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SUMMARY WITH CRITICAL APPRAISAL

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

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Context and Policy Issues

The risk of abdominal surgical site infection after surgery on the large intestine without antibiotics is significant and older studies suggest the incidence is approximately 40%.[1] Possible sequelae of surgical site infections include prolonged hospital stay, hospital readmission, and decreased survival.[1] The use of perioperative intravenous antibiotics (e.g. 2nd generation cephalosporins with aerobic and anaerobic coverage) 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 is debate on the optimal approach. The debate includes whether or not mechanical bowel preparations and/or oral antibiotics should be used as a standard part of the preoperative regimen.[3]

At least one frequently cited surgical guideline (2013)[4] and a systematic review (2011)[5] have recommend against the routine use of MBP in colonic surgery due to the lack of clear benefit versus no MBP, the distress that MBP administration causes patients, and the potential adverse effects on postoperative complications (possible prolonged ileus and spillage of bowel contents). However, the role of MBP plus oral antibiotic prophylaxis was not precisely delineated in these publications.

In addition to MBP, 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.

While there is some evidence that suggests that MBP should not be used alone,[3] there is renewed interested in determining the role of MBP, together with preoperative oral antibiotics. Recent retrospective analyses of large databases have suggested that there is an important role for the combination of MBP and oral antibiotics in reducing postoperative surgical site infections in elective colorectal surgery.[6] The objective of this report is to review the clinical effectiveness, cost-effectiveness, and evidence-based guidelines related to intravenous antibiotic prophylaxis (alone) compared to intravenous antibiotics plus oral prophylaxis and/or MBP.

Research Questions

1. What is the comparative clinical effectiveness of parenteral prophylaxis with or without oral antibiotics and/or mechanical bowel preparation (MBP) as part of preparation for colorectal procedures?
2. What is the cost-effectiveness of parenteral prophylaxis with or without oral antibiotics and/or mechanical bowel preparation (MBP) as part of preparation for colorectal procedures?
3. What are evidence-based guidelines informing the use of parenteral prophylaxis with or without oral antibiotics and/or mechanical bowel preparation (MBP) as part of preparation for colorectal procedures?

Key Findings

Evidence at high risk for bias, using incidence of surgical site infection from two RCTs, suggests that there is benefit to adding MBP to intravenous antibiotics and that there is no benefit to adding oral antibiotics to intravenous antibiotics. Because of the poor quality of these studies, confidence in these findings is low. The incremental benefit of adding both MBP and oral antibiotics to intravenous antibiotics is unknown, as no RCTs making those comparisons were identified.

There was no relevant evidence identified that would inform the cost-effectiveness of parenteral prophylaxis with oral antibiotics and/or mechanical bowel preparation.

Four guidelines recommend the use of mechanical bowel preparation plus oral antibiotic before colorectal surgery, and three of these guidelines recommend intravenous antibiotic prophylaxis in the context of colorectal surgery. One guideline suggests that MBP is not required, but oral antibiotics are recommended in the context of colon resection for sigmoid diverticulitis. Two guidelines explicitly recommend against the use of MBP without oral antibiotics. 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 are from studies of adults.

The data upon which the guidelines were based had the same limitations as the RCT evidence relevant for this review. The data upon which the recommendations were made lacked RCTs that used intravenous antibiotics alone as a comparator. Therefore, while the guidelines recommended both MBP and oral antibiotic prophylaxis, these recommendations did not stem from a knowledge of the incremental benefit associated with adding MBP and oral antibiotics to intravenous antibiotics.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Ovid Medline, Embase, PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases and a focused Internet search. No methodological filters were applied to limit retrieval by publication type. The search was limited to English language documents published between January 1, 2013 and March 1, 2018.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. 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 colorectal procedures (e.g., planned procedures such as colonoscopy, hemicolectomy, sigmoid colectomy, anterior resection)
Intervention	Parenteral prophylaxis only (e.g., intravenous antibiotics)
Comparator	Parenteral prophylaxis with:

	• Oral antibiotics (e.g., neomycin and metronidazole, kanamycin, or any viable alternatives for use in a Canadian context) and/or • Mechanical bowel preparation as adjuvant therapy to parenteral prophylaxis
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 trials, evidence based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2013. Citations that included both emergency and planned procedures were included if the majority of patients were undergoing planned procedures.

