GUIDELINE PROTOCOL

EAES, SAGES and ESCP Rapid Guideline: Bowel preparation for minimally invasive colorectal resection

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Conflicts of interest

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INTRODUCTION

Background

Bowel preparation has been an integral part of the preoperative workup before colorectal surgery. It consists of a bundle of measures, that include mechanical bowel cleansing, oral or intravenous antibiotics, enemas, or a combination *[1]*. The expected benefit is a decrease in the incidence of infectious complications, such as superficial surgical site infection and organ space infection *[2]*. Mechanical bowel preparation may cause discomfort to the patient, loss of significant amount of fluids that may lead to dehydration, with implications on the intraoperative and perioperative management.

With the advent of minimally invasive surgery and enhanced recovery programs, the clinical merit of bowel preparation has been questioned. National and international guidelines have recommended using a combination of oral antibiotics with mechanical bowel preparation *[6,7]*. These were based upon head-to-head comparisons between options, which, however, does not allow for assessment of intervention effects within the same analysis model. Advanced meta-analytical techniques allow for comparison of multiple interventions, enhancing the precision of effect estimates, potentially resulting in higher certainty of the evidence compared to pairwise comparisons *[5]*.

Members of the European Association for Endoscopic Surgery (EAES) have prioritized bowel preparation for minimally invasive colorectal surgery in a survey of the EAES Guidelines Subcommittee (31.8% among respondents; 95% confidence interval, 25.9%-37.7%) *[6]*.

Objective

The aim of this rapid guideline is to provide evidence-informed, state-of-the-art, trustworthy recommendations on bowel preparation prior to minimally invasive colorectal surgery, with the objective to support general and colorectal surgeons, other healthcare professionals, and patients in clinical decision making, and ultimately improve patient outcomes and experience.

METHODS

The present protocol adheres to applicable AGREE-S and PRISMA-P reporting standards *[7,8]*. It will be registered at the International Practice Guideline Registry Platform. We will invite EAES members and other stakeholders through email newsletter and invitation on the social media to comment on the content. Reasonable comments will be considered by the steering group to be incorporated in an amended protocol.

Terminology

This guideline will apply to minimally invasive elective colorectal resections, laparoscopic or robotic. We will exclude hand-assisted laparoscopic surgery and single-incision laparoscopic surgery procedures.

Mechanical bowel preparation refers to any oral medication with the intent to cleanse the bowel from its contents, administered between 12-48 hours prior to surgery. By oral and intravenous antibiotics, we refer to any antibiotics given orally or intravenously between 12-48 hours prior to surgery, not before induction to anesthesia or intraoperatively, for purposes of infection prophylaxis.

Funding

This project is funded by EAES. The funding body had no influence on the development of this protocol and will not have any influence on the guideline development process.

Steering group

The steering group will consist of two general surgeons performing minimally invasive colorectal surgery. A member of the steering group is chair of the EAES Guidelines Subcommittee.

Guideline methodologist

The project will be steered by a certified guideline methodologist (certificate number 2021-L2-V1-00001), who has participated in the development of more than 15 clinical practice guidelines and has vast experience in evidence

synthesis. A member of the EAES Guidelines Subcommittee who has undergone formal training to become guideline methodologist, will assume parts of this role under supervision from the senior methodologist.

Guideline panel and external advisors

The guideline panel will consist of 7 general/colorectal surgeons whose colorectal surgery practice consists primarily of minimally invasive surgery, 1 anesthetist, 1 infectious disease specialist, 1 wound care nurse and 1 patient representative. The patient representative will have undergone laparoscopic colorectal surgery with mechanical/oral bowel preparation. He/she will be ordinary panel member with equal participation and voting rights. The author of a recent systematic review and network meta-analysis on the topic will be invited to participate as external advisor (with no voting rights or active participation in the evidence-to-decision framework), as per Guidelines International Network principles *[9]*. The guideline panel's and external advisor's contribution will be acknowledged by authorship in the resulting journal publication of this guideline.

Guideline question

The question that will be addressed by this rapid guideline is:

<u>Should mechanical, oral antibiotic, intravenous antibiotic, any combination, or no bowel preparation be used before minimally invasive colorectal surgery?</u>

The interventions of interest are:

- Mechanical bowel preparation + intravenous antibiotics
- Intravenous antibiotics
- Intravenous antibiotics with an enema
- Intravenous and oral antibiotics
- *Mechanical bowel preparation + intravenous antibiotics + oral antibiotics*
- Mechanical bowel preparation + oral antibiotics
- Oral antibiotics

Subgroup analyses, if sufficient data will be available, will address minimally invasive right colectomy, minimally invasive left colectomy/rectal resection; intracorporeal and extracorporeal anastomosis.

