Is Single-Dose Antimicrobial Prophylaxis Sufficient to Control Infections in Gastrointestinal Oncological Surgeries?

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Abstract

Surgical site infections (SSIs) represent one of the most important complications occurring postoperatively following surgical procedures. The SSI incidence is higher following gastrointestinal (GI) surgeries compared to any other surgery. It contributes to one of the majority of morbidity and mortality in patients undergoing GI surgeries. The accepted practice worldwide for the prevention and control of SSIs is providing antimicrobial prophylaxis. The appropriate antimicrobial and dose are chosen depending on the microbial flora, complications, and patient risk factors. The objective of this review was to determine the sufficient number of prophylactic antimicrobial doses that would be efficacious and safe in controlling the SSIs following GI oncological surgeries. Single-dose antimicrobial prophylaxis has shown the same efficacy as the multiple-dose antimicrobial regimen in controlling SSIs in esophageal, gastric, and colorectal surgeries. The advantages of a single-dose regimen include less chance of emergence of resistance, less chance for allergies or toxicity, and less cost. The addition of metronidazole with single-dose antimicrobial prophylaxis in colorectal surgery should be considered due to its beneficial effect in further reducing infections. Further randomized controlled trials are needed for the literature to determine the efficacy and safety of single-dose antimicrobial prophylaxis in patients undergoing esophageal and colorectal surgeries. In addition, studies are required to determine the individual effectiveness of metronidazole in controlling SSIs in colorectal surgeries.

Introduction And Background

In any surgery, there is always a process of breaching the normal protective barriers of the human body. There is an increased risk of infections when protective barriers such as skin and mucous membrane are cut through for manipulation. Surgical site infections (SSIs) represent one of the most important complications occurring postoperatively following surgeries [1]. SSIs can be classified into types based on the depth of the infection. It can involve the skin and subcutaneous fat (superficial incisional SSIs), deep tissues such as muscles (deep incisional SSIs), or even extending beyond these limits (organ/space SSIs). SSIs further complicate the postoperative outcomes in patients who undergo surgery, thus negatively impacting the health and wellness of the patient. It not only contributes to morbidity and mortality but also to the cost and quality of life. Therefore, it is crucial to prevent and control SSIs. The accepted practice worldwide for preventing and controlling SSIs is providing antimicrobial prophylaxis to patients undergoing any surgical procedures. The types of SSIs are shown in Figure 1.

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Out of the surgical procedures, gastrointestinal (GI) surgeries pose an important unique issue in terms of SSIs. Patients undergoing GI surgeries have a high risk of SSIs following elective or emergency GI operations than other surgeries. This is because the GI tract serves as a home for many microbial flora that have the potential to breach the mucosal barrier during the surgery and spread superficially or to other places to cause infections. Thus, the incidence of SSIs is higher following GI surgeries than any other surgery, with an average incidence being 10%–25% reported in various studies [2,3]. Surgical procedures in the GI tract can involve the esophagus, stomach, small intestine, colon, and rectum. This list can also include biliary surgeries. One of the most common indications for GI surgery is cancer.

For SSI antimicrobial prophylaxis, the antimicrobial drugs can be given either as a single-dose regimen or multiple-dose regimen in which the postoperative continuation of antimicrobials is warranted. However, each regimen has its strengths and limitations, which vary among different surgical procedures. There are reviews published in the literature comparing the efficacy of a single-dose regimen to multiple-dose antimicrobial prophylaxis in preventing and controlling SSIs in patients undergoing orthognathic procedures, orthopedic procedures, and other major surgeries. In the review article by McDonald et al., the authors concluded that there was no clear superiority of either single dose or more extended duration antimicrobial prophylaxis in preventing infection in major surgeries [4]. Marcussen et al. reported that a single dose of preoperative antimicrobial decreased infection and alveolar osteitis in lower third molar surgical extraction applying osteotomy [5]. In the meta-analysis by Slobogean et al. comparing single-versus multiple-dose antibiotic prophylaxis in preventing SSIs in the surgical treatment of closed fractures, the results could not demonstrate the superiority of multiple-dose antimicrobial prophylaxis over a single-dose regimen [6].