Critical Appraisal of Individual Studies

The included randomized studies (RCT) were critically appraised using the Downs and Black checklist[7] and guidelines were assessed with the AGREE II instrument.[8] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described in narrative format.

Summary of Evidence

Quantity of Research Available

A total of 385 citations were identified in the literature search. Following screening of titles and abstracts, 356 citations were excluded and 29 potentially relevant reports from the electronic search were retrieved for full-text review. Twelve potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 33 publications were excluded for various reasons, while 8 publications met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Two randomized controlled trials [9,10] and six evidence based guidelines[2,3,11-14] met the inclusion criteria for this report. Detailed characteristics of the studies and a description of the guidelines are presented in Appendix 2.

Study Design

Two open-label, 2-group, parallel, RCTs were included[9,10] and of these, one RCT[9] used blinded assessors for the main outcomes.

Six clinical practice guidelines were included[2,3,11-14] and of these, four reported using systematic literature searches and quality assessment of the literature.[2,3,11,14]

Country of Origin

The RCTs were published by authors from Japan,[9] and India.[10] The clinical practice guidelines were published by medical/surgical societies in the United States[2,11-14] and from the World Health Organization.[3]

Patient Population

One RCT enrolled 40 patients undergoing emergency (n=14) or elective (n=26) open colorectal surgery.[10] One RCT enrolled 515 patients undergoing elective laparoscopic colorectal surgery for colorectal cancer, but for the purposes of this report, only the subgroup of 72 patients who did not use MBP provide relevant data for this report.[9] One guideline was intended for application to patients undergoing colorectal surgery,[11] three guidelines were intended for application to patients undergoing a variety of surgeries (with specific subsections on colorectal surgeries),[2,3,12] one guideline was intended for application to patient undergoing surgery for sigmoid diverticulitis,[13] and one guideline was intended for children undergoing elective colorectal surgery.[14]

Interventions and Comparators

One RCT compared MBP versus no MBP in patients using intravenous cefuroxime and intravenous metronidazole (N=40).[10]

One RCT compared oral metronidazole plus oral kanamycin and intravenous cefmetazole versus intravenous cefmetazole alone (N=515).[9] Most patients used preoperative MBP and therefore would not meet inclusion criteria for this report, but there was a relevant subgroup analysis of 70 patients who did not use MBP.

The guidelines included recommendations on the use of preoperative intravenous antibiotics, preoperative oral antibiotics and MBP. Relevant recommendations were extracted that focused on the comparisons salient to this report.[2,3,11-14] Two guidelines made no explicit recommendations on preoperative intravenous antibiotic use.[11,13] Four guidelines made explicit recommendations about intravenous antibiotics.[2,3,12,14]

Outcomes

Surgical site infection was the outcome considered in one RCT with a relevant subgroup analysis.[9] In one RCT, authors reported surgical site infection, wound hematoma, intra-abdominal collection, anastomotic leak, enterocutaneous fistula and deaths.[10]

Summary of Critical Appraisal

One small RCT was included that had inadequate justification of sample size and no description of randomization technique.[10] It was rated as poor quality because of unclear description of the interventions, lack of information regarding patient follow up, inadequate description of statistical methods, unclear presentation of distribution of baseline prognostic factors in treatment groups, unclear methods of allocation concealment and unclear sample size justification.

One moderate quality RCT was included in which blinded assessors evaluated clinical outcomes.[9] Investigators used sealed envelopes for randomization to treatment groups (not computer generated). Randomization was stratified by several factors, including MBP status. Stratification at the time of randomization would be expected to increase power of subgroup analyses to detect differences between treatment groups within a given

subgroup, but the overall trial was not designed to demonstrated differences between treatment groups for the subgroup of patients not using MBP. The no-MBP subgroup analysis (n=70) was the analysis relevant to this report.

