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Review

Efficacy and safety of selective decontamination of the digestive tract in oesophageal surgery: A systematic review and meta-analysis

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ABSTRACT

Objectives: Oesophagectomy is a complex surgery with high mortality and morbidity caused by postoperative infectious complications such as pneumonia and anastomotic leakage. Selective decontamination of the digestive tract (SDD) with non-absorbable antimicrobial agents may lower the density of pathogenic organisms in the oropharynx and oesophagus, thereby providing a perioperative prophylactic strategy. While SDD has shown benefits in intensive care units and lower gastrointestinal surgery, its efficacy and safety in oesophagectomy remains unclear. This study aimed to evaluate the efficacy and safety of perioperative SDD in patients undergoing oesophagectomy.

Methods: A systematic review and meta-analysis were conducted, including all relevant studies published up to April 3, 2025. The primary outcome was the efficacy, defined as reduced incidence of pneumonia, anastomotic leakage, surgical site infection and mortality. Safety, measured by reported side effects, was the secondary outcome.

Results: Of 628 articles screened, six studies comprising 1074 patients were included. Of these, 487 (45.3%) received SDD and 587 (54.7%) received placebo or standard care. None of the studies focused primarily on the safety of SDD, and side effects were not systematically reported. SDD was significantly associated with a lower incidence of pneumonia (OR: 0.42, 95% CI: 0.30–0.58, $P < 0.01$), anastomotic leakage (OR: 0.43, 95% CI: 0.29–0.65, $P < 0.01$) and 30-day mortality (OR: 0.25, 95% CI: 0.07–0.94; $P = 0.04$). Although significant, 30-day mortality should be interpreted with caution due to the limited number of studies and the high risk of bias among them. No significant reduction was observed for in-hospital mortality or surgical site infections.

Conclusions: The meta-analysis indicates that perioperative SDD may reduce pneumonia and anastomotic leakage after oesophagectomy. However, the large heterogeneity, risk of bias and the lack of adequate safety assessment make the available studies insufficient to advance a qualitative recommendation on the topic. For this, a large randomised controlled trial is imperative.

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1. Introduction

Oesophagectomy is a highly complex surgical procedure and is associated with significant morbidity and mortality. Postoperative complications occur in 59% of cases, with pulmonary infections being the most common and anastomotic leakage the most severe [1].

Pathogens responsible for postoperative infectious complications following oesophagectomy originate from the microbiota of the oropharyngeal and upper digestive tract [2–4]. Through regurgitation and aspiration, these pathogens can cause pneumonia. Moreover, they have been implicated in the pathogenesis

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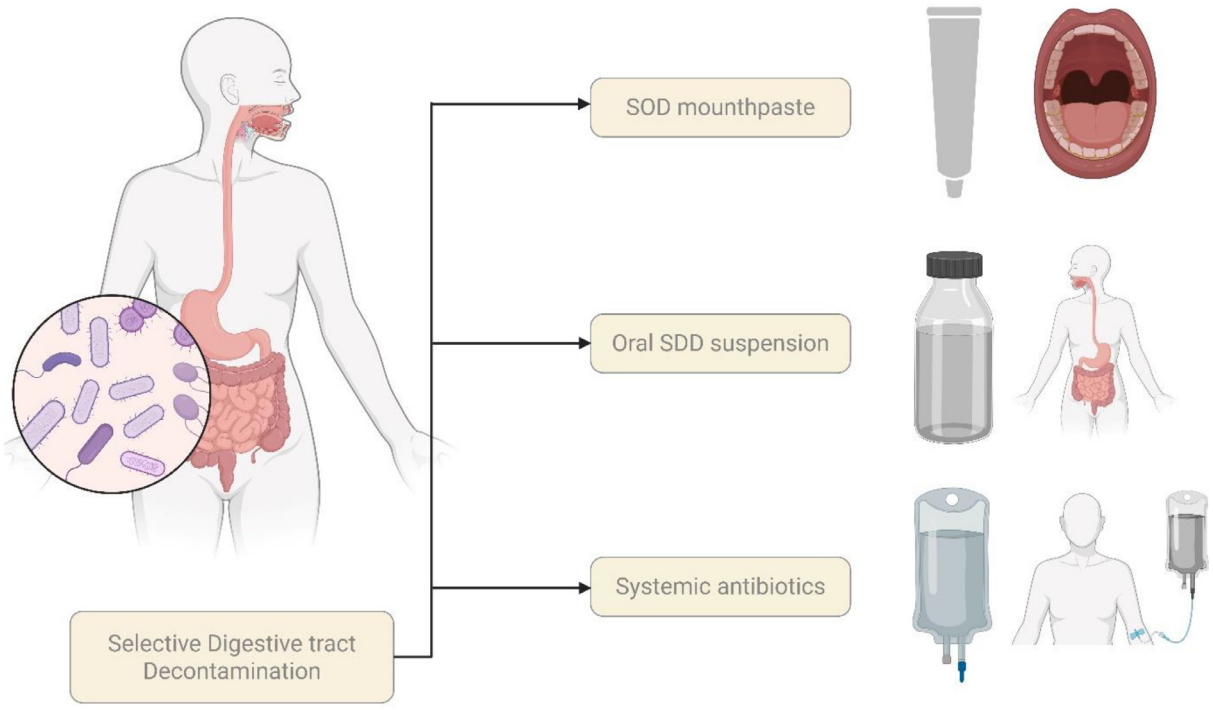


Fig. 1. Selective digestive tract decontamination, a prophylactic antimicrobial therapy. SDD, selective digestive tract decontamination; SOD, selective oropharyngeal decontamination. Created in BioRender. Grootenhuis, J. (2025) https://BioRender.com/7pqmuv0.

of anastomotic leakage. It is hypothesised that, in alongside the impaired blood supply, these microorganisms provoke a localised inflammatory response at the anastomotic site, resulting in micro-abscess formation. This inflammatory process may contribute to anastomotic dehiscence and ultimately result in anastomotic leakage [5–7]. Therefore, eliminating these pathogens prior to surgery and throughout the recovery period may reduce the risk of respiratory infections and anastomotic leakage (AL).

