MBP+IV (n=95) ▪ 26 (27.3) ○ MBP+IV+PO (n=95) ▪ 8 (8.42) ○ Statistical difference between groups ▪ *P* = 0.001 • **Superficial, n (%)** ○ MBP+IV (n=95) ▪ 16 (16.8)	*"Preoperative oral antibiotics, as adjunct therapy to systemic antibiotics and mechanical bowel preparation, significantly reduced surgical site infections and minimized the readmission rates in clean contaminated, contaminated, and dirty types of colorectal surgery."* (p.1291)

Main Study Findings	Authors' Conclusion
○ MBP+IV+PO (n=95) ▪ 6 (6.31) ○ Statistical difference between groups ▪ *P* = 0.02 • **Deep, n (%)** ○ MBP+IV (n=95) ▪ 7 (7.36) ○ MBP+IV+PO (n=95) ▪ 1 (1.05) ○ Statistical difference between groups ▪ *P* = 0.03 • **Organ/space, n (%)** ○ MBP+IV (n=95) ▪ 4 (4.21) ○ MBP+IV+PO (n=95) ▪ 0 (0) ○ Statistical difference between groups ▪ *P* = 0.04 **Adverse effects** • **Rate of postoperative ileus/days, mean (SD)** ○ MBP+IV (n=95) ▪ 4.23 (±1.7) ○ MBP+IV+PO (n=95) ▪ 3.96 (±1.26) ○ Statistical difference between groups ▪ *P* = 0.23 • **Hospital readmissions, n (%)** ○ MBP+IV (n=95) ▪ 4 (4.21) ○ MBP+IV+PO (n=95) ▪ 0 (0) ○ Statistical difference between groups ▪ *P* = 0.04 • **Follow-up surgical procedures, n (%)** ○ MBP+IV (n=95) ▪ 2 (2.1) ○ MBP+IV+PO (n=95) ▪ 0 (0) ○ Statistical difference between groups ▪ *P* = 0.15 • **Pneumonia while hospitalized, n (%)** ○ MBP+IV (n=95) ▪ 3 (3.15) ○ MBP+IV+PO (n=95) ▪ 2 (2.1) ○ Statistical difference between groups ▪ *P* = 0.65 • **Acute respiratory distress syndrome while hospitalized, n (%)** ○ MBP+IV (n=95) ▪ 1 (0.52)	

Main Study Findings	Authors' Conclusion
○ MBP+IV+PO (n=95) ▪ 1 (1.05) ○ Statistical difference between groups ▪ *P* = 0.31 • **Catheter-associated infection while hospitalized, n (%)** ○ MBP+IV (n=95) ▪ 1 (1.05) ○ MBP+IV+PO (n=95) ▪ 2 (2.1) ○ Statistical difference between groups ▪ *P* = 0.56 • **Urinary tract infection while hospitalized, n (%)** ○ MBP+IV (n=95) ▪ 0 (0) ○ MBP+IV+PO (n=95) ▪ 1 (1.05) ○ Statistical difference between groups ▪ *P* = 0.31 • **Gastrointestinal bleeding while hospitalized, n (%)** ○ MBP+IV (n=95) ▪ 1 (1.05) ○ MBP+IV+PO (n=95) ▪ 1 (1.05) ○ Statistical difference between groups ▪ *P* = 0.99 • **Sepsis while hospitalized, n (%)** ○ MBP+IV (n=95) ▪ 1 (1.05) ○ MBP+IV+PO (n=95) ▪ 0 (0) ○ Statistical difference between groups ▪ *P* = 0.31	
Uchino (2017)[19]	
SSI • **Overall, n (%)** ○ MBP+IV (n=162) ▪ 37 (22.8) ○ MBP+IV+PO (n=163) ▪ 26 (16) ○ Statistical difference between groups ▪ *P* = 0.13 ○ Association between overall SSI and no PO (multivariate logistic regression), OR (95% CI) ▪ 3.33 (1.33 to 8.33) ▪ Statistical difference between groups • *P* = 0.01 • **Incisional, n (%)** ○ MBP+IV (n=162) ▪ 27 (16.7)	*"We confirmed the efficacy of preoperative oral antibiotic use for the prevention of SSI. Our study shows that preoperative oral antimicrobial prophylaxis in addition to intraoperative antibiotic prophylaxis significantly decreases the incidence of incisional SSI in comparison to intravenous antibiotic prophylaxis alone after surgery for CD. Therefore, we recommend the use of oral antimicrobial prophylaxis with MBP in patients with CD. To evaluate whether this approach has a similar efficacy in APR (abdominoperineal resection), further evaluations restricted to the APR procedure are needed."* (p.7)