Two high quality[3,11] clinical practice guidelines were included. These two guidelines were developed by professionals with relevant expertise and systematic methods were applied to search for evidence. The key recommendations are unambiguous, easily identifiable and their relationship to the supporting evidence is clear.

Four moderate quality[2,12-14] clinical practice guidelines were included. These guidelines were rated as moderate quality because of lack of clear description of literature search methods,[12,13] and the methods for formulating the recommendations from the evidence were not clearly stated.[2,14]

Further detail regarding strengths and limitations are presented in Appendix 3.

Summary of Findings

1. *What is the comparative clinical effectiveness of parenteral prophylaxis with or without oral antibiotics and/or mechanical bowel preparation (MBP) as part of preparation for colorectal procedures?*

Findings from the RCTs are summarized below and details are available in Appendix 4.

The authors of one moderate quality RCT concluded that intravenous cefmetazole was not inferior to oral kanamycin plus oral metronidazole and intravenous cefmetazole, based on the incidence of surgical site infections, in 515 patients with colorectal cancer undergoing laparoscopic resection.[9] This was based on a non-inferiority boundary of 5% (absolute change). In this trial, a subgroup analysis of patients who did not receive preoperative MBP was performed comparing patients taking intravenous cefmetazole versus patients taking oral kanamycin plus oral metronidazole and intravenous cefmetazole (n=70). The odds ratio for surgical site infection in this subgroup showed no statistically significant difference between groups.

One low quality RCT compared MBP use to no MBP use in patients also receiving intravenous antibiotics before undergoing colorectal surgery.[10] The rates of surgical site infection were similar between the two groups and there was one death in the group not receiving MBP. Interpretation of these results is limited due to poor reporting of the results.

2. *What is the cost-effectiveness of parenteral prophylaxis with or without oral antibiotics and/or mechanical bowel preparation (MBP) as part of preparation for colorectal procedures?*

There were no relevant cost-effectiveness studies identified.

3. *What are evidence-based guidelines informing the use of parenteral prophylaxis with or without oral antibiotics and/or mechanical bowel preparation (MBP) as part of preparation for colorectal procedures?*

Recommendations from the guidelines are summarized below and details are presented in Appendix 4.

Four guidelines recommend the use of mechanical bowel preparation plus oral antibiotic before colorectal surgery.[2,3,11,12] Three of these guidelines also recommend intravenous antibiotic prophylaxis in the context of colorectal surgery.[2,11,12] One guideline suggests that MBP is not required, but oral antibiotics are recommended in the context of colon resection for sigmoid diverticulitis.[13] Two guidelines explicitly recommend against the use of MBP without oral antibiotics.[3,14] One guideline made specific recommendations on oral antibiotic drug selection.[2] The 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 are from studies of adults.[14]

Two guidelines made no explicit recommendations on preoperative intravenous antibiotic use.[11,13] Four guidelines made explicit recommendations about intravenous antibiotics.[2,3,12,14]

Limitations

A significant limitation of this review is that very few relevant studies were identified. Both RCTs included in this report used open-label methodology. This may reduce confidence in the study results since unblinded assessment of outcomes may introduce bias.

The 2 included RCTs were performed in Asian populations (India, Japan). It is possible that there are differences in treatment practices and patient populations in these countries, relative to Canadian standards of practice.

A significant limitation was the lack of RCTs or systematic reviews that used intravenous antibiotics only in a treatment arm. References used to support recommendations in the guidelines also had this limitation. One poor quality RCT compared MBP intravenous antibiotics to intravenous antibiotics alone.[10] One RCT compared oral antibiotics plus intravenous antibiotics to intravenous antibiotics alone, in a subgroup analysis.[9] No RCTs were found that compared intravenous antibiotics alone to MBP plus oral antibiotics and intravenous antibiotics.

There may be differences in risk of infection by condition (e.g. sigmoid diverticulitis, cancer) or surgical approach (e.g. laparoscopic versus open). The literature identified for this review did not provide enough data to make conclusions regarding antibiotic or MBP approaches in these subgroups of patients.

