Systematic Reviews

PROTOCOL

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Antibiotic prophylaxis for the prevention of surgical site infections following colorectal surgery: protocol for network meta-analysis of randomized trials

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Abstract

Background Surgical site infections continue to be a significant challenge following colorectal surgery. These can result in extended hospital stays, hospital readmissions, increased treatment costs, and negative effects on patients' quality of life. Antibiotic prophylaxis plays a crucial role in preventing infection during surgery, specifically in preventing surgical site infections after colorectal surgery in adult patients. However, the optimal antibiotic regimen is still unclear based on current evidence. Considering the limitations of existing reviews, our goal is to conduct a comprehensive systematic review and network meta-analysis of randomized controlled trials to evaluate the comparative benefits and harms of available antibiotic prophylaxis regimens for preventing surgical site infections following colorectal surgery in adult patients.

Methods We will search the Medline, EMBASE, CINAHL, Scopus, and Cochrane Central Register of Controlled Trials databases to identify relevant randomized controlled trials. We will include trials that (1) enrolled adults who underwent colorectal surgeries and (2) randomized them to any systemic administration of antibiotic (single or combined) prophylaxis before surgery compared to an alternative systemic antibiotic (single or combined antibiotic), placebo, control, or no prophylactic treatment. Pairs of reviewers will independently assess the risk of bias among eligible trials using a modified Cochrane risk of bias instrument for randomized trials. Our outcomes of interest include the rate of surgical site infection within 30 days of surgery, hospital length of stay, 30-day mortality, and treatment-related adverse effects. We will perform a contrast-based network meta-analysis using a frequentist random-effects model assuming a common heterogeneity parameter. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach will be utilized to assess the certainty of evidence for treatment effects.

Discussion By synthesizing evidence from available RCTs, this study will provide valuable insight for clinicians, patients, and health policymakers on the most effective antibiotics for preventing surgical site infection.

Systematic review registration PROSPERO CRD42023434544.

Keywords Antibiotic prophylaxis, Surgical site infection, Colorectal surgery, Network meta-analysis

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Background

Surgical site infections (SSIs) are infections that involve the skin, subcutaneous tissue, fascia, or muscle of the incision after surgery and can occur within 30 days of an operation [1]. Surgical site infections following colorectal surgery remain an important challenge [2]. Despite antibiotic prophylaxis for colorectal surgery, 10 to 25% of patients experience SSI after surgery. SSIs following colorectal surgery lead to increased patient morbidity and mortality and result in prolonged hospital length of stay, hospital readmissions, higher treatment costs, and negative effects on patients' quality of life [3–6].

Various studies have assessed the economic impact of SSIs in different countries [7–9]. In 2009, Scott estimated that the annual cost of SSI in the USA ranged from 3 to 10 billion USD [7]. In 2013, Shepard et al. conducted a study on the financial impact of SSIs in hospitals. They found that SSIs increase the cost of hospitalizations and diminish hospital profits due to prolonged length of stay [8]. In 2009, Tanner et al. estimated that SSIs accounted for an attributable cost of £30 million per year in the UK [9].

Perioperative antimicrobial prophylaxis is a preventive measure used in clean and clean-contaminated surgical procedures to reduce the occurrence of SSI [10]. The effectiveness of different antibiotics for preventing infections has been extensively studied for various surgical procedures, including first-generation cephalosporins (such as cephaloridine and cefazolin), second-generation cephalosporins (such as cefuroxime), third-generation cephalosporins (such as cefonicid and cefotaxime), β-lactam and β-lactamase inhibitors (such as amoxicillin–clavulanic acid and ampicillin-sulbactam), and fluoroquinolones (including ciprofloxacin and levofloxacin) [11–20].

This systematic review and network meta-analysis aims to significantly advance the understanding of antibiotic prophylaxis for preventing SSIs following colorectal surgery in adult patients by addressing several critical gaps and shortcomings in the existing literature [6, 21].

Firstly, previous reviews have often failed to provide a comprehensive assessment of the overall certainty of evidence supporting different antibiotic prophylaxis regimens. Many have relied on subjective probability ranking or simple pairwise comparisons without robustly evaluating the quality of included studies. Our review will employ Grading of Recommendations Assessment, Development and Evaluation (GRADE), to systematically assess the quality of evidence across studies. By doing so, we will enhance the reliability of recommendations for clinical practice and policy-making, ensuring that the decisions are based on the strongest available evidence.