Main Study Findings	Authors' Conclusion
○ MBP+IV+PO (n=163) ▪ 12 (7.4) ○ Statistical difference between groups ▪ *P* = 0.01 • **Organ/space, n (%)** ○ MBP+IV (n=162) ▪ 17 (10.5) ○ MBP+IV+PO (n=163) ▪ 15 (9.2) ○ Statistical difference between groups ▪ *P* = 0.72	
Hata (2016)[20]	
SSI • **All, n (%)** ○ MBP+IV (n=290) ▪ 37 (12.8) ○ MBP+IV+PO (n=289) ▪ 21 (7.3) ○ Statistical difference between groups ▪ OR (95% CI) • 0.54 (0.31 to 0.94) • *P* = 0.03 • **Superficial incision, n** ○ MBP+IV (n=290) ▪ 26 ○ MBP+IV+PO (n=289) ▪ 15 ○ Statistical difference between groups ▪ OR (95% CI) • 0.56 (0.29 to 1.07) • *P* = 0.08 • **Deep incision, n** ○ MBP+IV (n=290) ▪ 1 ○ MBP+IV+PO (n=289) ▪ 1 ○ Statistical difference between groups ▪ OR (95% CI) • 1.00 • *P* = 1.00 • **Organ/space, n** ○ MBP+IV (n=290) ▪ 10 ○ MBP+IV+PO (n=289) ▪ 7 ○ Statistical difference between groups ▪ OR (95% CI) • 0.70 (0.26 to 1.85) • *P* = 0.47	*"Our multicenter randomized controlled trial has shown that in patients undergoing elective laparoscopic colorectal surgery, the oral and IV ABX significantly reduces the incidence of SSIs compared to the IV prophylaxis alone (OR = 0.536; 95% CI: 0.305–0.940; p = 0.028)."* (p.1085)

Main Study Findings	Authors' Conclusion

Adverse effects
• **Enteritis/colitis/diarrhea, n (%)**
  ○ MBP+IV (n=290)
  ▪ 9 (3.1)
  ○ MBP+IV+PO (n=289)
  ▪ 4 (1.4)
  ○ Statistical difference between groups
  ▪ OR (95% CI)
  • 0.44 (0.13 to 1.44)
  • *P* = 0.17
• **Remote site infection, n (%)**
  ○ MBP+IV (n=290)
  ▪ 5 (1.7)
  ○ MBP+IV+PO (n=289)
  ▪ 6 (2.1)
  ○ Statistical difference between groups
  ▪ OR (95% CI)
  • 1.21 (0.37 to 4.01)
  • *P* = 0.76
• **Postoperative noninfectious complication, n (%)**
  ○ MBP+IV (n=290)
  ▪ 12 (4.1)
  ○ MBP+IV+PO (n=289)
  ▪ 11 (3.8)
  ○ Statistical difference between groups
  ▪ OR (95% CI)
  • 0.92 (0.40 to 2.11)
  • *P* = 0.99	

Ikeda (2016)[21]	

SSI
• **Total, n (%)**
  ○ MBP+IV (n=256)
  ▪ 20 (7.8)
  ○ MBP+IV+PO (n=255)
  ▪ 20 (7.8)
  ○ Statistical difference between groups
  ▪ Absolute difference (90% CI for non-inferiority)
  • -0.03 (-4.00 to 3.94)
  • *P* = 0.017
  ▪ OR (95% CI)
  • 1.00 (0.52 to 1.90)
  • *P* = 0.99
• **Incisional, n (%)**
  ○ MBP+IV (n=256)
  ▪ 14 (5.5)
  ○ MBP+IV+PO (n=255)
  ▪ 15 (5.9)
  ○ Statistical difference between groups
  ▪ OR (95% CI)
  • 0.93 (0.44 to 1.96)
  • *P* = 0.84
	"Intravenous perioperative antimicrobial prophylaxis alone is not inferior to combined preoperative oral and intravenous perioperative prophylaxis with regard to SSI in patients with colorectal cancer undergoing elective laparoscopic resection." (p.1608)

