Systematic review

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Selective decontamination of the digestive tract in upper gastrointestinal surgery: systematic review with meta-analysis of randomized clinical trials

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Background: **Infectious complications are common after gastrointestinal surgery. Selective decontamination of the digestive tract (SDD) might reduce their incidence. SDD is used widely in colorectal resections, but its role in upper gastrointestinal resection is less clear. The aim of this study was to investigate the impact of SDD on postoperative outcome in upper gastrointestinal surgery.**

Methods: **Studies investigating SDD in upper gastrointestinal surgery were included after search of medical databases (PubMed, Ovid, Cochrane Library and Google Scholar). Results were analysed according to predefined criteria. The incidence of perioperative overall complications and death was pooled. Risk of bias was assessed using the revised Cochrane risk-of-bias tool.**

Results: **Some 1384 studies were identified, of which four RCTs were included in the final analysis. These studies included 415 patients, of whom 213 (51·3 per cent) received standard treatment/placebo and 202 (48·7 per cent) had SDD. The incidence of anastomotic leakage (odds ratio (OR) 0·39, 95 per cent c.i. 0·19 to 0·80; $P = 0·010$) and pneumonia (OR 0·42, 0·23 to 0·78; $P = 0·006$) was reduced in patients receiving SDD. Rates of surgical-site infection ($P = 0·750$) and mortality ($P = 0·130$) were not affected by SDD.**

Conclusion: **SDD seems to be associated with reduction of anastomotic leakage and pneumonia following upper gastrointestinal resection, without affecting postoperative mortality.**

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Introduction

Gastrointestinal surgery is frequently followed by infectious complications[1], which are associated with longer hospital stay and increased costs[2]. Surgical-site infection (SSI) contributes up to 20 per cent of all hospital-acquired infections[3]. Several risk factors are known to be involved, including prolonged duration of surgery, low preoperative serum albumin level, high intraoperative blood loss, ASA grade, high BMI and perioperative hypothermia[4–6].

The gut microbiome appears to play a critical role in the development of postoperative infectious complications[7,8]. For potentially contaminated surgical procedures, preoperative antibiotic prophylaxis with intraoperative repetition for longer procedures is considered to be the standard of care[9]. Preoperative decontamination of the digestive tract by intake of oral, commonly non-absorbable, antibiotics can be added to this schedule. Selective decontamination of the digestive tract (SDD) is believed to target *Staphylococcus aureus*, yeast and pathogenic Gram-negative bacteria, representing risk factors for postoperative infection, and is continued until there is normal passage of stool and food intake[10,11].

In colorectal surgery[12], SDD in combination with mechanical bowel preparation is used widely, and a recent RCT[13] demonstrated that SDD significantly reduced postoperative infectious complications. The situation is less clear regarding SDD in upper gastrointestinal surgery[10,14]. The aim of this study was to conduct a systematic review and meta-analysis of the current evidence for the role of SDD, focusing on postoperative complications and mortality reported in RCTs in upper gastrointestinal surgery.

Methods

This study adhered to the PRISMA guidelines[15] for performance of the meta-analysis.

Online medical databases (PubMed, Ovid, Cochrane Library and Google Scholar) were searched using a search term (*Appendix S1*, supporting information) and combinations of 'selective digestive decontamination', 'gastrointestinal surgery' and 'upper GI'. The last online database search was performed on 3 June 2019. Relevant articles specified in the reference list of identified articles were included. The studies included investigated SDD before upper gastrointestinal surgery, and only RCTs involving human subjects were considered. Only studies with at least an English abstract and published within the last 25 years were included. Those focusing on lower gastrointestinal surgery and SDD in the setting of transplantation were excluded. Inclusion of the selected studies was validated independently by three researchers. Data extraction and the assessment of quality and risk of bias across studies was performed independently by two researchers. In case of any differences, the subject was discussed until consensus was reached.

Postoperative complications (SSI, pneumonia, anastomotic insufficiency) were analysed as reported by the study authors within the time frames reported using authors' definitions of specific complications. Postoperative mortality was assessed as stated by the authors, including death during the hospital stay as well as within 30 days from surgery.

The study was registered in the PROSPERO database (registration number CRD42020144720).

Statistical analysis

Review Manager version 5.3 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) was used to conduct the meta-analysis. Outcomes were encoded as dichotomous variables, and odds ratios (ORs) were calculated by assessing the incidence of respective outcomes. Study heterogeneity was assessed by estimating I^2. Studies with an I^2 statistic above 33 per cent were considered to have high heterogeneity. Assuming random differences by chance in treatment procedure, patient characteristics and local differences, the Mantel–Haenszel statistical method was used with a random-effects model when I^2 was 33 per cent or above in the test for heterogeneity, and with a fixed-effect model when I^2 was less than 33 per cent. For statistical significance, a bilateral 95 per cent c.i. was defined. For the analysis of risk of bias, the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) was employed. Funnel plots of included ORs were created using Review Manager version 5.3.