Conclusions and Implications for Decision or Policy Making

A total of eight relevant publications, including two randomized controlled trials [9,10] and six clinical practice guidelines[2,3,11-14] were identified. The populations in these publications were patients undergoing colorectal surgery related to various colorectal disorders.

Poor quality evidence using incidence of surgical site infection from two RCTs suggested that there is benefit to adding MBP to intravenous antibiotics[10] and that there is no benefit to adding oral antibiotics to intravenous antibiotics.[9] Because of the high risk of bias related to these studies, confidence in these findings is low. The incremental benefit of adding both MBP and oral antibiotics to intravenous antibiotics is unknown as there were no RCTs identified.

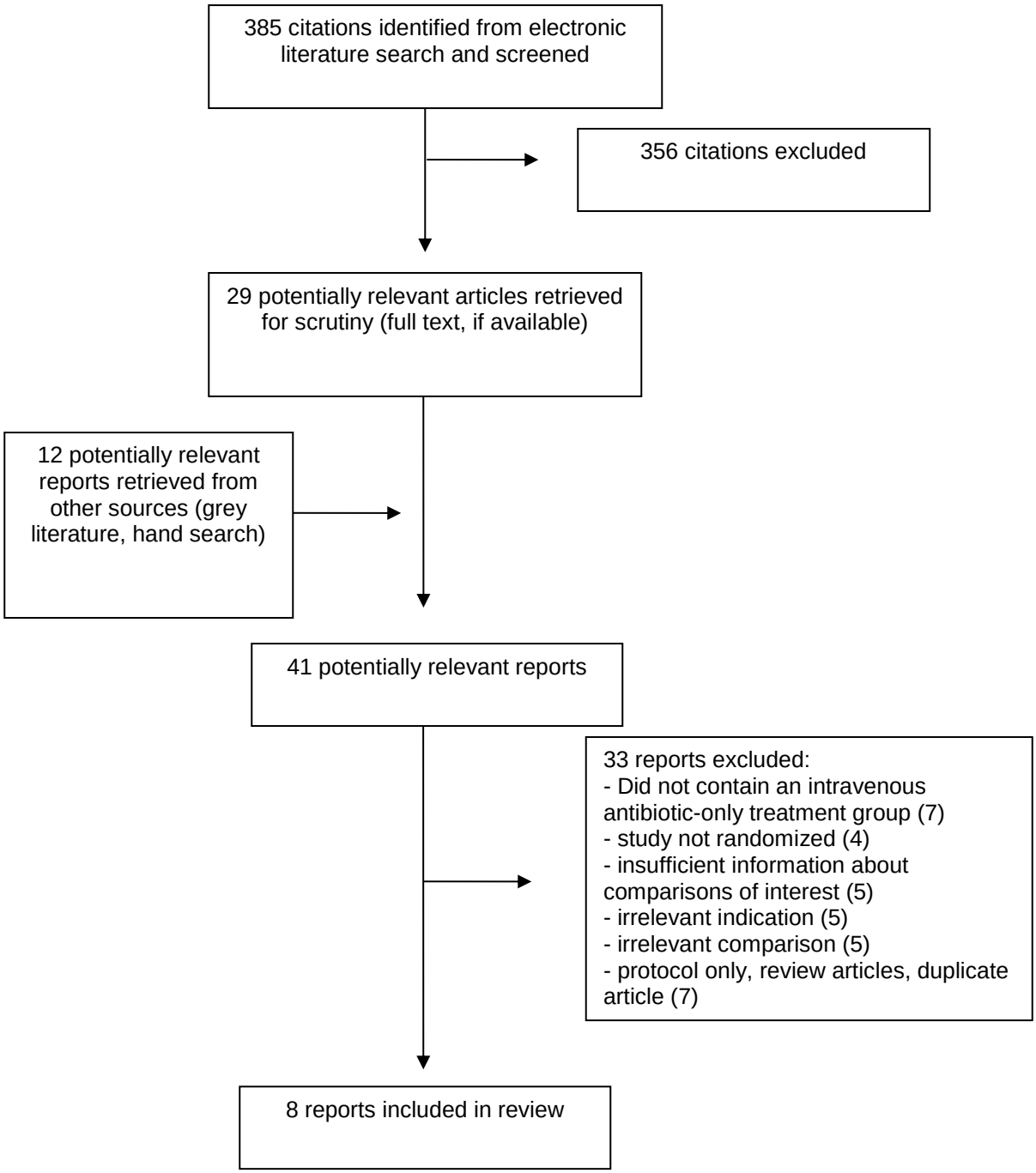
Of the five guidelines relevant to adults, four guidelines recommended using both MBP and oral antibiotics for infection prophylaxis in patients undergoing colorectal surgery.[2,3,11-13] The authors of the included pediatric guideline[14] suggested that the data in adults support using both MBP and oral antibiotics, but that there was uncertainty extrapolating those data to pediatric populations. One guideline recommended that MBP could be used alone in the context of colorectal surgery for sigmoid diverticulitis.[13] One guideline suggested that intravenous antibiotics with MBP but without oral antibiotics should not be used since it is not better than intravenous antibiotics alone, in the context of colorectal surgery.[3]