Single-dose antimicrobial prophylaxis is more economical and medically desirable [7]. However, there is a high risk of the emergence of resistance as antimicrobials are given for a longer duration in the case of multiple-dose antimicrobial prophylaxis. In addition to contributing to the emergence of microbial resistance, antimicrobial therapy for a more extended period increases the risk of allergic reactions and adverse events in those patients [7]. Despite the proven efficacy, safety, and importance of antimicrobial prophylaxis in GI surgeries, there is no clear explanation for the sufficient number of doses of antimicrobial therapy that is efficacious and safe to control and prevent SSIs in GI surgeries. Thus, the purpose of this traditional review is to study the effectiveness and safety of single-dose antimicrobial prophylaxis compared to multiple-dose antimicrobial prophylaxis in the control and prevention of SSIs in patients undergoing GI oncological surgeries.

**Review Method**

This traditional review was designed, and its results were reported using the Scale for the Assessment of
We included predominantly randomized controlled trials (RCTs) to provide the highest level of evidence with minimal bias and errors. This study did not have any constraint on any age limit. The studies published between January 2005 and May 2021 were included. Among the studies chosen, it was confirmed that all the studies included human subjects and published in the English language. Studies that did not have full-text available were excluded. Databases used to retrieve articles included PubMed and Cochrane library. These databases were examined for pertinent articles that could be included in this review using appropriate keywords; the keywords and Medical Subject Headings (MeSH) terms used included “Anti-Bacterial Agents,” “Stomach neoplasms,” “Colorectal neoplasms,” “Esophageal neoplasms,” “Surgical wound infections,” “Single-dose antibiotic prophylaxis,” and “Multiple-dose antibiotic prophylaxis.” The Boolean search method was used in PubMed to combine the keywords and MeSH words. Two authors (AK and MR) independently searched PubMed and Cochrane library using the keywords mentioned above and selected the relevant articles based on titles and abstract. Full-text articles of the selected studies were retrieved, and three authors (AK, MR, and SS) examined all the full-text articles for eligibility and relevance. Other authors helped in the final assessment of the included studies. The quality assessment of the included RCTs was performed using the Cochrane Handbook for Systematic Reviews of Interventions. One of the authors (JLD) evaluated the risk of bias in the chosen RCTs.

Results

The preliminary database searches identified a total of 47 articles. Of these, 14 articles that were found to be duplicates were subsequently removed. In PubMed, we applied filters for study type, studies involving humans, and studies in the English language. In the Cochrane library, in addition to year, we applied the filters including study type as trials, and source as Embase. After the application of the filters, a total of 15 articles were identified. We did the preliminary screening of these articles by reading the titles and abstracts, and we excluded seven articles that were not relevant and did not meet the inclusion criteria.

A total of eight studies were included for the review. Of the eight studies, two studies included patients who underwent esophageal cancer surgery. Three studies were on patients who underwent gastric cancer surgeries, and three studies were on patients who underwent colorectal cancer surgeries. Six out of the eight studies were RCTs, and no RCTs involved esophageal cancer surgery. The two studies on esophageal cancer were non-comparative prospective and retrospective studies. The study characteristics are presented in Table 1. The risk of bias assessment and the summary of the risk of bias of all the included RCTs are shown in Figures 2, 3.
| Study                        | Type of study         | Type of cancer                      | Sample size | Details of the surgical procedure                                                                 | Mean duration of operation in minutes (SD vs MD) |
|------------------------------|-----------------------|-------------------------------------|-------------|---------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Ruol et al. (2000) [9]       | Prospective non-comparative study | Esophageal cancer                   | 82          | Total esophageal resection = 3<br>Partial esophageal resection = 79                                | Median operative length = 350 minutes         |
| Hochreiter et al. (2018) [10]| Retrospective study   | Esophageal cancer                   | 173         | Transthoracic esophagectomy with abdominal and mediastinal lymphadenectomy for all the included patients | 275 vs 262.1 (not significant)                |
| Mohri et al. (2007) [11]     | RCT                   | Gastric cancer                      | 486         | Total/proximal gastrectomy = 172 (SD = 78; MD = 94)<br>Distal gastrectomy = 288 (SD = 147; MD = 141)<br>Wedge resection = 3 (SD = 2; MD = 1)<br>Gastrojejunostomy = 23 (SD = 16; MD = 7)<br>Total gastrectomy = 132 (SD = 66; MD = 66)<br>Proximal / distal gastrectomy = 193 (SD = 98; MD = 95) | 232 vs 234 (not significant)                  |
| Haga et al. (2012) [12]      | RCT                   | Gastric cancer                      | 325         | Distal gastrectomy plus lymphadenectomy for all the included patients                              | 181.5 vs 185 (not significant)               |
| Imamura et al. (2012) [13]   | RCT                   | Gastric cancer                      | 355         | Low anterior resection = 38 (SD = 20; MD = 18)<br>Right hemicolecotomy = 23 (SD = 10, MD = 13)<br>Left hemicolecotomy = 6 (SD = 5, MD = 1)<br>Other types = 26 (SD = 13; MD = 13) | 207 vs 212 (not significant)                 |
| Ahn and Lee (2012) [14]      | RCT                   | Colorectal cancer                   | 93          | Conventional method = 262 (SD = 129; MD = 133)<br>Laparoscopic method = 115 (SD = 61; MD = 54)      | 178.8 vs 170 (not significant)               |
| Fujita et al. (2007) [15]    | RCT                   | Colorectal cancer                   | 377         | Open = 120 (SD = 45; MD = 75)<br>Laparoscopic = 69 (SD = 44; MD = 25)<br>Laparoscopic assisted = 126 (SD = 70; MD = 56) | Not mentioned                                |
| Nusrath et al. (2020) [16]   | RCT                   | All clean-contaminated oncological surgeries | 315     |                                                                                                   |                                                |