Results

The initial search resulted in 1384 studies investigating SDD in gastrointestinal surgery, of which four RCTs[10,14,16,17] met the inclusion criteria and were included in the final analysis (*Fig. 1*). The studies included patients undergoing gastrectomy and oesophagectomy, mainly for malignant disease. A total of 415 patients were analysed, of whom 213 received standard-of-care treatment/placebo and 202 had SDD before surgery. Three of the four studies used polymyxin B, tobramycin and amphotericin B as SDD, four times daily with a cephalosporin as the perioperative intravenous antibiotic (*Table 1*). A study by Tetteroo and colleagues[18] did not meet the inclusion criterion of publication within the last 25 years and was not included in the analysis.

Anastomotic leak

All 415 patients were eligible for the analysis of anastomotic insufficiency. This complication occurred in 28 of 213 patients (13·1 per cent) receiving standard-of-care treatment and in 12 of 202 (5·9 per cent) after SDD. SDD had a protective effect on anastomotic leakage (OR 0·39, 95 per cent c.i. 0·19 to 0·80; $P = 0·010$), and heterogeneity was low ($I^2 = 0$ per cent) (*Fig. 2*). In the study by Schardey and co-workers[16], leak rates were reduced significantly in the SDD group (2·9 per cent *versus* 10·6 per cent in the control group; $P = 0·049$) (*Table 2*). In the Schardey study, anastomotic insufficiency was defined as a total intestinal wall defect at the suture line, diagnosed by a positive dye test or radiological contrast study. Riedel *et al.*[17] found a reduction in anastomotic insufficiency by SDD of 16 *versus* 25 per cent, although no *P* value was given, nor was leakage defined. Farran and colleagues[14] reported no influence of SDD on anastomotic insufficiency (2·5 *versus* 5·9 per cent; $P = 0·405$) (*Table 2*), which was diagnosed by oral administration of methylene blue, clinical leak through a wound or drains, or radiological contrast examination. Roos *et al.*[10] reported a reduction in anastomotic insufficiency by SDD (12·5 per cent *versus* 23·3 per cent in the control group), but gave no *P* value; they defined leakage using a combination of clinical presentation, blood results, and confirmation by CT or X-ray.

Pneumonia

The incidence of postoperative pneumonia in 324 eligible patients from three studies[14,16,17] indicated that 42 of 170 (24·7 per cent) in the control group were affected compared with 19 of 154 (12·3 per cent) after SDD, giving