Secondly, existing reviews focused on individual antibiotics or limited comparisons between a few regimens. In contrast, our review will utilize network meta-analysis that allows for simultaneous comparison of multiple antibiotic regimens across studies. By exploring a broader spectrum of prophylactic strategies, we aim to identify the most effective and optimal regimens for reducing SSIs after colorectal surgery.

By synthesizing and critically appraising the most recent and relevant evidence, our review aims to fill gaps left by previous literature, offering a robust and nuanced analysis of antibiotic prophylaxis strategies for SSIs after colorectal surgery. Ultimately, our findings will contribute to improved clinical decision-making, better patient outcomes, and informed healthcare policies aimed at optimizing surgical care and reducing the burden of SSIs in this patient population.

Methods

Registration and reporting

Our protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) guidelines [22]. We registered this protocol in PROSPERO (CRD42023434544) and will follow the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) extension statement for reporting of systematic reviews incorporating network meta-analysis (NMA) of health care interventions [23].

Search strategy

An experienced medical librarian developed database-specific search strategies to search Medline, EMBASE, CINAHL, Scopus, and Cochrane Central Register of Controlled Trials to find relevant randomized controlled trials (RCTs) (Appendix). Our search strategies will be restricted to English-language publications. We will review the reference lists of the included studies and relevant reviews for potentially eligible RCTs not captured by our search.

Eligibility criteria and study selection

We will include clinical trials that (1) enrolled adults (age 18 years and older) who underwent colorectal surgery and (2) randomized them to any systemic administration of antibiotic prophylaxis (including oral, intramuscular, and intravenous routes), either as single or combined, before surgery. This includes digestive decontamination antibiotics. Comparators will be alternative systemic antibiotics (single or combined), placebo, control, or no prophylactic treatment. Additionally, selective digestive decontamination antibiotics administrated orally will be included. We will exclude studies with vaginal, (intra) rectal, topical, and subcutaneous routes of antibiotic administration. We will exclude RCTs that used antibiotic prophylaxis during or after surgery. Our outcomes of

interest include the rate of SSI within 30 days of surgery, hospital length of stay, 30-day mortality, and treatment-related adverse effects.

We will use Covidence [24], an online systematic review software, to screen for eligible studies. Pairs of reviewers will screen titles and abstracts of records identified through searches. Subsequently, the same pairs of reviewers independently will review the full reports of those identified as potentially eligible to confirm eligibility. Disagreements will be resolved through discussion or by the involvement of a third reviewer if needed.

Data extraction and risk of bias assessment

We will use a standardized form and a comprehensive instruction manual for data abstraction. To ensure the consistency and accuracy of the data extraction, calibration exercises will be performed before the data extraction. Pairs of reviewers will extract the following information from eligible studies: (i) study characteristics, such as author names, publication year, country of origin, and funding source; (ii) population-related details, including the number of patients randomized, participants' mean age, percentage of females, type of surgical procedure (e.g., elective, emergency), duration of surgery, and length of hospital stay; (iii) characteristics of intervention and comparison(s), such as dosage, formulation, and route of administration, duration of treatment, and timing of antibiotic prophylaxis; and (iv) outcomes of interest.

Pairs of reviewers will independently assess the risk of bias among eligible trials using a Cochrane risk of bias instrument (RoB 1.0) for randomized trials considering issues related to random sequence generation, allocation concealment, blinding of participants, healthcare providers, and data collectors/adjudicators, and incomplete outcome data (>20% missing data will be considered as high risk of bias) [25, 26]. We will use a modified version with the following answers "definitely yes" or "probably yes" (considered as low risk of bias), or "definitely no" or "probably no" (considered high risk of bias) rather than the standard responses (high, low, or unclear) [25]. This approach ensures that our risk of bias assessments do not rely on an "unclear" response option. Reviewers will resolve disagreements in data extraction and risk of bias assessment by discussion and, if needed, adjudication by a third reviewer. To visualize the risk of bias assessments, we will use the Robvis tool (https://mcguinlu.shinyapps.io/robvis).