The data upon which the guidelines were based suffered from the same limitations as the RCT evidence relevant for this review; recommendations were made in the absence of RCTs that had patients using IV antibiotics alone as prophylaxis. The incremental benefit of adding MBP and oral antibiotics to an IV antibiotic prophylaxis regime is therefore unclear, and the recommendations seem to have been made based non-randomized evidence. There was no relevant evidence identified that would inform the cost-effectiveness of parenteral prophylaxis with oral antibiotics and/or mechanical bowel preparation. High quality randomized trials examining the incremental clinical benefit and the cost effectiveness of mechanical bowel preparation with or without oral antibiotics as additions to IV prophylaxis are required to make definitive conclusions.

References

1. Nelson RL, Gladman E, Barbateskovic M. Antimicrobial prophylaxis for colorectal surgery. Cochrane Database Syst Rev [Internet]. 2014 May 9 [cited 2018 Mar 9];(5). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001181.pub4/epdf
2. Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm [Internet]. 2013 [cited 2018 Mar 9];70(3):195-283. Available from: http://www.ajhp.org/content/ajhp/70/3/195.full.pdf
3. Global guidelines for the prevention of surgical site infection [Internet]. Geneva (CH): World Health Organization; 2016. [cited 2017 Mar 27]. Available from: http://apps.who.int/iris/bitstream/handle/10665/250680/9789241549882-eng.pdf
4. Gustafsson UO, Scott MJ, Schwenk W, Demartines N, Roulin D, Francis N, et al. Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations. World J Surg. 2013 Feb;37(2):259-84.
5. Guenaga KF, Matos D, Wille-Jorgensen P. Mechanical bowel preparation for elective colorectal surgery. Cochrane Database Syst Rev. 2011 Sep 7;(9):CD001544.
6. Koller SE, Bauer KW, Egleston BL, Smith R, Philp MM, Ross HM, et al. Comparative effectiveness and risks of bowel preparation before elective colorectal surgery. Ann Surg. 2017 Feb 1.
7. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health [Internet]. 1998 Jun [cited 2018 Mar 26];52(6):377-84. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf
8. Brouwers M, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in healthcare. CMAJ [Internet]. 2010 Dec [cited 2018 Mar 26];182(18):E839-E842. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3001530/pdf/182e839.pdf
9. Ikeda A, Konishi T, Ueno M, Fukunaga Y, Nagayama S, Fujimoto Y, et al. Randomized clinical trial of oral and intravenous versus intravenous antibiotic prophylaxis for laparoscopic colorectal resection. Br J Surg. 2016 Nov;103(12):1608-15.
10. Patial T, Sharma K, Mokta K, Jaswal KS, Thakur V, Ganesun NKV. Mechanical bowel preparation versus no bowel preparation in open colorectal surgery: a prospective study. Saudi Surgical Journal. 2017;5(3).
11. Carmichael JC, Keller DS, Baldini G, Bordeianou L, Weiss E, Lee L, et al. Clinical practice guidelines for enhanced recovery after colon and rectal surgery from the American Society of Colon and Rectal Surgeons and Society of American Gastrointestinal and Endoscopic Surgeons. Dis Colon Rectum. 2017 Aug;60(8):761-84.
12. Ban KA, Minei JP, Laronga C, Harbrecht BG, Jensen EH, Fry DE, et al. American College of Surgeons and Surgical Infection Society: Surgical site infection guidelines, 2016 update. J Am Coll Surg. 2017 Jan;224(1):59-74.
13. Feingold D, Steele SR, Lee S, Kaiser A, Boushey R, Buie WD, et al. Practice parameters for the treatment of sigmoid diverticulitis. Dis Colon Rectum. 2014 Mar;57(3):284-94.
14. Rangel SJ, Islam S, Peter SD, Goldin AB, Abdullah F, Downard CD, et al. Prevention of infectious complications after elective colorectal surgery in children: an American Pediatric Surgical Association Outcomes and Clinical Trials Committee comprehensive review. J Pediatr Surg. 2015;50(1):192-200.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Randomized Controlled Studies