Selective decontamination of the digestive tract (SDD) is a prophylactic antibiotic strategy consisting of oral, non-absorbable antimicrobial agents (e.g., colistin, tobramycin and amphotericin B) to prevent infections by reducing gastrointestinal colonisation with aerobic gram-negative rods and yeasts, while preserving anaerobic bacteria [8,9]. The two main types of SDD strategies are: the orally ingested regimen, commonly referred to as SDD, and the oropharyngeal applied topical regimen, known as SOD. In clinical practice, combinations of these approaches, as well as the addition of intravenous antibiotics to the regimen, are employed (Fig. 1). The term 'SDD' in the literature is often used to refer to any of these variations.

SDD improves outcome in intensive care unit (ICU) patients by reducing the incidence of postoperative infectious complications (including surgical site infection, ventilator-associated pneumonia and anastomotic leakage) after elective lower gastrointestinal tract surgery [9–12]. The most commonly reported side effects of enteral application of SDD are gastrointestinal symptoms, particularly nausea, vomiting and diarrhea. Although the topical and enteral application of SDD is deemed non-absorbable, serious systemic side effects such as nephrotoxicity, a well-known side effect of parenteral tobramycin, have been described in the ICU setting [13,14]. Also, *Clostridioides difficile* outbreaks and overgrowth of other gram-positive bacteria and antibiotic resistance in these strains have been reported in ICU settings [15,16]. In fragile patients and in patients after gastro-intestinal surgery, clotting of the SDD with subsequent esophageal or jejunal obstruction has been reported [17].

SDD might be a promising strategy to reduce morbidity (especially pneumonia and anastomotic leakage) after oesophagectomy, but robust data about efficacy and safety is lacking.

A recent systematic review by Oei et al. [18] summarised the available evidence and found that perioperative SDD was associated with a lower incidence of postoperative pneumonia and anastomotic leakage after oesophagectomy. However, this review included only five studies, all of which were evaluated as having a high or serious risk of bias. Furthermore, this review did not address the safety profile of SDD.

Other systematic reviews in this field have either relied exclusively on randomised controlled trials (RCTs) or included a broader range of gastrointestinal surgeries beyond oesophagectomies. Notably, none of these reviews focused on the safety profile of SDD. Hence, the primary objective of this systematic review and meta-analysis was to assess the efficacy of perioperative SDD compared to placebo or standard care in patients undergoing oesophagectomy; the secondary objective was to assess its safety.

2. Methods

2.1. Search strategy

Two researchers (JG and WS) searched the online medical databases PubMed, Embase, Cochrane, and Web of Science. The last online database search was performed on April 3, 2025. This strategy included search (MeSH) terms related to "selective digestive tract decontamination" and "oesophageal surgery" (Supporting Information). Inclusion criteria were studies involving humans undergoing oesophagectomy, in which any variation of SDD prophylaxis was administered, with a primary focus on the efficacy and/or safety of SDD. No restrictions were applied regarding language or publication date. Two independent researchers (JG and WS) used Rayyan™, (www.rayyan.com, MA) a web-based software program, followed by screening of titles and abstracts [19]. Discrepant opinions were discussed after reading the full-text article and a third reviewer (JS) was involved to resolve the discrepancy when con-

sensus could not be reached. In the second phase, full-text screening took place, by two independent reviewers (JG and WS) who independently reached a 100% consensus on selection. This study adhered to the PRISMA guidelines, and was conducted following the protocol registered in PROSPERO (CRD42024554150).

2.2. Data extraction and outcomes

The two reviewers independently read the full-texts, extracted, and verified the data. For each included article, details were gathered regarding study design, intervention and control or placebo, participant numbers and outcomes.

The primary outcome of interest was the efficacy of perioperative SDD in oesophagectomy, defined by the incidence of pneumonia, anastomotic leakage, surgical site infections, and mortality. The secondary outcome was safety, defined as the occurrence of side effects. Outcomes were analysed according to the definitions and time frames specified by the study authors.

2.3. Risk of bias assessment

Two reviewers (JG and WS) independently assessed the risk of bias in the included articles. Discrepancies were resolved through consensus meetings. Randomised controlled trials (RCT's) were evaluated using the revised Cochrane risk of bias tool (RoB 2) [20]. The risk of bias was classified as low if all domain-level were rated low, high if at least one domain was rated high, and medium if one or more domains were rated as medium risk without any high-risk domains, or if the risk was unclear with no domains rated as high or medium risk. Retrospective cohort studies were assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS) for cohort studies, which assigns a star rating based on predefined criteria [21]. Cohort studies were categorised as having poor (1–3 stars), moderate (4–6 stars) or high (7–9 stars) methodological quality. Next to this, the NOS-scores where converted to AHRQ standards (good-, fair- or poor quality) [22]. Publication bias was assessed using funnel plots.

2.4. Data synthesis and analysis

R version 4.4.1 with meta package was used to conduct the meta-analysis [23]. Odds ratios (ORs) were calculated with a 95% confidence interval for assessing the incidence of outcomes. A random effects model was used to determine the overall effect and, I^2 tests were used to assess heterogeneity between studies. The I^2 values categorised heterogeneity into: not significant (I^2: 0%–40%), moderate (I^2: 30%–60%), substantial (I^2: 50%–90%) and considerable (I^2:75%–100%) [24].