Fig. 1 PRISMA diagram for the review

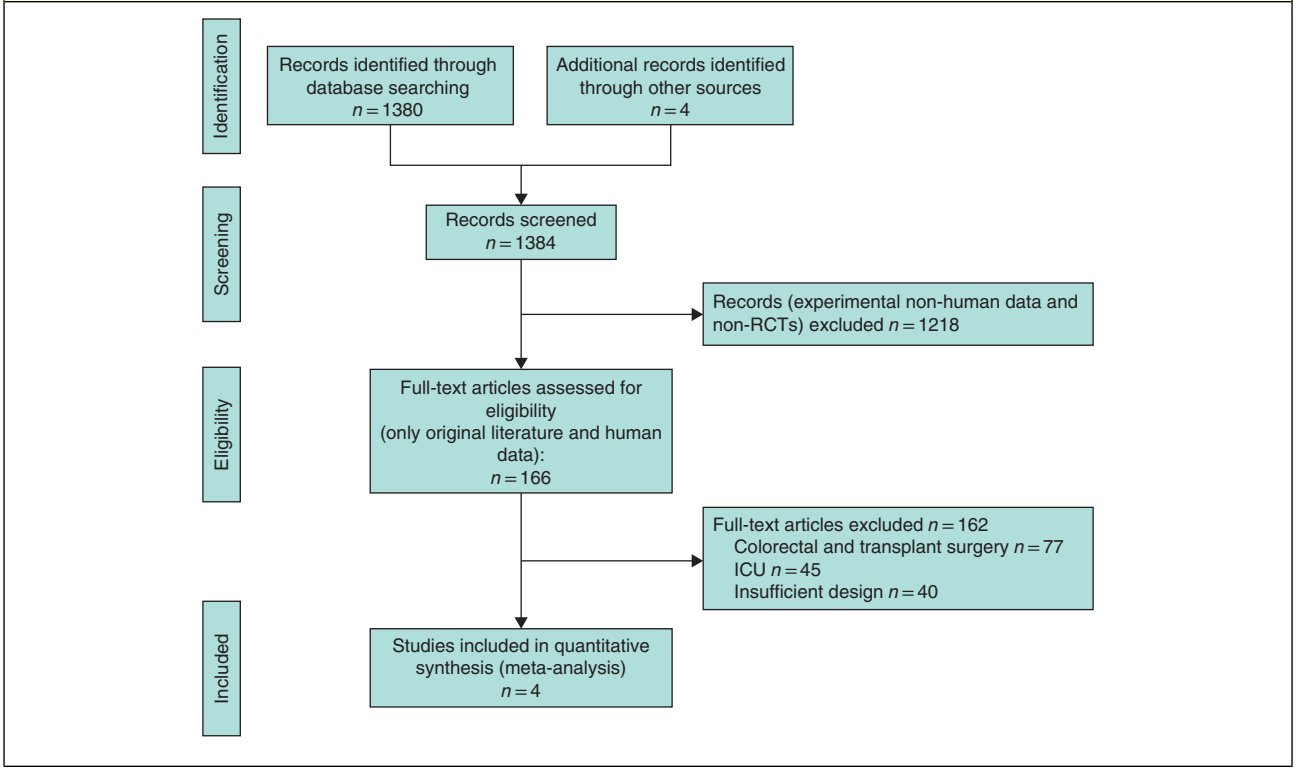


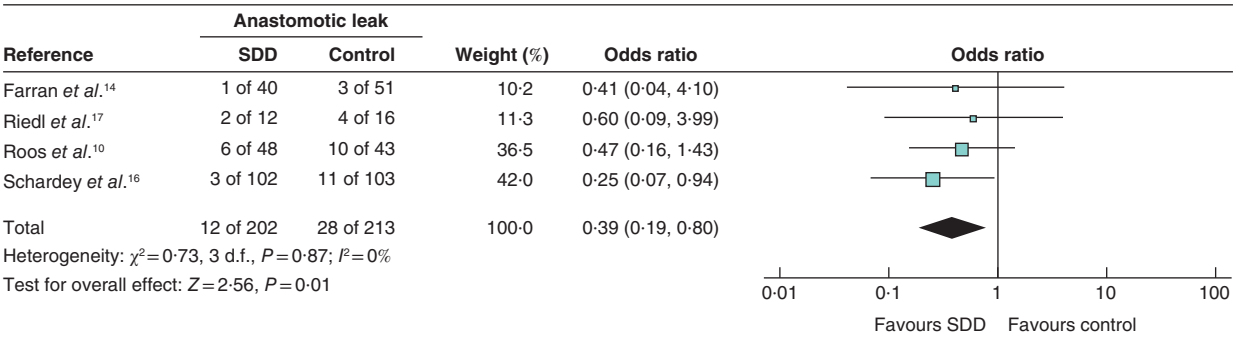
Table 1 Details of selective decontamination for included RCTs

Reference	Year	No. of patients		Resection	Perioperative parenteral antibiotics	SDD	Regimen
		Control	SDD				
Schardey *et al.*[16]	1997	103	102	Gastrectomy	Cefotaxime	Polymyxin B 100 mg, tobramycin 80 mg, amphotericin B 500 mg, vancomycin 125 mg	4 times daily, from 1 day before surgery to POD7
Riedl *et al.*[20]	2001	16	12	Transthoracic resection of oesophagus and cardia	Cefazolin	Polymyxin B 100 mg, tobramycin 80 mg, amphotericin B 200 mg	4 times daily, from 4–7 days before surgery to POD7
Farran *et al.*[17]	2008	51	40	Gastrectomy, oesophagectomy	Amoxycillin/ clavulanic acid	Erythromycin 500 mg, gentamicin 80 mg, nystatin sulphate 100 mg	4 times daily, from 12 h before surgery to POD5
Roos *et al.*[11]	2011	43	48	Oesophageal, gastric and hepatopancreatobiliary resections	Cefuroxime/ metronidazole	Polymyxin B 100 mg, tobramycin 80 mg, amphotericin B 500 mg	4 times daily, from 2 days before surgery until normal bowel function or minimum of POD3

SDD, selective decontamination of the digestive tract; POD, postoperative day.

an OR of 0·42 (95 per cent c.i. 0·23 to 0·78; $P = 0·006$) in favour of SDD, with low heterogeneity ($I^2 = 0$ per cent) (*Fig. 3*). Schardey and colleagues[16] demonstrated a significant reduction in pneumonia after SDD (8·8 per cent *versus* 22·3 per cent in the control group; $P = 0·012$) (*Table 2*). Pneumonia was diagnosed when four of the following five criteria occurred: body temperature above 38·5°C, leucocyte count greater than 10^4 or less than

Fig. 2 Forest plot comparing anastomotic insufficiency following selective decontamination of the digestive tract *versus* standard treatment in upper gastrointestinal resections



A Mantel–Haenszel fixed-effect model was used for meta-analysis. Odds ratios are shown with 95 per cent confidence intervals. SDD, selective decontamination of the digestive tract.