Author(year), country	Study Design, N	Population Characteristics	Comparisons	Outcomes of Interest
Ikeda(2016)[9] 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 *Versus* MBP + cefmetazole IV	Surgical site infection, incisional site infection, organ/space infection, anastomotic leakage, intra-abdominal abscess, post-op complications
Patial(2017)[10] India	Open-label RCT, single center, N=20	Emergency or elective open colorectal surgery	cefuroxime IV and metronidazole IV *versus* MBP + cefuroxime IV and metronidazole IV	Surgical site infection, wound hematoma, enterocutaneous fistula, anastomotic leakage

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 Clinical Practice Guidelines

Intended users/ target population	Interventions and practice considered*	Outcomes considered	Evidence Collection, Selection, Synthesis	Recommendations development and evaluation	Guideline validation
American Society of Colon and Rectal Surgeons (ASCRS) & Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) 2017[11]					
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[3]					
Surgical team (surgeons, nurses, technical support staff, anaesthetists)	The use of MBP with/without oral antibiotics before elective colorectal surgery; IV antibiotics before surgery(type of surgery not specified)	Surgical site infection, anastomotic leakage	Systematic literature search, meta-analysis where needed	Quality assessment of the literature	Contains an evaluation plan.
American College of Surgeons (ACS) and Surgical Infection Society Surgical Site Infection Guidelines *Update* 2016[12]					
Surgeons and surgical staff	The use of MBP with/without oral	Surgical site infection,	For this update, there was a focus	Internal and external experts consulted	NR

Table 3: Characteristics of Included Clinical Practice Guidelines

Intended users/ target population	Interventions and practice considered*	Outcomes considered	Evidence Collection, Selection, Synthesis	Recommendations development and evaluation	Guideline validation
	antibiotics before elective colorectal surgery; IV antibiotics	anastomotic leakage, *C difficile,* ileus, length of hospital stay, readmission	on "recent literature" (methods not described)	together "to reach consensus agreement on the final guidelines"	
ASCRS Practice Parameters for the Treatment of Sigmoid Diverticulitis 2014[13]					
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
American Pediatric Surgical Association (APSA) - Prevention of infectious complications after elective colorectal surgery in children 2014[14]					
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 4: Strengths and Limitations of Randomized Controlled Trials using Downs and Black[7]