3. Results

The search yielded 628 articles, of which 273 duplicates. The remaining 355 articles were screened based on title and abstract, resulting in 17 full-text articles being assessed for eligibility. Of these, 11 articles were excluded. Six were review articles that did not contribute any additional studies beyond those already identified through the search [12,25–29]. In the RCT performed by de Roos et al. [30] in an elective gastrointestinal surgery population, the exact number of oesophagectomies within a combined subgroup of oesophageal/gastric resections was not specified. The authors were contacted for post-factum subgroup analysis; however, the original data were no longer available. An accompanying cost-effectiveness analysis based on the same study by de Roos et al. was also excluded, as it did not contain original data on efficacy or safety outcomes [31]. In addition, one conference abstract describing a poster presentation was excluded due to insufficient methodological and outcome information [32]. One letter to the editor that did not contain original data [33]. Finally, one article was excluded [34] because it described a study population that had already been reported in a previous publication [35], albeit in the context of a different research question.

In total, six articles were included in the final analysis (Fig. 1) [35–40]. These six studies (three RCTs, three retrospective cohort studies) included a total of 1074 patients who underwent oesophagectomy of which 487 (45.3%) received perioperative SDD. Detailed information on the included studies is presented in Table 1 and Figure 2.

3.1. Prophylactic strategies

3.1.1. Digestive tract decontamination

Various SDD formulations were used. The most frequently used regimen, reported in three studies (N = 260 patients), consisted of polymyxin, tobramycin and amphotericin B ('PTA'). This combination was administered orally, either as a single suspension [35,37] or sequentially as separate agents [40]. One study added oral vancomycin to PTA ('PTA-V') to extend coverage to Gram-positive bacteria [38]. Another study also included vancomycin but replaced amphotericin B with nystatin ('PTN-V'), which has roughly similar antifungal activity and minimal systemic absorption [39]. Additionally, one trial used a combination of erythromycin, gentamycin and nystatin ('EGN') [36]. Notably, erythromycin is a macrolide antibiotic that, in contrast to colistin, is systemically absorbed. Also, it has reduced efficacy against aerobic gram-negative bacteria, which are common pathogens in postoperative infections following oesophagectomy [41].

All six included studies employed a four-times-daily dosing regimen, though the specific dosages varied. For polymyxin, the following formulations and doses were used; polymyxin E (100–200 mg) and polymyxin B (100 mg). Tobramycin was administered at either 80 mg or as tobramycin sulphate (121.7 mg). Among the four studies that included amphotericin B, all used a dose of 500 mg four times daily.

All studies initiated the prophylaxis prior to surgery, ranging from 12 h to 7 d before the procedure. The SDD prophylaxis was continued until postoperative d 3 (N = 1), 5 (N = 2), 7 (N = 2), or 10, including continuation in cases where an infection occurred and had not yet resolved (N = 1).

3.1.2. Selective oropharyngeal decontamination

SOD was applied in addition to SDD in two of the six studies. In the study by Tetteroo et al., the intervention involved a combination of both SOD and SDD, administered from 3 d preoperatively until the 10th day postoperatively [35]. Janssen et al. [42] indicated to both employ SDD and SOD, but the exact regimen was not mentioned. Direct contact with the authors clarified that the SDD was used both pre- and postoperatively, SOD paste was applied for three days postoperatively only.

3.1.3. Systemic prophylaxis

All but one study mentioned the use of systemic antibiotic prophylaxis in addition to SDD, administered preoperatively. The regimens included a combinations of metronidazole with cefotaxime, cefamandole or cefazolin; amoxicillin with clavulanic acid; or cefazolin alone. Systemic antibiotic prophylaxis was initiated as early as three days preoperatively in the intervention group of Tetteroo et al., whereas in most other studies, it began immediately prior to surgery. The postoperative duration of systemic antibiotics varied, ranging from administration until the end of surgery to up to 4 d postoperatively in patients expected to remain in the ICU for more than 72 h.

Table 1
overview of articles included in systematic review.

Author	Number of patients /surgery	Design	Systemic	SOD	SDD	Dosage and duration of SOD and SDD prophylaxis	Route of SDD	Efficacy outcomes	Side effects
Tetteroo 1990	SDD N = 56 Control N = 58 (right sided thoracotomy and median upper laparotomy)	RCT, not blinded.	CTX MET	PTA P 2% T 2% A 2%	PTA (Polymyxin E) P 200mg T 80mg A 500mg	**Dosage SOD:** 4 dd **Duration SOD:** started on the day of admission and continued until POD 10 (or longer if infection was not resolved). **Dosage SDD:** 4 dd **Duration SDD:** started on the day of admission and continued until POD 10 (or longer if infection was not resolved).At the time, patients were admitted one day or several days prior to surgery. **Systemic, intervention group:** CTX from 3 days preoperative until POD1 (4dd 1 gr, 5 days in total), on the day of surgery 4dd 500mg MET. **Systemic, control group:** 1gr FAM + 500mg MET, 4dd, 24h perioperatively.	Mouth, nasogastric tube or needle jejunostomy.	Pneumonia Surgical site infections Mortality, in hospital	Taste, vomiting, nausea, allergy.
Riedl 2001	SDD N = 25 Control N = 45 (open transthoracic)	Partially RCT Patient was allowed to choose between SDD or no SDD, if patient could not decide, randomisation followed.	CFZ	-	PTA (Polymyxin B) P 100 mg T 80 mg A 200 mg	**Dosage SDD:** 4dd;pre-op P and T diluted in nutritional supplement (Meritene), and postop in saline. After 1 hour, amphotericin B suspension. **Duration SDD:** Starting 4-7 days before surgery until at least 1 week after surgery. **Systemic:** 2gr CFZ at start of surgery and 8 hours after.	Pre-op p.o., postop and intubated: 3 mL in the oral cavity, 1 mL in each nostril, 5 mL by gastric tube. Postop and extubated: exclusive via gastric tube. If given through gastric tube, it was closed afterwards for 30 min each time. Amphotericin B was postop always given through gastric tube.	Pneumonia Anastomotic leakage Surgical site infections Mortality, in hospital	Not mentioned
Farran 2008	SDD N= 18 Control N = 24 (open Ivor Lewis, three field Akiyama, transhiatal)*	RCT, double blind, placebo controlled	AMX CLA	-	EGN E 500 mg G 80 mg Ns 100 mg	**Dosage SDD:** 20 mL 4dd **Duration SDD**: 12h prior to, until POD 5. **Systemic:** 2g AMX and 200mg CLA at start of surgery.	p.o. or by nasogastric tube followed by two hours of disconnection.	Pneumonia Anastomotic leakage Mortality, in hospital	Intolerance