Main Study Findings	Authors' Conclusion

• **Perineal incision, n (%)**
  ○ MBP+IV (n=12)
  ▪ 3 (25)
  ○ MBP+IV+PO (n=13)
  ▪ 2 (15)
  ○ Statistical difference between groups
  ▪ OR (95% CI)
  • 1.83 (0.25 to 13.47)
  • *P* = 0.65
• **Abdominal incision, n (%)**
  ○ MBP+IV (n=256)
  ▪ 11 (4.3)
  ○ MBP+IV+PO (n=255)
  ▪ 13 (5.1)
  ○ Statistical difference between groups
  ▪ OR (95% CI)
  • 0.84 (0.37 to 1.90)
  • *P* = 0.67
• **Organ/space, n (%)**
  ○ MBP+IV (n=256)
  ▪ 6 (2.3)
  ○ MBP+IV+PO (n=255)
  ▪ 5 (2.0)
  ○ Statistical difference between groups
  ▪ OR (95% CI)
  • 1.20 (0.36 to 3.98)
  • *P* = 1.00
 	
Adverse effects
• **Intra-abdominal abscess, n (%)**
  ○ MBP+IV (n=256)
  ▪ 0
  ○ MBP+IV+PO (n=255)
  ▪ 2 (0.8)
  ○ Statistical difference between groups
  ▪ OR (95% CI)
  • NR
  • *P* = 0.25
• **Anastomotic leakage, n (%)**
  ○ MBP+IV (n=244)
  ▪ 6 (2.5)
  ○ MBP+IV+PO (n=242)
  ▪ 3 (1.2)
  ○ Statistical difference between groups
  ▪ OR (95% CI)
  • 2.01 (0.50 to 8.12)
  • *P* = 0.50	

Hjalmarsson (2015)[18]	

SSI at 28wks post-surgery
• **Incisional, n (%)**
  ○ TSM PO (n=486)
  ▪ 34 (7)
	"Orally administered TSM as prophylaxis before elective colorectal surgery results in a low rate of organ/space SSI but an increased rate of incisional SSI compared with intravenously

Main Study Findings	Authors' Conclusion
○ CXM IV (n=499) ▪ 18 (3.6) ○ Statistical difference between groups ▪ *P* = 0.02 • **Organ/space, n (%)** ○ TSM PO (n=486) ▪ 8 (1.6) ○ CXM IV (n=499) ▪ 9 (1.8) ○ Statistical difference between groups ▪ *P* = 0.95 **Adverse effects at 28wks post-surgery** • **Surgical site dehiscence, n (%)** ○ TSM PO (n=486) ▪ 4 (0.8) ○ CXM IV (n=499) ▪ 12 (2.4) ○ Statistical difference between groups ▪ *P* = 0.08 • **Anastomotic leakage, n (%)** ○ TSM PO (n=486) ▪ 17 (3.5) ○ CXM IV (n=499) ▪ 17 (3.4) ○ Statistical difference between groups ▪ *P* = 0.95 • **Septicemia, n (%)** ○ TSM PO (n=486) ▪ 3 (0.06) ○ CXM IV (n=499) ▪ 6 (1.2) ○ Statistical difference between groups ▪ *P* = 0.30 • **Pneumonia, n (%)** ○ TSM PO (n=486) ▪ 11 (2.3) ○ CXM IV (n=499) ▪ 14 (2.8) ○ Statistical difference between groups ▪ *P* = 0.53 • **Urinary tract infection, n (%)** ○ TSM PO (n=486) ▪ 23 (4.7) ○ CXM IV (n=499) ▪ 27 (5.4) ○ Statistical difference between groups ▪ *P* = 0.43	*administered cefuroxime and metronidazole. Thus, when considering orally administered TSM, because of environmental concerns or for economic reasons, the slightly increased infection rate has to be kept in mind."* (p.604)

Main Study Findings	Authors' Conclusion

Health care outcomes at 28wks post-surgery
• **Days antibiotics were administered while in-hospital, mean (95% CI)**
  ○ TSM PO (n=486)
  ▪ 6.8 (5.7 to 7.8)
  ○ CXM IV (n=499)
  ▪ 6.8 (6.0 to 7.6)
  ○ Statistical difference between groups
  ▪ *P* = 1.00
• **Post-operative days in hospital, mean (95% CI)**
  ○ TSM PO (n=486)
  ▪ 8.1 (7.5 to 8.6)
  ○ CXM IV (n=499)
  ▪ 8.1 (7.6 to 8.6)
  ○ Statistical difference between groups
  ▪ *P* = 1.00
• **Health care contacts for SSIs, mean (95% CI)**
  ○ TSM PO (n=486)
  ▪ 5.5 (3.6 to 7.4)
  ○ CXM IV (n=499)
  ▪ 5.0 (3.7 to 6.3)
  ○ Statistical difference between groups
  ▪ *P* = 0.68	