Data synthesis

For direct comparisons, we will pool data for all outcomes reported by at least two trials addressing the same comparison. For dichotomous outcomes (e.g., SSI, treatment-related adverse effects), we will calculate the relative risk (RR) and 95% confidence interval (CI) as effect measure, and for the duration of hospital stay, we will calculate the mean difference and 95% CI as effect measure. We will use a DerSimonian-Laird random-effects model for the meta-analysis of direct comparisons and assess heterogeneity between trials for each direct comparison using Cochran's Q and I^2 statistics.

We will evaluate the feasibility of conducting NMA for each outcome by examining network connectivity, ensuring that there are more trials available than the number of intervention nodes, and confirming the presence of at least 10 trials in any network. Additionally, we will use the NMA-studio web application (https://www.nmastudioapp.com) to evaluate the transitivity assumption [27]. We will examine the distribution of potential prognostic factors (such as the mean age of participants, type of surgical procedure, and duration and timing of antibiotic therapy) across treatment comparisons to investigate potential intransitivity. In cases where it is not feasible to perform NMA (due to insufficient studies to construct a network or disconnected fragments for the outcome network), we will conduct a conventional pairwise meta-analysis using the DerSimonian-Laird random-effects model for any comparison informed by at least two trials. For any direct comparison with at least ten trials contributing to the meta-analysis, we will assess small-study effects using Harbord's test for binary outcomes and Egger's test for duration of hospital stay [28, 29].

We will perform contrast-based NMA using a frequentist random-effects model assuming a common heterogeneity parameter [30, 31]. The coherence (i.e., consistency) assumption at the network level will be confirmed through the "design-by-treatment" model (global test) [30]. Additionally, we will use a side-splitting approach to evaluate local incoherence in each closed loop of the network, which involves calculating the difference between direct and indirect evidence [32, 33]. We will create a network diagram at the intervention level to visualize the available evidence and will present a league table showing relative effect estimates for all interventions. To explore the impact of important prognostic factors on network estimates of effect, we will examine the following subgroups when feasible by running network meta-regression: (1) cancer vs noncancer population, (2) sex (male vs female), (3) bowel preparation vs no bowel preparation, (4) surgical procedure (elective vs emergency), and (5) risk of bias (low vs high risk). All the statistical analyses will be performed using Stata (StataCorp, Release 18.0, College Station, TX, USA).

Assessing certainty of the evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach will be utilized to assess the certainty of evidence for treatment effects. We will first assess the certainty of direct estimates, considering conventional GRADE guidance, i.e., starting certainty of the evidence for RCTs as high, and consider rating down based on the risk of bias, inconsistency, indirectness, or publication bias [34, 35]. Certainty ratings for indirect estimates start at the lowest GRADE rating of the direct comparisons that contributed to the most dominant first-order loop, with further rating down for intransitivity when present [35, 36]. The certainty of the evidence for network estimates will be informed by the higher rating of the direct and indirect evidence [35] considering issues related to imprecision and incoherence.

GRADE minimally contextualized approach for treatment hierarchy

To optimize the interpretation of NMA findings, we will apply a minimally contextualized approach in which we categorize interventions based on their effect estimates (from most to least effective/harmful) and their associated certainty of evidence. For each benefit outcome, we plan to group interventions into three categories: (1) the reference intervention (placebo) and interventions no different from placebo, which we will call "among the least effective;" (2) interventions superior to placebo but not superior to other intervention(s), which we will describe as "among the intermediate;" and (3) interventions that proved superior to at least one among the intermediate interventions, which we defined as "among the most effective." Next, these interventions will be divided into those with moderate or high certainty, and those with low or very low certainty [37, 38].

We will use the same approach for treatment-related adverse effects, but we will group interventions into three categories as follows: (1) interventions that are no more harmful than placebo; (2) interventions that are less harmful than some alternatives, but more harmful than placebo; and (3) interventions that are among the most harmful.

Discussion

SSI poses a significant challenge following colorectal surgery, presenting both clinical and economical burdens. Given its high incidence rate and substantial socioeconomic impact, coupled with the variability in surgical practices due to limited comparative effectiveness data on preventive interventions, there is a critical need for a rigorous systematic review and network meta-analysis to guide evidence-based SSI prevention strategies.