(*continued on next page*)

Table 1 (*continued*)

Author	Number of patients /surgery	Design	Systemic	SOD	SDD	Dosage and duration of SOD and SDD prophylaxis	Route of SDD	Efficacy outcomes	Side effects
Näf 2010	SDD N = 134 Control N = 68 (Most probably open transhiatal)	prospective SDD cohort (N=81), retrospective SDD cohort (N =53), and retrospective cohort without SDD (N= 68).	FAM MET	-	PTNV (Polymyxin) P 100 mg T 80 mg N 500 mg V 125 mg	**Dosage SDD:** 10 mL 4dd **Duration SDD:** Starting at the day before surgery (minimum of 4 doses prior to surgery), until POD 7. **Systemic:** 2gr FAM + 500mg MET, 30-60 min prior to surgery, repeating dose if surgery exceeded 4 hours.	Oral, and prophylaxis was continued intraoperatively and postop via gastric tube.	Pneumonia Anastomotic leakage Mortality, 30-day	Nausea
Janssen 2021	SDD N = 179 Control N = 317 (Ivor Lewis, totally minimally invasive oesophagectomy, intrathoracic anastomosis)	Retrospective cohort study	CFZ MET	PTA Ps 2% T 2% A 2%	PTA (Polymyxin E) Ps 100 mg T 80 mg A 500 mg	**Dosage SOD:** times of application per 24h is not mentioned. **Duration SOD:** started after surgery and continued until extubation. **Dosage SDD:** 10 mL 4dd. **Duration SDD:** 3 days prior to surgery until POD 3. **Systemic:** 2gr CFZ + 500mg MET, 30-60 min prior to surgery, repeating dose if surgery exceeded four hours. In patients who were expected to be on the ventilator postoperatively for >48 h and/or expected to remain in ICU for >72 h, CTX i.v. 4 dd 1 g was administered for four days.	p.o. and swallowed, not mentioned how SDD was administered if patient was still intubated.	Pneumonia Anastomotic leakage Surgical site infections Mortality, in hospital Mortality, 30-day Mortality, 90-day Mortality, 1 year	Did not have access to data regarding patient (non)compliance, possible side effects or intolerance.
Merboth 2022	SDD N = 75 Control N = 75 (RAMIE Ivor Lewis vs open Ivor Lewis (at least thoracic open))	Retrospective cohort study with a historical comparison cohort. RAMIE+SDD vs. open oesophagectomy without SDD.	-	-	PTAV (Polymyxin E) Ps118 mg Ts121.75 mg A 500 mg V ? mg	**Dosage 1st part SDD:** 10 mL 4 dd **Dosage 2nd part SDD:** Vancomycin solution or capsules (no dosage mentioned). **Duration SDD:** 2 doses on the evening prior to surgery, first postop dose of 20 mL at the side of the anastomosis via gastric tube. Post operatively 10mL 4dd until POD 5.	Oral, or by gastric tube	Pneumonia Anastomotic leakage Surgical site infections Mortality, 30-days Mortality, 90-days	Not mentioned.

SDD, selective decontamination of the digestive tract; SOD, selective oropharyngeal decontaminiation; CTX, cefotaxime; P, polymyxin E; T, tobramycin; A, amphotericin B; E, erythromycin; G, gentamycin; N, nystatin; V, vancomycin; MET, metronidazole; CFZ, Cefazolin;
CXM, cefuroxime; FAM, cefamandole; AMX, amoxicillin; CLA, clavulanic acid; s, sulphate; POD, postoperative day(s).
* For tumours located below the carina, an Ivor-Lewis procedure (two-field: laparotomy and right thoracotomy) was performed. For tumours located above the carina, a three-field procedure according to Akiyama (laparotomy, right thoracotomy, and left cervicotomy) was applied. Patients with pulmonary capacity <75% of predicted values were considered unfit for transthoracic resection and therefore underwent transhiatal oesophagectomy (two-field: laparotomy and left cervicotomy) with manual cervical anastomosis as described above.