**TABLE 1: Characteristics of the included studies in this review**

RCT, randomized controlled trial; SD, single-dose group; MD, multiple-dose group
FIGURE 2: Risk of bias in the included randomized controlled trials

| Study                  | D1 | D2 | D3 | D4 | D5 | D6 | D7 |
|------------------------|----|----|----|----|----|----|----|
| Mohri et al. [11]      | +  | -  | -  | -  | +  | +  | +  |
| Haga et al. [12]       | +  | -  | -  | -  | +  | +  | +  |
| Imamura et al. [13]    | -  | -  | X  | X  | +  | +  | +  |
| Ahn and Lee [14]       | +  | -  | -  | -  | +  | +  | +  |
| Fujita et al. [15]     | +  | X  | -  | -  | +  | +  | +  |
| Nusrath et al. [16]    | -  | X  | -  | -  | +  | +  | +  |

D1: Random sequence generation  
D2: Allocation concealment  
D3: Blinding of participants and personnel  
D4: Blinding of outcome assessment  
D5: Incomplete outcome data  
D6: Selective reporting  
D7: Other sources of bias  

| Judgement | | | | | | | |
|------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| High       | Low       | Unclear   |

The randomized controlled trials included for the risk of bias assessment are studies by Mohri et al. [11], Haga et al. [12], Imamura et al. [13], Ahn and Lee [14], Fujita et al. [15], and Nusrath et al. [16].

FIGURE 3: Summary of risk of bias of all the included randomized controlled trials

Discussion

Esophageal Oncological Surgeries: Appropriate Dose for Controlling SSIs and Other Infectious Complications

Esophageal cancer though rare is an invasive and aggressive disease with a poor prognosis and very low survival rate. The poor prognosis is due to various factors such as very late presentation of disease and other surgical procedural difficulties [9,17]. The treatment for esophageal cancer is resection of the tumor, which provides positive outcomes and improvement in the quality of life [9]. The infectious postoperative complications of esophageal surgery include SSIs, abscesses, pneumonia, and urinary tract infections. The serious complications include anastomotic leak and fistula. One of the leading causes of complication in the early postoperative days of esophageal surgery is pneumonia. Compared to other GI surgeries, esophageal surgeries are usually associated with a longer duration of operation, more blood loss, and a different microflora in the operative field [10]. Esophageal surgeries involve both the thorax and abdomen. Staphylococci and gram-negative bacteria are the causative organisms of SSIs and abscesses. But polymicrobial aerobic and anaerobic organisms are also commonly detected [18].
There are not many published studies in the literature that compared the efficacy of single-dose antimicrobial prophylaxis to multiple-dose antimicrobial prophylaxis in esophageal surgeries. In Ruol et al.'s prospective non-comparative study, a total of 82 patients with esophageal cancer who underwent surgery were included. These patients were given a single dose of ceftriaxone as antimicrobial prophylaxis. In addition, three doses of metronidazole were given (preoperatively and postoperatively). Only one patient had postoperative SSI though the overall infection rate was 17%. Even though this study was a non-comparative prospective study, the results showed that a single dose of antimicrobial agent plus metronidazole could provide adequate prophylaxis and less costly for patients undergoing major esophageal surgeries [9].