ABX = Antibiotic prophylaxis; APR = Abdominoperineal resection; CD = Crohn's disease; CI = Confidence interval; CXM = Cefuroxime and metronidazole; IV = Intravenous; MBP = Mechanical bowel preparation; n = Number; OR = Odds ratio; PO = Per os (i.e., by mouth); SD = Standard deviation; SSI = Surgical site infection; TSM = Trimethoprim-sulfamethoxazole and metronidazole; wks = weeks

Table 10: Summary and Relevant Excerpts from Clinical Practice Guidelines

Description of Recommendations and Supporting Evidence
American Society of Colon and Rectal Surgeons (ASCRS) & Society of American Gastrointestinal and Endoscopic Surgeons 2017[26]
Guidance relevant to the current review *"Mechanical bowel preparation plus oral antibiotic bowel preparation before colorectal surgery is the preferred preparation and is associated with reduced complication rates. Grade of recommendation: weak recommendation based on moderate-quality evidence, 2B."* (p. 764) *"A bundle of measures should be in place to reduce surgical site infection. Grade of recommendation: strong recommendation based on moderate-quality evidence, 1B."* (p. 765) ***Overall notes of relevance to the current review*** While these guidelines do not make explicit recommendations about intravenous antibiotic use, they do suggest using a bundle of preventive measures and cite ertapenem as an example of a preoperative antibiotic (p. 764), and describe the use of antibiotic prophylaxis as an important component of (p. 765)
American College of Surgeons (ACS) and Surgical Infection Society Update 2016[22]
Guidance relevant to the current review *"Combination mechanical and antibiotic (oral) preparation is recommended for all elective colectomies."* (p. 61)

Description of Recommendations and Supporting Evidence
"The literature generally supports the administration of prophylactic antibiotics within 1 hour before incision, or within 2 hours for vancomycin or fluoroquinolones….. Whenever possible, providers should use hospital specific antibiograms and diverse antibiotic agents to decrease resistance among pathogens. As discussed previously, in elective colorectal procedures, a combination of oral antibiotic bowel preparation and IV prophylactic antibiotics should be used." (p. 66)
Prevention, Diagnosis and Management of Anastomotic Leakage (ASGBI and ACGBI) 2016[23]
Guidance relevant to the current review No explicit recommendations are made; rather, the source described the evidence synthesis and Delphi processes undertaken. ***Overall notes of relevance to the current review*** • Findings and information of relevance pertain only to the prevention of anastomotic leakage as the outcome of interest • Findings and information of relevance are not explicitly limited to elective procedures only (i.e., reference to emergency procedures is made throughout the document) • Guidance is not presented in the form of explicit recommendations; rather, described as 'considerations' ***Evidence presented of relevance to the current review*** *"Preoperative broad-spectrum intravenous antibiotics are routinely used in elective and emergency colorectal surgery, with the goal of reducing postoperative infective complications and this practice is recommended by ACPGBI[49]. In the USA, some surgeons routinely use non-absorbable oral antibiotics such as Tobramycin and Amphotericin B - also known as selective decontamination of the digestive tract (SDD). A systematic review has indicated that SDD reduces anastomotic leak rates from 7.4% to 3.3%[50]. This finding has also been replicated in a recent study of over 8,000 colorectal resections, demonstrating both lower surgical site infection and anastomotic leak rates in the treatment group[51]. Despite this, SDD is not currently in widespread practice in the United Kingdom and Ireland."* (p. 11) ***Results of Delphi process relevant to the current review*** • 26% of Delphi respondents either agreed or strongly agreed that preoperative IV antibiotics are important for reducing risk of anastomotic leakage • 74.1% of Delphi respondents either agreed or strongly agreed that preoperative oral antibiotics are important for reducing risk of anastomotic leakage ***Guidance relevant to the current review:*** • Both preoperative IV and oral antibiotics are presented as interventions for reducing risk of anastomotic leakage
World Health Organization (WHO) Global Guidelines for the Prevention of Surgical Site Infection 2016[9]
Guidance relevant to the current review *"The panel suggests that preoperative oral antibiotics combined with mechanical bowel preparation (MBP) should be used to reduce the risk of SSI in adult patients undergoing elective colorectal surgery. (Conditional recommendation, moderate quality evidence)"* (p. 76) *"The panel recommends that MBP alone (without administration of oral antibiotics) should not be used for the purpose of reducing SSI in adult patients undergoing elective colorectal surgery. (Strong recommendation, moderate quality evidence)."* (p. 76) The WHO guidelines suggest that "Surgical Antibiotic Prophylaxis" (could be parenteral or non-parenteral) be administered "prior to surgical incision when indicated" (p. 72) but does not specify which surgical procedures this is indicated for. ***Overall notes of relevance to the current review***