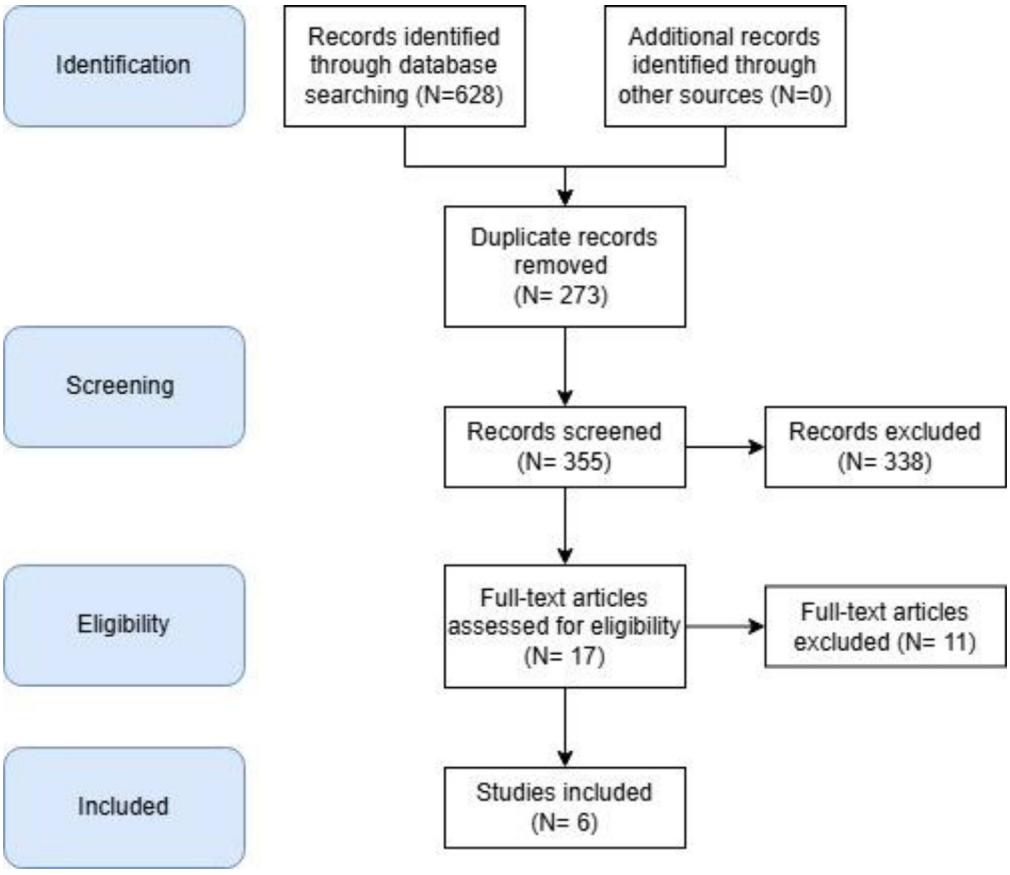


Fig. 2. PRISMA flowchart.

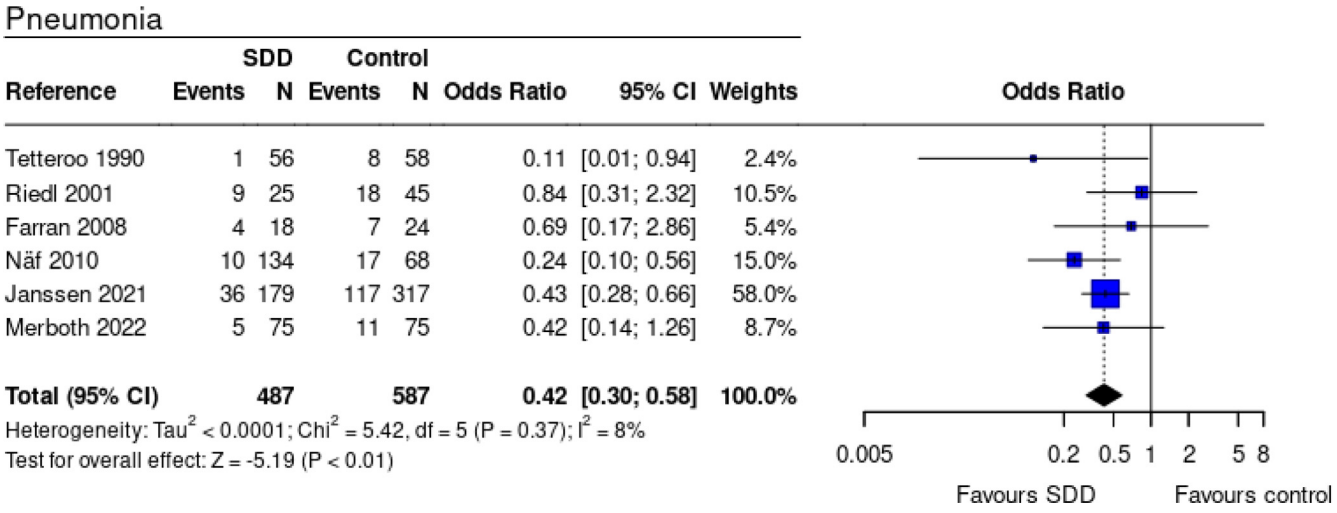


Fig. 3. Forest plot comparing postoperative pneumonia following selective decontamination of the digestive tract (SDD) vs control group in oesophageal resections.

3.2. Efficacy

3.2.1. Pneumonia

All six articles used pneumonia as an endpoint, with a total of 1074 evaluable patients (Fig. 3). In the SDD group, 65 (13.3%) of 487 patients developed pneumonia, compared to 178 (30.3%) of 587 patients in the control group. The overall result was statistically significant in favour of SDD (OR: 0.42, 95% CI: 0.30–0.58, $P < 0.01$), with minimal heterogeneity (I^2: 8%, $P = 0.37$).

3.2.2. Anastomotic leakage

Anastomotic leakage was reported in five studies, including a total of 960 patients [36,38,39,42,43]. In the SDD group, 36 (8.4%) of 431 patients developed AL, compared to 100 (18.9%) of 529 patients in the control group. The OR was 0.43 (95% CI: 0.29–0.65, $P < 0.01$) indicating that SDD significantly reduced the occurrence of AL, with no heterogeneity observed across studies ($I^2 = 0\%$, $P = 0.67$) (Figure 4). Four of the five studies provided a clear definition of AL, with the oesophagectomy Complications Consensus Group (ECCG) definition used by two of them [44].