Table 2 Outcomes of included studies

Postoperative complication rate (%)*	Schardey *et al.*[16]	Riedl *et al.*[17]	Farran *et al.*[14]	Roos *et al.*[10]
Overall	30·4 *versus* 44·7	–	–	–
P	0·049			
Pneumonia	8·8 *versus* 22·3	42 *versus* 56	12·5 *versus* 19·6	–
P	0·012		0·269	
Anastomotic insufficiency	2·9 *versus* 10·6	16 *versus* 25	2·5 *versus* 5·9	12·5 *versus* 23·3
P	0·049		0·405	
Surgical-site infection	4·9 *versus* 3·8	0 *versus* 0	–	33·3 *versus* 39·5
P	1·000			
Mortality	4·9 *versus* 10·6	0 *versus* 6	5 *versus* 5·9	–
P	0·100		0·615	

*Selective decontamination of the digestive tract (SDD) *versus* control group respectively.

5×10^3 cells per μl, positive auscultation examination, lung infiltration on X-ray, or positive bacteriology. Riedl *et al.*[17] found a reduction in postoperative pneumonia from 56 to 42 per cent with SDD, although no *P* value was given (*Table 2*); they used the definition of pneumonia from the Robert Koch Institute. Farran and colleagues[14] reported no influence of SDD on postoperative pneumonia (12·5 *versus* 19·6 per cent; $P = 0·269$) (*Table 2*). Pneumonia was defined when two of the following characteristics were present: purulent respiratory secretion, fever, radiological infiltrates, rhonchi, positive auscultation of the chest, and positive bacteriology of respiratory secretions.

Surgical-site infection

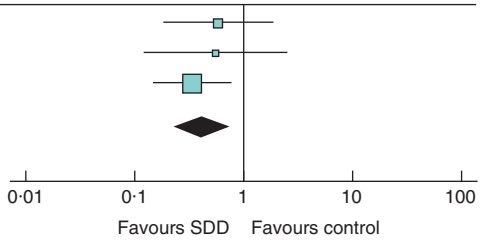
SSI included wound infections as well as abscess formation, although definitions were inconsistent between the included studies. Of 324 patients, 21 of 162 (13·0 per cent) in the control group and 21 of 162 patients (13·0 per cent) in the SDD group were diagnosed as having an SSI (OR 0·89, 95 per cent c.i. 0·43 to 1·82; $P = 0·750$), with low heterogeneity ($I^2 = 0$ per cent) (*Fig. 4*). No individual study found a significant difference in SSI rates between control and SDD groups.

Mortality

Again, 324 patients were eligible for evaluation. Some 15 of 170 patients (8·8 per cent) died in the control group compared with seven of 154 (4·5 per cent) in the SDD group. Although there was a tendency in favour of SDD, significance was not reached (OR 0·50, 95 per cent c.i. 0·20 to 1·23; $P = 0·130$), with low heterogeneity ($I^2 = 0$ per cent) (*Fig. 5*). Of the three included studies, two[14,16] found no improvement in mortality and one[17] showed benefit for SDD (0 *versus* 6 per cent), but no *P* value was provided (*Table 2*).

Fig. 3 Forest plot comparing postoperative pneumonia following selective decontamination of the digestive tract *versus* standard treatment in upper gastrointestinal resections

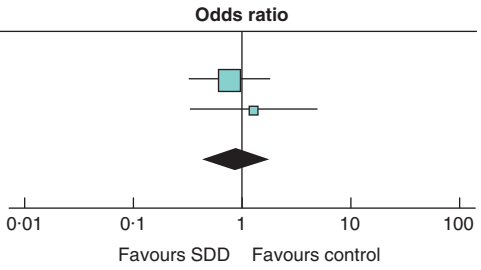
	Pneumonia				
Reference	SDD	Control	Weight (%)	Odds ratio	Odds ratio
Farran *et al.*[14]	5 of 40	10 of 51	23·3	0·59 (0·18, 1·88)	
Riedl *et al.*[17]	5 of 12	9 of 16	13·6	0·56 (0·12, 2·53)	
Schardey *et al.*[16]	9 of 102	23 of 103	63·1	0·34 (0·15, 0·77)	
Total	19 of 154	42 of 170	100·0	0·42 (0·23, 0·78)	
Heterogeneity: $\chi^2 = 0{\cdot}72$, 2 d.f., $P = 0{\cdot}70$; $I^2 = 0\%$					
Test for overall effect: $Z = 2{\cdot}74$, $P = 0{\cdot}006$					



A Mantel–Haenszel fixed-effect model was used for meta-analysis. Odds ratios are shown with 95 per cent confidence intervals. SDD, selective decontamination of the digestive tract.