Item	Citation	
	Ikeda, 2016[9]	Patial, 2017[10]
Reporting		
Is the hypothesis/aim/objective of the study clearly described?	⊕	X
Are the main outcomes to be measured clearly described in the Introduction or Methods section?	⊕	X
Are the characteristics of the patients included in the study clearly described?	⊕	X
Are the interventions of interest clearly described?	⊕	⊕
Are the distributions of principal confounders in each group of subjects to be compared clearly described?	⊕	X
Are the main findings of the study clearly described?	⊕	X
Does the study provide estimates of the random variability in the data for the main outcomes?	⊕	X
Have all important adverse events that may be a consequence of the intervention been reported?	⊕	?
Have the characteristics of patients lost to follow-up been described?	n/a	X
Have actual probability values been reported for the main outcomes?	⊕	⊕
External Validity		
Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	?	?
Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	?	?
Were the staff, place, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	?	?
Internal Validity – Bias		
Was an attempt made to blind study subjects to the intervention they have received?	X	X
Was an attempt made to blind those measuring the main outcomes of the intervention?	⊕	X
In trials and cohort studies do the analyses adjust for different lengths of follow-up of patients or in case-control studies is the time period between the intervention and outcome the same for cases and controls?	n/a	?
Were the statistical tests used to assess the main outcomes appropriate?	⊕	?
Was compliance with the intervention/s reliable?	⊕	⊕
Were the main outcome measures used accurate (valid and reliable)?	⊕	⊕
Internal Validity – Confounding		
Were the patients in different intervention groups or were the cases and controls recruited from the same population?	⊕	⊕
Were study subjects in different intervention groups or were the cases and controls recruited over the same period of time?	⊕	⊕
Were study subjects randomized to intervention groups?	⊕	⊕
Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	⊕	?
Was there adjustment for confounding in the analyses from which the main findings were drawn?	⊕	?

Item	Citation	
	Ikeda, 2016[9]	Patial, 2017[10]
Were losses of patients to follow-up taken into account?	n/a	?
Power		
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	⊕	X
Additional Critical Appraisal Points		
Was conflict of interest mentioned?	⊕	⊕

Legend: ⊕ = Yes; X = No; ? = Unclear

Table 5: Strengths and Limitations of Guidelines using AGREE II[8]

Strengths	Limitations
American Society of Colon and Rectal Surgeons (ASCRS) & Society of American Gastrointestinal and Endoscopic Surgeons(SAGES) 2017[11]	
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. 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.	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).
World Health Organization (WHO) Global Guidelines for the Prevention of Surgical Site Infection 2016[3]	
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.	Rigour of development • Criteria for selecting the evidence were not fully described in the guideline but are available in the attached online appendices. Applicability • The guideline did not describe facilitators of and barriers to its application.

Table 5: Strengths and Limitations of Guidelines using AGREE II[8]

Strengths	Limitations
• 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.	
American College of Surgeons (ACS) and Surgical Infection Society *Update* 2016[12]	
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

Table 5: Strengths and Limitations of Guidelines using AGREE II[8]

Strengths	Limitations
	application.
ASCRS Practice Parameters for the Treatment of Sigmoid Diverticulitis 2014[13]	
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 from if 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[14]	
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). • 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	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 recommendations were not explicitly considered for our comparison of interest (PO antibiotics). Editorial Independence • Funding unclear. There was no conflict of interest statement.

Table 5: Strengths and Limitations of Guidelines using AGREE II[8]

Strengths	Limitations
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.	
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 = oral; 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 Author's Conclusions

Table 6: Summary of Findings of Included Randomized Controlled Trials

Main Study Findings	Author's Conclusions
Ikeda(2016)[9]	
Subgroup of Interest (n = 70): Patients who did not use MBP: • Incidence of infection was not provided for this subgroup • IV versus IV+PO: OR 1.07, 95% CI: 0.22 to 5.19; *P* = 1.00	• The authors did not make conclusions regarding the subgroup analysis
Patial(2017)[10]	
Incidence of events, IV versus MBP+IV, n • SSI: 4 vs 5 • Wound hematoma: 1 vs 1 • Intra abdominal collection: 3 vs 0 • Anastomotic leak 1 vs 0 • Enterocutaneous fistula 1 vs 1 • Death: 1 vs 1 • Total: 11 vs 7; *P* =0.20	• "This study suggests that patients who undergo MBP before colorectal surgery, have a slightly higher rate of wound infection but have similar rates of the anastomotic leak when compared to patients not undergoing MBP. Although the results of this study are for the omission of MBP, our study was limited by a small sample size, varied distribution of diagnosis and lack of a quantitative bacterial count. We opine that MBP is not necessarily essential for safe colorectal surgery. Healing of the loaded bowel is more than feasible. More powerful randomized clinical trials and meta‐analysis are needed to accept or deny the role of bowel preparation in colorectal surgery." (page 105)