Description of Recommendations and Supporting Evidence
• These WHO guidelines do not comment on the use of intravenous antibiotics specifically in the context of colorectal surgeries, but the primary studies that the recommendations are based on are provided in an appendix to the WHO report. These studies used intravenous antibiotics in almost all patients. • Recommendations are based on a systematic review that included 13 RCTs (years 1994 to 2012) comparing MBP plus intravenous antibiotics versus intravenous antibiotics alone.
American Pediatric Surgical Association (APSA) - Prevention of infectious complications after elective colorectal surgery in children 2015[25]
Guidance relevant to the current review *"Use of MBP alone (without enteral antibiotics) for the indication of reducing infectious complications is not recommended as it provides no benefit over parenteral prophylaxis alone (Grade A recommendation based on Class I evidence from adult data). Data are limited in children but support the same recommendation (Grade C recommendation based on Class II/III evidence)."* (p. 198) *"Available Class I evidence strongly supports the use of enteral antibiotics combined with an MBP for reducing SSIs in the adult population (compared with no preparation or MBP only), however, data are limited surrounding the efficacy and safety profiles of this practice for colorectal conditions in children. Further data are needed before a recommendation can be made (no recommendation)."* (p. 198) *"Parenteral antibiotic prophylaxis should include one of the [Surgical Care Improvement Project] SCIP-approved agents (Grade A recommendation based on Class I evidence for equivalence among the SCIP agents, Table 3). Although second-generation cephalosporins offer the convenience and cost benefit of single-agent prophylaxis, increasing data from the adult literature suggest they may be inferior to the multiagent SCIP regimens (Grade B recommendation based on an increasing body of Class II evidence). In patients with a suspected or documented beta-lactam allergy, ciprofloxacin combined with metronidazole should be considered as the next line of prophylaxis (Grade B recommendation based on an increasing body of Class II evidence to suggest superiority over other SCIP-compliant regimens). Pediatric dosing for all SCIP-compliant antibiotic agents should follow guidelines as currently endorsed by the ASHP."* (p. 196)
ASCRS Sigmoid Diverticulitis 2014[33]
Guidance relevant to the current review • Regarding elective or emergency surgery for sigmoid diverticulitis: *"Oral mechanical bowel preparation is not required; however, the use of oral antibiotics may decrease surgical site infections after elective colon resection. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B."* (p. 91) ***Overall descriptive notes of relevance to the current review*** • No specific recommendations are given on intravenous antibiotic use in the context of surgery for sigmoid diverticulitis.
Clinical practice guidelines for antimicrobial prophylaxis in surgery (ASHP, IDSA, SIS, SHEA). 2013[2]
Guidance relevant to the current review *"In most patients, MBP combined with a combination of oral neomycin sulfate plus oral erythromycin base or oral neomycin sulfate plus oral metronidazole should be given in addition to i.v. prophylaxis. The oral antimicrobial should be given as three doses over approximately 10 hours the afternoon and evening before the operation and after the MBP. Alternative regimens for patients with beta-lactam allergies include (1) clindamycin plus an aminoglycoside, aztreonam, or a fluoroquinolone and (2) metronidazole plus an aminoglycoside or a fluoroquinolone. Metronidazole plus aztreonam is not recommended as an alternative because this combination has no aerobic gram-positive activity. (Strength of evidence for prophylaxis = A.)"* (p. 226) *"A single dose of second-generation cephalosporin with both aerobic and anaerobic activities (cefoxitin or cefotetan) or cefazolin plus metronidazole is recommended for colon procedures (Table 2). In institutions where there is increasing resistance to first- and second-generation cephalosporins among gram-negative isolates from SSIs, the expert panel recommends a single dose of ceftriaxone plus metronidazole over routine use of carbapenems. An alternative regimen is ampicillin–sulbactam."* (p. 226)