Further subgroup analyses will address mechanical bowel preparation + intravenous antibiotics + oral antibiotics with good aerobic and anaerobic intravenous antibiotic cover, and additional oral antibiotics; and mechanical bowel preparation + intravenous antibiotics with incomplete cover + oral antibiotics with good aerobic and anaerobic cover.

This guideline will refer to adult patients who are deemed fit for minimally invasive surgery, undergoing elective colorectal resection, regardless of the indication.

Selecting outcomes of interest and setting minimal important differences

The steering group will develop a list of candidate outcomes. Panel members and external advisors will vote on the importance of the outcomes using the GRADE scale *[10]* and propose additional important or critical outcomes. The median score for each outcome will be calculated, and important (score 4-6) and critical (score 7-9) items will be selected. In case there is wide variation in panel members' and external advisors' judgements (i.e., insufficient importance and critical importance for a given outcome), they will have an online meeting steered by the methodologist to discuss their judgements and arrive at consensus. We will make every effort to prioritize patient-important outcomes and limit the number of outcomes, as per Cochrane guidance *[11]*.

Furthermore, panel members and external advisors will be asked to set minimal important differences per outcome, following a fully contextualized approach *[12]* (e.g., "If 'major complications' was the only outcome of interest, which difference between any of the interventions would be clinically important"), with multiple choice responses (e.g., 5 out of 1000; 10 out of 1000, etc.), and the option to provide an alternate response. We will select the median minimal important difference for each outcome, unless there is substantial variation in responses, in which case panel members will convene online to reach consensus under the guidance of the methodologist.

Systematic review

In a scoping search of the literature, we identified a recent systematic review and network meta-analysis addressing the question of this guideline. We will contact the primary author of this review to collaborate in the role of an external advisor, as above. We will update the search on PubMed using the respective search string used in the original review, to identify any additional records published since the date of the original search. The search will be confined to the English language. Two systematic reviewers will screen any additional records in a blinded manner using the platform *Rayyan [13]*. Conflicts will be resolved by discussion after unblinding, and the methodologist will adjudicate remaining disagreements. The same reviewers, in collaboration with the methodologist, will select articles based on full text screening. They will extract study and patient population characteristics, and outcome data in duplicate; the first author will resolve disagreements. We will assess risk of bias assessment of randomized trials using RoB 2.0, per outcome or per group of outcomes, if these share similar follow-up features (e.g., timing and method of assessment) *[11,12]*. We will provide detailed risk of bias judgements and we will summarize these using the *robvis* tool *[14]*.

Evidence synthesis methodology

Network meta-analysis is a popular statistical method that synthesizes direct and indirect evidence; it allows estimation of the relative effectiveness between any pair of interventions within a network of interventions. It can also generate a relative ranking of interventions.

For dichotomous outcomes, we will extract for each group the number of events and the sample size, and we will estimate the study-specific odds ratios along with their corresponding 95% confidence intervals. A continuity correction will be applied to studies with zero-cell counts. For any continuous outcomes we will extract for each group the mean, the sample size, the standard deviation and we will estimate the study-specific standardized mean differences along with their corresponding 95% confidence intervals.

We will create network plots for each outcome to visualize the structure of intervention comparisons. The nodes correspond to the interventions and the edges display the observed intervention comparisons. We will set the size of nodes and thickness of edges proportional to the number of participants randomized to each intervention and each comparison respectively.

For each outcome, we will conduct a random effects network meta-analysis within a frequentist framework using methods derived from graph theory *[15]*. All analyses will be performed in R software, using the "netmeta" package *[16,17]*.

The effect estimates (direct, indirect and mixed) will be expressed as odds ratios (OR) or standardized mean differences (MD) for dichotomous outcomes and continuous variables, respectively, along with 95% CIs.
Forest plots and league tables will be used to display the results. We will provide also the 95% prediction intervals for all outcomes.

A fundamental assumption of network meta-analysis is transitivity, which suggests that the distribution of effect modifiers is similar across intervention comparisons. The statistical manifestation of transitivity is consistency (or coherence) which, refers to the statistical agreement between the observed direct and indirect sources of evidence. Incoherent NMA results can be less interpretable and reliable. We will apply the node-splitting approach and the net heat plot to locally check for consistency in our networks *[18,19]*.