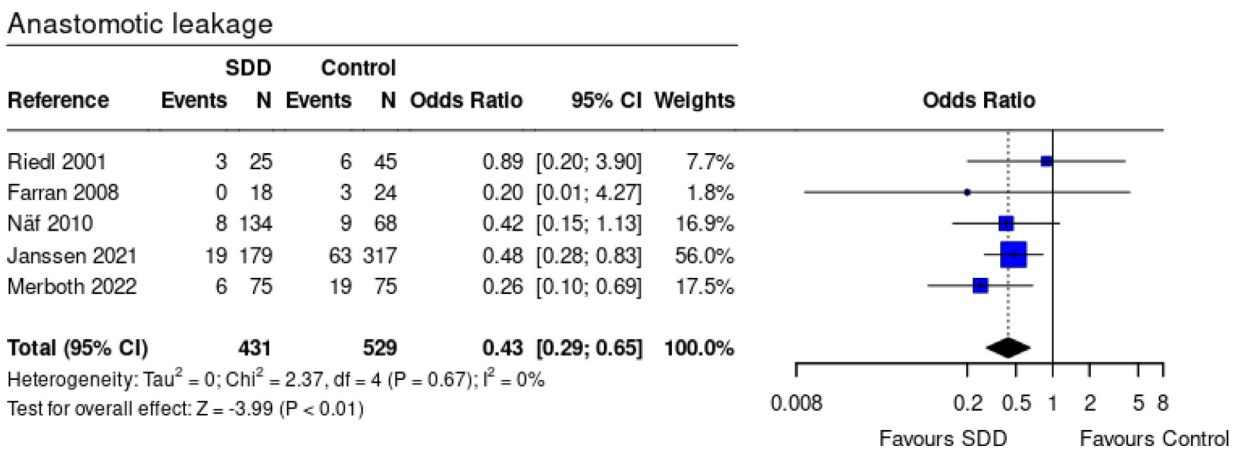


Fig. 4. Forest plot comparing anastomotic leakage following selective decontamination of the digestive tract (SDD) vs control group in oesophageal resections.

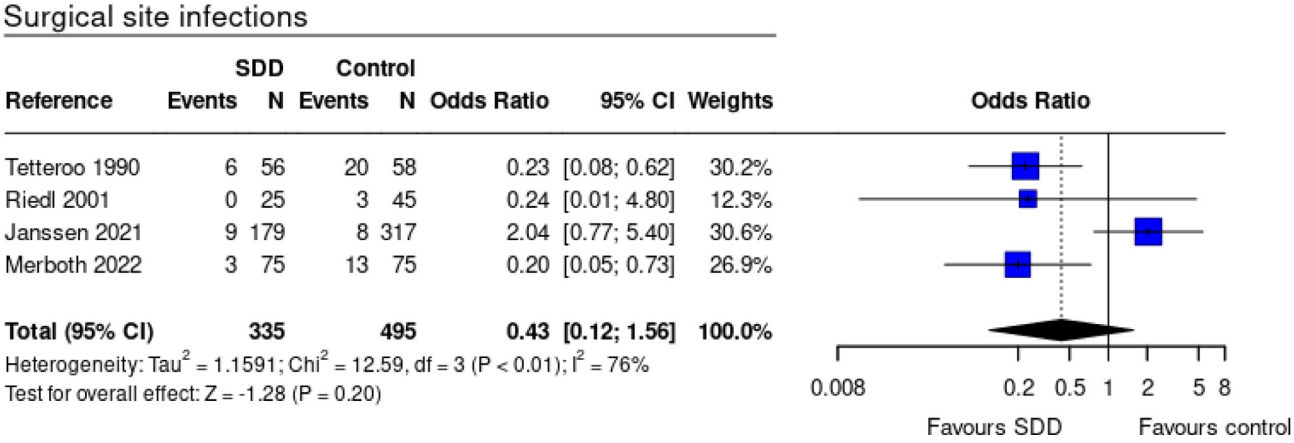


Fig. 5. Forest plot comparing surgical site infections (SSI) following selective decontamination of the digestive tract (SDD) versus control group in oesophageal resections.

3.2.3. Surgical site infections

Surgical site infections (SSIs) were reported in four studies, including 830 patients. In three studies, there were fewer SSIs in the SDD groups [35,38,43] and one study showed slightly more SSIs in the SDD group, although this did not reach statistical significance [42]. Taken together, 18 of 335 patients (5.4%) in the SDD group developed SSIs, compared to 44 (8.9%) of 495 patients in the control group. The combined OR was 0.43 (95% CI: 0.12–1.56), indicating that SDD was not associated with a reduction in SSIs in these studies ($P = 0.20$), with considerable heterogeneity (I^2 value of 76%) (Fig. 5).

3.2.4. Mortality

All six publications assessed mortality, two studies reported mortality without specifying a specific time point, we assumed in-hospital mortality [35,36]. In the SDD group, seven of 278 patients (2.5%) died during their hospital stay, compared to 19 of 444 patients (4.3%) in the control group. This numerical difference was not statistically significant (OR: 0.60, 95% CI: 0.24 to 1.50; $P = 0.28$). No heterogeneity was observed (I2 = 0%) (Fig. 6). At the 30-d mortality endpoint, a total of 848 patients from three studies were eligible for evaluation (Fig. 7). In the SDD group, seven of 388 patients (1.8%) died, compared to 26 (5.7%) of 460 patients in the control group, reaching significance favouring SDD (OR 0.25, 95% CI: 0.07 to 0.94; $P = 0.04$), with moderate to significant heterogeneity ($I^2 = 57\%$).

Ninety-day mortality was only assessed in the studies by Janssen et al. and Merboth et al. In the SDD group, 14 of 254 patients (5.5%) died, compared to 25 of 392 (6.4%) patients in the control group (OR: 0.66, 95% CI: 0.14–3.06; $P = 0.59$). One-year mortality was only assessed in one study (Janssen et al.), with a nearly significant difference in favor of the control group at one year (20.4% vs 26.8%, $P = 0.056$).

3.3. Safety including side effects

None of the included studies systematically documented side effects. Side effects related to SDD prophylaxis were reported in only three studies (Table 1). Overall, nausea, though mild in severity, was the most common side effect. In addition, the more subjective 'intolerance' was also reported.

The RCT conducted by Tetteroo et al. reported a single case of an allergic reaction to SDD, although the type and severity of the reaction were not specified. Additionally, issues related to of non-compliance were noted, including unpleasant taste (N = 2), as well as vomiting and nausea (N = 4) [35].