Description of Recommendations and Supporting Evidence
• Recommended oral antibiotics (to be used with MBP) include: erythromycin base (adults: 1g, children: 20mg/kg); metronidazole (adults: 1g, children: 15mg/kg; neomycin (adults: 1g, children: 15mg/kg). (p. 198) • Recommended intravenous antibiotics include: cefazolin plus metronidazole, cefoxitin, cefotetan, ampicillin-sulbactam, ceftriaxone plus metronidazole, ertapenem (p. 200)

ACPGBI = The Association of Coloproctology of Great Britain and Ireland; ACS = American College of Surgeons; APSA = American Pediatric Surgical Association; ASCRS = American Society of Colon and Rectal Surgeons; ASGBI = Association of Surgeons of Great Britain and Ireland; ASHP = American Society of Health-System Pharmacists; g = gram; IDSA = Infectious Diseases Society of America; IV = Intravenous; kg = kilogram; MBP = Mechanical bowel preparation; mg = milligram; RCT = Randomized controlled trial; SCIP = Surgical Care Improvement Project; SDD = Selective decontamination of the digestive tract; SHEA = Society for Healthcare Epidemiology of America; SIS = Surgical Infection Society; SSI = Surgical site infection; WHO = World Health Organization

Appendix 5: Overlap between Included Systematic Reviews

Table 11: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation		
	Koullouros, 2017[16]	Chen, 2016[15]	Nelson, 2014[1]
Aeberhard, 1981			x
Barber, 1979			x
Becker, 1991			x
Beggs, 1982	x		x
Cai, 1992			x
Condon, 1983	x		x
Coppa, 1983	x		x
Coppa, 1988			x
Dion, 1980	x		x
Espin-Basany, 2005	x	x	x
Fluckiger, 1980			x
Ishida, 2001	x	x	x
Kaiser, 1983			x
Keighley, 1979			x
Kling, 1989	x		x
Kobayashi, 2007	x	x	x
Lau, 1988	x		x
Lazorthes, 1982	x		x
Lewis, 1981	x		x
Lewis, 2002	x	x	x
McArdle, 1995			x
Oshima, 2013	x	x	
Peruzzo, 1987			x
Petrelli, 1988			x
Playforth, 1988	x		x
Raahave, 1988	x		
Reynolds, 1989			x
Rohwedder, 1983	x		
Sadahiro, 2014	x	x	
Schoetz, 1990			x
Stellato, 1990	x		x

Primary Study Citation	Systematic Review Citation		
	Koullouros, 2017[16]	Chen, 2016[15]	Nelson, 2014[1]
Takesue, 2000	x		x
Takesue, 2009		x	
Taylor, 1994			x
University of Melbourne, 1986	x		
University of Melbourne, 1987	x		x
Weaver, 1986	x		x
Yabata, 1997	x		x

Appendix 6: Additional References of Potential Interest

Relevant CADTH Reports

Bowel preparation for elective colorectal procedures: clinical effectiveness, cost-effectiveness and guidelines. Ottawa: CADTH; 2018 Jun.

Bowel preparation for colorectal procedures: a review of clinical effectiveness, cost-effectiveness and guidelines. Ottawa: CADTH; 2018 Apr.

Oral neomycin in preparation f or colorectal procedures: clinical effectiveness, cost effectiveness and guidelines. Ottawa: CADTH; 2018 Mar.

Non-Systematic Reviews

Turner M, et al. Practice guidelines and future directions of bowel preparation: science and history. In: Current Common Dilemmas in Colorectal Surgery pp 11-19; 2018 Feb.

Zelhart MD, Hauch AT, Slakey DP, Nichols RL. Preoperative antibiotic colon preparation: Have we had the answer all along? J Am Coll Surg. 2014;219(5):1070-1077.

Guideline with Unclear Evidentiary Basis and/or Method for Development

British Columbia Enhanced Recovery After Surgery (ERAS). Collaborative guidance on mechanical bowel preparation; 2015 Jun. http://enhancedrecoverybc.ca/wp-content/uploads/2015/02/MBP-Guidance_FINAL_APPROVED_DISTRIBUTED-20150629.pdf Accessed July 12, 2018.

Giamarellou H, et al. Guide to infection control in the hospital: preparing the patient for surgery. International Society for Infectious Diseases (ISID); 2018 Apr.

Non-Randomized Studies

Klinger AL, et al. The Role of bowel preparation in colorectal surgery: results of the 2012-2015 ACS-NSQIP data. Ann Surg; 2017 Oct. https://www.ncbi.nlm.nih.gov/pubmed/29064902

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