In another retrospective study by Hochreiter et al., 173 patients who underwent esophageal resection were studied to determine whether multiple-dose antimicrobial prophylaxis helps in reducing postoperative pneumonia and improve mortality. Out of 173 patients, 104 patients received only a single dose of moxifloxacin (control group). The remaining patients received a five-day postoperative therapy with moxifloxacin. In addition, Mezlocillin and metronidazole were given to all patients in both groups. SSI was seen in one patient in the multiple-dose group and two patients in the single-dose group. It showed no statistically significant difference between the two groups [10].

To the best of our knowledge, there are no RCTs in the literature on patients who underwent esophageal cancer surgery. In the studies mentioned above, i.e., Ruol et al. and Hochreiter et al., the single-dose antimicrobial prophylaxis was as effective as the multiple-dose regimen in controlling the SSIs and other infections [9,10]. Metronidazole was added along with the prophylactic antimicrobial agent in both studies. The exact role of the addition of metronidazole has to be further studied in patients undergoing esophageal surgery. The characteristics of the studies included and the incidence of SSIs are summarized in Table 2.

| Study             | Year published | Type of study                        | Single-dose group (n) | Multiple-dose group (n) | SSI in the single-dose group | SSI in the multiple-dose group |
|-------------------|----------------|--------------------------------------|-----------------------|-------------------------|-----------------------------|--------------------------------|
| Ruol et al. [9]   | 2000           | Non-comparative prospective study    | 82                    | No multi-dose group     | 1 (1.2%)                    | Not applicable                |
| Hochreiter et al. [10] | 2018          | Retrospective study                  | 104                   | 69                      | 2 (1.9%)                    | 1 (1.4%)                      |

**TABLE 2: Study characteristics and incidence of SSIs in esophageal oncological surgery**

SSI, surgical site infection

Efficacy and Safety of Single-Dose Versus Multiple-Dose Regimen in Gastric Surgeries for Gastric Cancer

Though not prevalent in western countries, gastric cancer is one of the most commonly diagnosed cancers in Asian countries like China, Japan, and India [19,20]. The commonly done gastric surgeries include distal gastrectomy, total gastrectomy, and sub-total gastrectomy. These procedures involve multiple intestinal anastomosis and manipulation of the liver and pancreas, leading to fistula formation and subsequent infection. Thus, gastric surgeries are associated with a higher incidence of SSIs. According to the studies published in the literature, the incidence of SSI following gastric surgeries is approximately 10%, and thus, the prevention of SSIs is crucial, like in other surgeries, in gastric surgeries [21]. One of the studies in the literature that studied the risk factors of SSIs after gastrectomy is the study by Migita et al. In this study, 842 patients who underwent gastrectomy were studied. The predictors of organ/space SSI were duration of operation, male gender, corticosteroid therapy, and total gastrectomy. The duration of hospital stay and re-operation rates were higher in patients who developed SSIs [19]. As gastric cancer is prevalent in Asian countries, it was found in various studies that the use of antimicrobial prophylaxis for the longer duration in gastric surgeries was widespread in Asian countries. Even though the importance of antimicrobial prophylaxis is well-known and accepted, the ideal number of doses of antimicrobial prophylaxis to prevent SSIs following gastric surgeries remains ambiguous.