CI= confidence interval; IV = intravenous antibiotic prophylaxis; MBP = mechanical bowel preparation; n/a = not applicable; NR = not reported; OR = odds ratio; PO = oral antibiotic prophylaxis; RCT = randomized controlled trial; RR = relative risk; SD = standard deviation; SSI = surgical site infection

Table 7: Summary of Clinical Practice Guidelines

Recommendations and Supporting Evidence
American Society of Colon and Rectal Surgeons (ASCRS) & Society of American Gastrointestinal and Endoscopic Surgeons 2017[11]
"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." (page 764) These guidelines do not make explicit recommendations about intravenous antibiotic use, but they do suggest using a bundle of preventative measures and cite intravenous ertapenem as an example of a preoperative intravenous antibiotic that could be used in the bundle. (page 765)
World Health Organization (WHO) Global Guidelines for the Prevention of Surgical Site Infection 2016[3]
"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)." Page 76 (This recommendation is based on a systematic review that included 13 RCTs (years 1994 to 2012) that compared MBP plus intravenous antibiotics versus intravenous antibiotics alone.) 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. The WHO guidelines suggest that "Surgical Antibiotic Prophylaxis" (could be parenteral or non-parenteral) be administered "prior to surgical incision when indicated" (page 72) but does not specify which surgeries this is indicated for.
American College of Surgeons (ACS) and Surgical Infection Society Update 2016[12]
"Combination mechanical and antibiotic (oral) preparation is recommended for all elective colectomies." (page 61) Regarding preoperative intravenous antibiotic use, the guideline states: "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." (page 66)
ASCRS Sigmoid Diverticulitis 2014[13]
Regarding elective or emergency surgery for sigmoid diverticulitis, the guidelines recommend: "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." (page 91) No specific recommendations are given on intravenous antibiotic use in the context of surgery for sigmoid diverticulitis.
American Pediatric Surgical Association (APSA) - Prevention of infectious complications after elective colorectal surgery in children 2014[14]
"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)." (page 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)." (page 198)

Table 7: Summary of Clinical Practice Guidelines

Recommendations and Supporting Evidence
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." (page 196)
Clinical practice guidelines for antimicrobial prophylaxis in surgery (ASHP, IDSA, SIS, SHEA). 2013[2]
Regarding oral antibiotics and MBP for colorectal procedures: "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.)" (page 226) *Oral Antibiotics for colorectal surgery prophylaxis recommended dose (used in conjunction with MBP)* • Erythromycin base: Adults (1g), Pediatrics (20mg/kg) • Metronidazole: Adults (1g), Pediatrics (15mg/kg) • Neomycin: Adults (1g), Pediatrics (15mg/kg) (page 198) Regarding intravenous antibiotics for colorectal procedures: "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." (page 226) Recommended intravenous agents (page 200) • Cefazolin plus metronidazole, cefoxitin, cefotetan, ampicillin-sulbactam, ceftriaxone plus metronidazole, ertapenem Alternative recommended agents in patients with beta lactam allergy (page 200) • Clindamycin plus aminoglycoside or aztreonam or fluoroquinolone, metronidazole plus aminoglycoside or fluoroquinolone

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Appendix 5: Additional References of Potential Interest

Randomized controlled study protocols:

Mulder T, Kluytmans-van den Bergh MFQ, de Smet AMGA, van ', V, Roos D, Nikolakopoulos S, et al. Prevention of severe infectious complications after colorectal surgery using preoperative orally administered antibiotic prophylaxis (PreCaution): study protocol for a randomized controlled trial. Trials. 2018 Jan 19;19(1):51, 2018.
PubMed: PM29351789

Abis GS, Oosterling SJ, Stockmann HB, van der Bij GJ, van EM, Vandenbroucke-Grauls CM, et al. Perioperative selective decontamination of the digestive tract and standard antibiotic prophylaxis versus standard antibiotic prophylaxis alone in elective colorectal cancer patients. Dan Med J. 2014 Apr;61(4):A4695, 2014.
PubMed: PM24814583