Farran et al. excluded four patients due to intolerance to the oral solution. However, it is unclear whether intolerance occurred in the intervention or placebo group, as no details of the intolerance were provided [36]. Näf et al. mentioned nausea as the most frequently observed side effect, although it was only rarely, and no specific number of affected patients was provided [39].

3.4. Bias

Funnel plots demonstrate a roughly even distribution, indicating no significant publication bias for pneumonia, anastomotic leakage

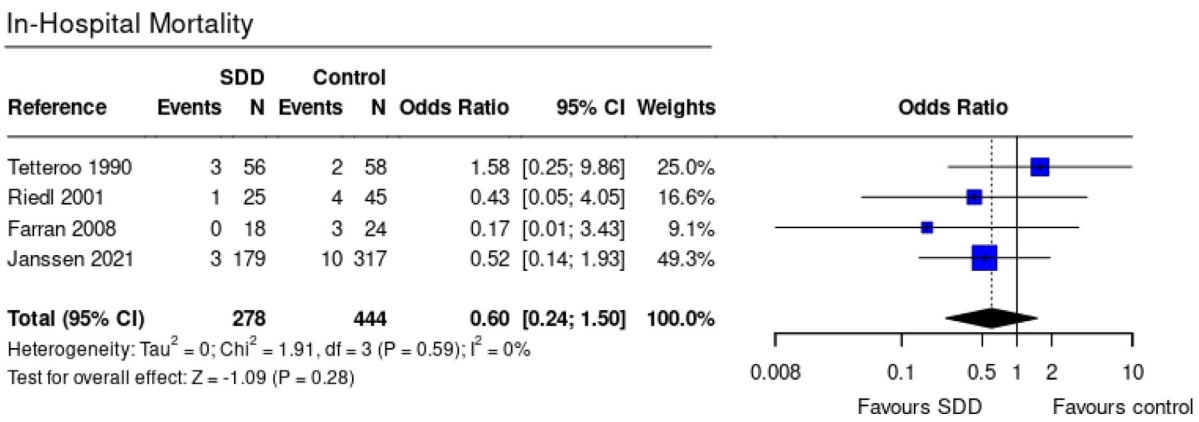


Fig. 6. Forest plot comparing postoperative in-hospital mortality following selective decontamination of the digestive tract versus control group in oesophageal resections.

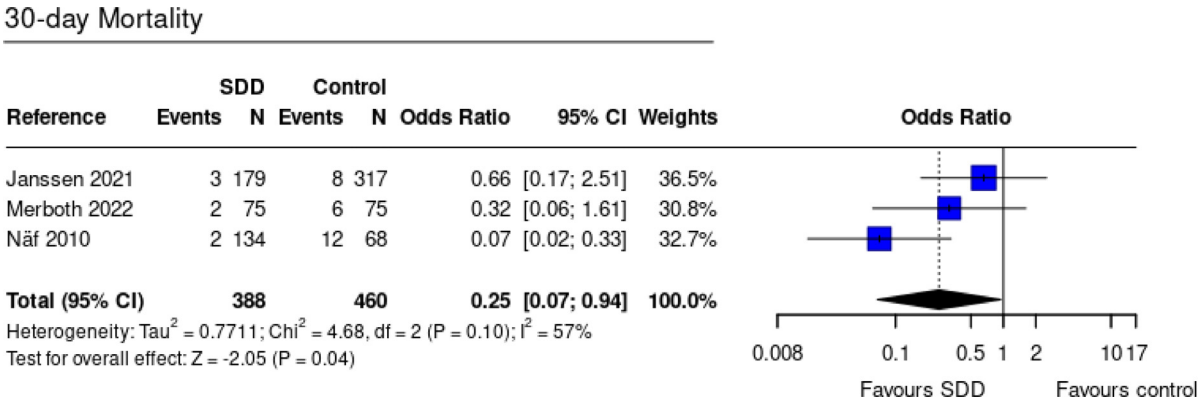


Fig. 7. Forest plot comparing postoperative 30-day mortality following selective decontamination of the digestive tract (SDD) versus control group in oesophageal resections.

nor mortality (Fig. 9, Supporting Information). In contrast, the funnel plot for surgical site infections (SSIs) revealed an outlier: the study by Janssen et al. which reported a low occurrence of SSIs (3.4%). This discrepancy is likely attributable to underreporting of SSIs due to the retrospective design of the study.

Of the three RCT's, one study [36] was judged to have a low risk of bias, one raised some concerns [35], and one study was considered at high risk of bias [40]. A major concern in the latter study was self-selection bias, as patients were allowed to choose between the control and intervention group and were randomised only if they did not want to choose. As a result, significant deviations from the intended intervention occurred, which further contributed to the risk of bias (pages 15-43, Supporting Information).

According to the Newcastle-Ottawa Scale (NOS), one study [39] demonstrated a moderate risk of bias, whereas two cohort studies [37,38] appeared to have a low overall risk of bias (pages 8-14, Supporting Information). When converted to the AHRQ classification [22], the latter two corresponded to poor and good quality, respectively. However, the study by Merboth et al. introduced a substantial methodological bias that was not adequately captured by the applied scoring systems. In this study, a minimally invasive surgical approach combined with SDD prophylaxis was compared to an open approach without SDD prophylaxis. As open techniques are more prone to SSIs and pneumonia, this design likely biased the results in favor of the SDD group [38]. Taking this into account, we consider the study by Janssen et al. to represent low risk of bias and good quality, whereas both studies by Merboth et al. and Näf et al. should be classified as high risk of bias and poor quality.