In this review, we managed to retrieve only a few RCTs to provide the highest level of evidence. These RCTs included patients with gastric cancer who underwent gastric surgeries to determine the effectiveness of single-dose antimicrobial prophylaxis in controlling SSIs. In this RCT by Mohri et al., patients with gastric cancer were randomized into two groups: single-dose prophylaxis group (n = 245) and multi-dose prophylaxis group (n = 245). The antibiotics used were cefazolin or ampicillin-sulbactam. The difference in the SSI incidence between the two groups was 0.9% (9.5% in the single-dose group vs. 8.6% in the multi-dose group). The incidence of SSIs did not show a significant difference between the two groups. Moreover, on subgroup analysis of patients receiving either cefazolin or ampicillin-sulbactam combination, there was no significant difference between the two antibiotic subgroups in terms of incidence of SSI [11]. A very
similar result was reported by the randomized study by Haga et al. In this study, though the overall incidence of SSIs was less in the multiple-dose group, there was no statistically significant difference between the single-dose and the multiple-dose groups [12]. Imamura et al. conducted an RCT to study the incidence of SSIs with intraoperative antimicrobial prophylaxis and intraoperative plus postoperative administration in a total of 355 patients who underwent distal gastrectomy for gastric cancer. In the intraoperative group (n = 176), 5% patients had SSIs compared to 9% in the extended group (n = 179). The statistical analysis showed that a single dose of intraoperative antimicrobial prophylaxis (which was given before the surgical incision and every three hourly as intraoperative supplements) was non-inferior to the multiple-dose prophylaxis [13].

All the studies mentioned above reported that single-dose antimicrobial prophylaxis for gastric cancer surgery was as effective as multiple-dose antimicrobial prophylaxis for controlling SSIs in patients undergoing gastric cancer surgery. The use of a multiple-dose antimicrobial regimen in gastric surgeries was not recommended in any of the studies, as mentioned earlier. The characteristics of the studies included and the incidence of SSIs are summarized in Table 3.

| Study                | Year published | Type of study | Single-dose group (n) | Multiple-dose group (n) | SSI in the single-dose group | SSI in the multiple-dose group |
|----------------------|----------------|---------------|-----------------------|-------------------------|------------------------------|------------------------------|
| Mohri et al. [11]    | 2007           | RCT           | 243                   | 243                     | 23 (9.5%)                    | 21 (8.6%)                    |
| Haga et al. [12]     | 2012           | RCT           | 164                   | 161                     | 15 (9.1%)                    | 10 (6.2%)                    |
| Imamura et al. [13]  | 2012           | RCT           | 176                   | 179                     | 8 (4.5%)                     | 16 (8.9%)                    |

**TABLE 3: Study characteristics and incidence of SSIs in gastric oncological surgery**

SSI, surgical site infection; RCT, randomized controlled trial

**Colorectal Oncological Surgery: The Role of Antimicrobial Prophylaxis and Addition of Metronidazole to the Regimen**

SSIs are ubiquitous in colorectal surgeries compared to gastric surgeries and other GI surgeries [22,23]. Surgical site infections have been associated with an increased duration of hospital stay, higher readmission rates, morbidity, and mortality. According to the published data, colorectal procedures are associated with 10%-15% of all SSIs [24-26]. The increased incidence of SSIs in colorectal surgeries is due to the presence of a vast majority of bacterial flora in the colon, especially in the distal colon. Colorectal cancer by itself has a very poor survival rate. In addition to the complications of colorectal surgery, SSIs contribute to the decrease in quality of life by increasing the period of hospital stay, readmissions, and other complications. Thus, antimicrobial prophylaxis plays a vital role in the prevention of SSI in patients undergoing colorectal surgeries.

There are not many published RCTs comparing the efficacy of single-dose antimicrobial prophylaxis in patients who underwent colorectal surgeries. One of the RCTs by Ahn and Lee included patients who underwent elective colorectal surgery. A total of 93 patients were included and were assigned to either the single-dose group (n = 48) or the three-dose group (n = 45). The antibiotic given was a second-generation cephalosporin and metronidazole. The overall postoperative infection rate did not differ between the two groups. The SSI incidence did not show any significant difference between the groups (11.1% in multiple-dose vs 10.4% in single-dose). Therefore, the number of doses was not found as an independent risk factor for SSIs. The crucial point to consider in this RCT is the addition of metronidazole along with the first-line agent in both groups [14].

Metronidazole plays a critical role in the prevention and reduction of SSIs, especially in colorectal surgeries. The importance of the addition of metronidazole is shown in the meta-analysis by Nelson et al. This meta-analysis reported that additional coverage aerobic and anaerobic organisms both showed statistically significant improvements in SSIs [27]. The common sources of microbial contamination of the surgical site in colorectal surgery are colonic flora, small intestinal flora, and skin flora. The organisms include aerobes and anaerobes. Metronidazole helps in controlling SSIs by covering anaerobes. Fujita et al. conducted an RCT in Japan to study the efficacy of single-dose antimicrobial prophylaxis in colorectal surgery. A total of 384 patients were randomized to either the single-dose group or the three-dose group. In this study, metronidazole was not given to both groups. Analysis of incisional SSIs showed that incisional SSI was significantly lower in the three-dose group (4.3%) than the single-dose group (14.2%). The multi-variate
analysis also showed a significant association of single-dose antibiotics with an increased risk of incisional SSI. On analysing organ or space SSI incidence, there was no significant difference between the two groups. The authors concluded that single-dose antibiotic prophylaxis is not efficacious in colorectal surgeries unless combined with metronidazole [15].