We will generate a hierarchy of treatments, using P-scores *[20]*. P-scores give the probabilities, for each intervention to be better than all competing interventions; the closer the P-score to 1 the better the intervention. We will use CiNEMA to evaluate the confidence placed in network effect estimates for the primary outcome regarding six areas, namely within study bias, reporting bias, indirectness, imprecision, heterogeneity and incoherence (inconsistency) *[21]*.

Evidence appraisal

Results of evidence syntheses will be summarized in evidence tables on MAGICapp *[22]*. We will use the CINeMA software to summarize risk of bias according to the contribution of each study to the network for the respective outcome *[21,23]*. The overall risk of (within study) bias will be based upon the highest proportion of risk of bias contributed to the network, as per CINeMA methodology *[21]*. Judgements on publication (reporting) bias will be based on comparison-adjusted funnel plots. Judgements on indirectness will be based on conceptual differences between the study populations, settings and interventions, and the presence of direct evidence; if only indirect evidence will be present (which does not allow for assessment of inconsistency), we will downgrade the evidence certainty by one level. Heterogeneity judgements will be based upon statistical calculations of heterogeneity and consistency. If substantial

heterogeneity or inconsistency will be found, we will downgrade the certainty in the evidence by one or two levels. Judgements on imprecision will be based upon minimal important differences that will be set by majority voting of the guideline panel in advance, according to principles of a fully contextualized approach (minimal important differences for each outcome were based upon the assumption that each outcome is the only outcome of interest) *[12]*.

For each outcome, we will stratify interventions by certainty (moderate-to-high or low-to-very low). We will then group interventions within each stratum into 3 groups according to their statistical ranking: among the best, inferior to the best/better than the worst, and among the worst. The classified rankings were considered by panel members as complementary to the GRADE evidence tables. This process facilitates assessment of both the certainty of the evidence on each intervention along with their ranking *[24]*.

Evidence to decision framework

The guideline panel will review the evidence tables and the stratified rankings. In an in-person consensus meeting, panel members will provide their judgements on:

- the magnitude of benefit of each intervention
- the magnitude of harm of each intervention
- the certainty of the evidence for each intervention
- any variability in patients' values and preferences
- costs or savings related to each intervention
- effect of each intervention on equity
- acceptability of each intervention
- feasibility of each intervention

Following the in-person meeting, panel members will vote on the direction and the strength of the recommendations in an online voting and will formulate the recommendation through a Delphi process. Modifications to the formulation of the recommendations will have to agree with the GRADE methodology to be considered *[23]*. Consensus will be defined as agreement above 80% among panel members.

Target users

The guideline aims to inform the practice and decisions of minimally invasive general and colorectal surgeons, anesthetists, and patients. A patient version of the manuscript written in lay language will accompany the guideline report.

Publication and dissemination strategy

This guideline is funded and sponsored by EAES and will be submitted for publication in *Surgical Endosccopy and Other Interventional Techniques*, official journal of the Association.

Feedback

The steering group will consider constructive comments on the guideline report through social media, letters to the editor and other, and consider such feedback in future updates of the guideline.

Monitoring, update and future steps

The use of the guideline will be reviewed by EAES members 2 years after publication via an online survey. An update of this guideline will be planned depending on the expected timing of publication of new studies, and will be implemented based on availability of new literature on the topic.

DISCUSSION

Implications for practice and research

We aim to summarize pertinent information on the outcome of the use of mechanical bowel preparation, oral antibiotics, and rectal enema, or any combination prior to minimally invasive colorectal resections, that will inform clinical practice and decision making of stakeholders. The systematic review and meta-analysis is also expected to offer insight into areas of development in research, identifying substantial evidence gaps or insufficiencies.

Strengths and limitations

There are documented limitations associated with the rapid review process, including lack of consistency across research techniques and reporting, as well as variation in the definitions associated with rapid reviews. There is also evidence to support rapid reviews as having similar conclusions to systematic reviews and other benefits such as accelerated time to conduct research, better use of resources and gaining an overview of evidence on a particular topic *[25-27]*. As such, the rapid review process is identified as having an important role in producing policy guidelines and supporting decision making.

Research ethics

All members of the guideline development group will declare any direct (financial) or indirect (intellectual) conflicts of interest. Conflicts will be managed according to Guidelines International Network principles; members with relevant direct or indirect conflicts will participate as external advisors, with no participation in the discussions about the direction and the strength of the recommendations, nor the voting procedure or the Delphi process to consolidate the recommendations *[28]*.

CONCLUSION

The rapid guideline will provide evidence-based recommendations on bowel preparation for laparoscopic colorectal surgery.

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