Our study offers several strengths compared to existing reviews. First, we will comprehensively evaluate the comparative effectiveness of all current interventional strategies for patients undergoing colorectal surgery. Second, we will employ the GRADE approach to assess the certainty of evidence supporting these treatments.

This network meta-analysis aims to evaluate the effectiveness of different antibiotic prophylaxis regimens in reducing the incidence of SSIs after colorectal surgery. By synthesizing evidence from available RCTs, this study will provide valuable insight to clinicians on the most effective antibiotics to prevent SSIs. One potential challenge may arise from the availability and diversity of treatment comparisons needed to construct robust networks for analysis.

To facilitate dissemination of our findings, we plan to publish our results in peer-reviewed journals and present them at national and international scientific conferences, thereby ensuring broad accessibility and impact.

Appendix

Search strategy

MEDLINE (OVID)

1 colorectal surgery.mp. or colorectal/
2 Colectomy/ or colectom*.mp.
3 1 or 2
4 exp Anti-Bacterial Agents/
5 Antibiotic Prophylaxis/
6 cefuroxime.mp. or Cefuroxime/
7 metronidazole.mp. or Metronidazole/
8 cefazolin.mp. or Cefazolin/
9 levofloxacin.mp. or Levofloxacin/
10 clindamycin.mp. or Clindamycin/
11 vancomycin.mp. or Vancomycin/
12 ciprofloxacin.mp. or Ciprofloxacin/
13 Ampicillin/ or ampicillin.mp.
14 aztreonam.mp. or Aztreonam/
15 cefotaxime.mp. or Cefotaxime/
16 cefoxitin.mp. or Cefoxitin/
17 cefotetan.mp. or Cefotetan/
18 ceftriaxone.mp. or Ceftriaxone/
19 Ertapenem/ or ertapenem.mp.
20 fluconazole.mp. or Fluconazole/
21 gentamicins.mp. or Gentamicins/
22 moxifloxacin.mp. or Moxifloxacin/
23 Piperacillin, Tazobactam Drug Combination/ or piperacillin.mp.
24 sultamicillin.mp.
25 sulbactam.mp. or Sulbactam/
26 Erythromycin/ or erythromycin.mp.
27 neomycin.mp. or Neomycin/

28 (antibacterial or antibiotic or antimicrobial or antiinfective or anti bacterial or anti biotic or antimicrobial or anti infective).mp. [mp = title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]
29 or/4–28
30 3 and 29
31 randomized controlled trial.pt.
32 controlled clinical trial.pt.
33 randomi?ed.ab.
34 placebo.ab.
35 drug therapy.fs.
36 randomly.ab.
37 trial.ab.
38 groups.ab.
39 or/31–38
40 exp animals/ not humans.sh.
41 39 not 40
42 30 and 41

Abbreviations

SSI	Surgical site infections
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
NMA	Network meta-analysis
RCT	Randomized controlled trial
RR	Relative risk
CI	Confidence interval
GRADE	Grading of Recommendations Assessment, Development and Evaluation

Authors' contributions

Shahrzad Motaghi: writing—review and editing, writing—original draft, methodology, conceptualization. Francesca Mulazzani: writing—review and editing. Samer G Karam: writing—review and editing. Fatemeh Mirzayeh Fashami: writing—review and editing. Tayler Buchan: writing—review and editing. Sara Ibrahim: writing—review and editing. Shahryar Moradi Falah Langeroodi: writing—review and editing. Sahar Khademioore: writing—review and editing. Rachel J Couban: writing—review and editing. Lawrence Mbuagbaw: writing—review and editing, supervision, methodology. Dominik Mertz: writing—review and editing, supervision, methodology. Mark Loeb: writing—review and editing, supervision, methodology, conceptualization.

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Declarations

Ethics approval and consent to participate

It should be noted that this protocol was developed without the involvement of any patients.

Consent for publication

Not applicable.

Competing interests

Mark Loeb served on an advisory board for Paladin Labs/Sunovian Pharmaceutics: distributor of the antibiotic daptomycin and Xediton: distributor of the antibiotic meropenem-vaborbactam.

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