To confirm the robustness of the data, we also performed sensitivity analyses excluding only the study by Merboth et al. (Supporting information, Fig. 1-4) and an analysis excluding both the studies by Merboth et al. and Näf et al. (Supporting Information, Fig. 5–8). The results remained statistically significant in favour of SDD for pneumonia (OR: 0.47, 95% CI: 0.28–0.66, $P < 0.01$; $I^2 = 14\%$) and anastomotic leakage (OR: 0.50, 95% CI: 0.30–0.84, $P < 0.01$; $I^2 = 0\%$). For surgical site infections, the effect remained non-significant (OR: 0.57, 95% CI: 0.11–2.90, $P = 0.49$; $I^2 = 80\%$). With regard to mortality, in-hospital mortality was unchanged, as this outcome was not reported in the studies by Merboth et al. and Näf et al.. Data on 30-day, 90-day, and 1-year mortality were only available from Janssen et al. and could therefore not be further analysed after exclusion of these two studies.

4. Discussion

Perioperative SDD was associated with a significant reduction in the incidence of postoperative pneumonia, anastomotic leakage, and 30-day mortality in patients undergoing oesophagectomy. These results are consistent with previous findings in elective colorectal surgery, where similar benefits on reduction of infectious complications have been reported [12,45,46].

Reported mortality rates vary across studies, particularly between the relatively high 1-year and the lower 30-day mortality. This discrepancy may reflect incomplete tumour resection, disease progression, and the profile of the average oesophagectomy patient, typically in the late sixties with multiple comorbidities. By contrast, Näf et al. reported a 30-day mortality of 17.6%, likely related to their retrospective cohort without SDD, including patients treated between 1995 and 2002. The higher mortality in that study may also reflect the absence of modern advances in perioperative care, including improvements in intensive care medicine, anaesthesia, and surgical techniques, which have substantially reduced early mortality in more recent cohorts.

The surgical site infection (SSI) rate was not significantly reduced in our meta-analysis. Even with the lower incidence in the study by Merboth et al., which was biased by comparing a minimally invasive surgical approach with SDD to an open surgical approach without SDD, the reduction of SSIs still did not reach statistical significance. This may be explained by the fact that open surgery is associated with greater tissue trauma and exposure, which can increase SSI risk.

The reported side effects were generally mild, primarily consisting of an unpleasant taste and smell, which sporadically led to nausea or vomiting. One case of an allergic reaction was documented, although no details were provided regarding its severity or whether it occurred in the intervention or control group. Comparable finding regarding efficacy and safety have been observed in colorectal surgery, where SDD is also administered for a limited duration. In this context, besides unpleasant taste or mild gastrointestinal discomfort such as nausea, no side effects have been reported [30,47–49].

Although side effects such as systemic toxicity, *Clostridioides difficile* outbreaks, and the emergence of antibiotic-resistant organisms have been reported in intensive care units (ICU) settings, these side effects may be linked to the prolonged use of SDD or the critically ill condition of ICU patients. While oesophagectomy patients can also experience critical disease, there are important differences between SDD use in the ICU and perioperative SDD regimens in oesophageal surgery. The latter are of shorter duration and are partially administered preoperatively, making direct extrapolation from ICU data to oesophagectomy patients unreliable. Even in the ICU setting, adverse events remain under-investigated, and no firm conclusions can be drawn regarding their clinical significance. To date, SDD is rarely used outside the Netherlands, largely due to concerns about its efficacy and the potential for inducing antibiotic resistance especially in ICU settings with a high endemicity of resistant microorganisms [16,50–52].

Another potential, yet unexplored, safety concern specific to esophagectomy is the risk of mediastinal contamination in cases of anastomotic leakage. While commonly used SDD antimicrobial agents (colistin, tobramycin, amphotericin B) are considered non-absorbable in the intestinal tract, anastomotic leakage could create an alternative absorption route, potentially altering their pharmacokinetics.

Several limitations of this study warrant consideration. First, the risk of bias varied considerably across both cohort studies and randomised controlled trials. The RCT by Riedl et al., in which participants could self-select into the intervention or control group, with randomisation applied only to those who declined to choose, was judged to be at high risk of bias. An even greater concern relates to the methodological limitations of two cohort studies. First, the study by Merboth et al., in which a minimally invasive surgical approach with SDD was compared to an open approach without SDD, thereby introducing substantial confounding bias. Second, the study by Näf et al. in which cohorts of different time periods are compared. Although repeated analyses excluding the study by Merboth et al. and Merboth et al. plus Näf et al. did not yield significant changes, the potential bias remains important, given that differences in surgical technique and time period can substantially influence outcome measures [53]. Regarding the safety outcomes, the potential for bias is even greater, as these outcomes were not systematically documented or reported. Second, the limited number of included studies may compromise the robustness of our conclusions. Third, as previously discussed, certain methodological aspects of the included studies introduce potential biases. Fourth, most evaluated studies are underpowered with respect to their primary endpoint. Fifth, the heterogeneity of SDD regimens across trials, involving different antimicrobial agents in studies reporting adverse effects, complicates the attribution of specific side effects to individual components. Sixth, the inconsistent documentation of SDD-related side effects introduces a significant reporting bias. Lastly, discrepancies in the definitions of AL and pneumonia hinder cross-study comparisons.

Further evidence is required prior to the broad implementation of this promising strategy for complication prevention, ideally through standardised SDD regimens, a focus on safety, and clearly defined postoperative complications. Addressing this need, the ongoing PERSuaDER trial (EU CT ID: 2023-504144-33) is currently evaluating the safety and efficacy of SDD in 854 patients across Belgium and the Netherlands, aiming to provide critical evidence for this specific patient population. To the best of our knowledge, this is the only ongoing randomised controlled trial investigating SDD in the context of oesophagectomy registered in major trial databases, including the International Standard Randomised Controlled Trial Number (ISRCTN), the EU Clinical Trials Register (CTIS and ECTR), and ClinicalTrials.gov.

In conclusion, perioperative SDD appears to be a promising and safe strategy for reducing pneumonia and anastomotic leakage rates in patients undergoing oesophagectomy. However, further high-quality research is necessary to establish both its efficacy and safety, necessitating larger, more methodologically robust studies.

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Supplementary materials

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