In the RCT by Nusrath et al., 105 patients who had colorectal malignancy were included. The incidence of SSI was seen more in the group that received an extended dose of antibiotics compared to the single-dose group. In addition, this study reported a higher incidence of remote infection in the single-dose group. However, the analysis and results showed that the single-dose antimicrobial prophylaxis was as efficacious as the multiple-dose regimen in controlling the SSIs [16].

Thus, single-dose antimicrobial prophylaxis with metronidazole may be considered an effective regimen in controlling the SSIs in patients undergoing colorectal surgeries. However, in addition to increased cost and increased risk of adverse events, the multiple-dose antibiotic regimen is associated with increased *Clostridium difficile* infection, which was proved by the meta-analysis by Nelson et al. [28]. Another Cochrane meta-analysis by Nelson et al. also reported that though SSIs were marginally higher with single-dose antibiotics, the regimen can be considered as benefits are more [27]. The characteristics of the studies included and the incidence of SSIs are summarized in Table 4.

| Study                   | Published year | Type of study | Single-dose group (n) | Multiple-dose group (n) | SSI in the single-dose group | SSI in the multiple-dose group |
|-------------------------|----------------|---------------|-----------------------|-------------------------|-----------------------------|-----------------------------|
| Ahn and Lee [14]        | 2013           | RCT           | 48                    | 45                      | 5 (10.4%)                   | 5 (11.1%)                   |
| Fujita et al. [15]      | 2007           | RCT           | 190                   | 187                     | 40 (21.1%)                  | 24 (12.8%)                  |
| Nusrath et al. [16]     | 2020           | RCT           | 53                    | 52                      | 10 (18.9%)                  | 13 (25%)                    |

**TABLE 4: Study characteristics and incidence of SSIs in colorectal oncological surgery**

SSI, surgical site infection; RCT, randomized controlled trial

**Limitations**

This review included RCTs predominantly due to the highest level of evidence they provide with only a few errors. Due to the scarcity of RCTs and other types of studies on this topic, only a limited number of studies were found appropriate to be included for this review. As most of the studies included in this review were randomized clinical trials, the sample size in some of the studies was limited. Only oncological GI surgeries were studied due to the availability of comprehensive data.

**Conclusions**

The objective of this review was to determine the sufficient number of prophylactic antimicrobial doses that would be efficacious and safe in controlling the SSIs in GI surgeries. SSIs contribute to the majority of morbidity and mortality in patients undergoing GI surgeries. In addition, they contribute to increased duration of hospital stay, thereby indirectly increasing the total cost incurred to a patient. Using antimicrobials for a more extended period in GI surgeries contributes to the development of resistance in microbes and allergies, and the total cost. The appropriate antimicrobial and dose are chosen depending on the microbial flora, complications, and patient risk factors.

Single-dose antimicrobial prophylaxis has shown the same efficacy as the multiple-dose antimicrobial regimen in controlling and preventing SSIs in esophageal, gastric, and colorectal surgeries. A single-dose antimicrobial regimen has the following advantages: less chance of emergence of resistance, less chance for allergies or toxicity, and less cost. Thus, in patients undergoing GI surgeries, single-dose antimicrobial prophylaxis would be sufficient to control major SSIs and complications. The addition of metronidazole to single-dose antimicrobial prophylaxis, especially in colorectal surgery, should be considered due to its beneficial effect in further reducing SSIs. We recommend further randomized controlled trials to determine the efficacy and safety of single-dose antimicrobial prophylaxis in patients undergoing esophageal and colorectal surgeries to provide high-quality evidence with minimal bias. In addition, further studies are needed to determine the individual efficacy of metronidazole in controlling the SSIs in colorectal surgeries.

**Additional Information**
Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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