Fig. 4 Forest plot comparing surgical-site infection following selective decontamination of the digestive tract *versus* standard treatment in upper gastrointestinal resections

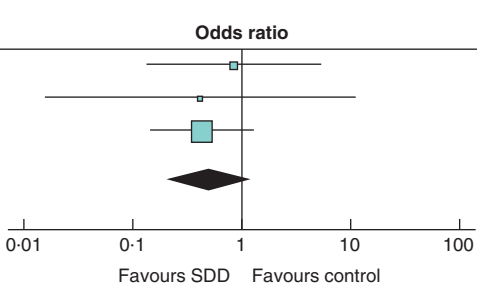
	Surgical-site infection				
Reference	SDD	Control	Weight (%)	Odds ratio	Odds ratio
Riedl *et al.*[17]	0 of 12	0 of 16		Not estimable	
Roos *et al.*[10]	16 of 48	17 of 43	76·0	0·76 (0·32, 1·80)	
Schardey *et al.*[16]	5 of 102	4 of 103	24·0	1·28 (0·33, 4·89)	
Total	21 of 162	21 of 162	100·0	0·89 (0·43, 1·82)	
Heterogeneity: $\chi^2 = 0{\cdot}40$, 1 d.f., $P = 0{\cdot}53$; $I^2 = 0\%$					
Test for overall effect: $Z = 0{\cdot}32$, $P = 0{\cdot}75$					



A Mantel–Haenszel fixed-effect model was used for meta-analysis. Odds ratios are shown with 95 per cent confidence intervals. SDD, selective decontamination of the digestive tract.

Fig. 5 Forest plot comparing postoperative mortality following selective decontamination of the digestive tract *versus* standard treatment in upper gastrointestinal resections

	Mortality				
Reference	SDD	Control	Weight (%)	Odds ratio	Odds ratio
Farran *et al.*[14]	2 of 40	3 of 51	17·7	0·84 (0·13, 5·30)	
Riedl *et al.*[17]	0 of 12	1 of 16	8·8	0·41 (0·02, 11·05)	
Schardey *et al.*[16]	5 of 102	11 of 103	73·5	0·43 (0·14, 1·29)	
Total	7 of 154	15 of 170	100·0	0·50 (0·20, 1·23)	
Heterogeneity: $\chi^2 = 0{\cdot}39$, 2 d.f., $P = 0{\cdot}82$; $I^2 = 0\%$					
Test for overall effect: $Z = 1{\cdot}50$, $P = 0{\cdot}13$					



A Mantel–Haenszel fixed-effect model was used for meta-analysis. Odds ratios are shown with 95 per cent confidence intervals. SDD, selective decontamination of the digestive tract.

Publication bias

Funnel plots showed even distribution within the pseudo 95 per cent c.i., suggesting no publication bias for incidence of anastomotic insufficiency, pneumonia, SSI or mortality (*Fig. S1*, supporting information). Analysis using the Cochrane risk-of-bias tool (RoB 2) for randomized trials revealed 'some concerns' in the randomization process and deviations from intended interventions in the study by Riedl and colleagues[17]. The other included studies[10,14,16] had a low risk of bias (*Fig. S2*, supporting information).

Discussion

This meta-analysis has demonstrated a reduction in anastomotic leakage and postoperative pneumonia after SDD for upper gastrointestinal surgery. Anastomotic leak was not defined uniformly, but adhered to a common basis. Three of the four studies identified a reduction in leak rates, and two of the three included studies showed a reduction in pneumonia, although in these two studies there was a threefold to fourfold difference in the prevalence of pneumonia, probably reflecting differences in definition.

In the study by Schardey *et al.*[16], which used tobramycin, polymyxin B, amphotericin B and vancomycin for SDD, a concurrent effect of reduced bacterial oropharyngeal colonization was found[19]. This might relate to the reduced incidence of pneumonia, as microaspiration is associated with postoperative pneumonia[20].

The number of eligible RCTs for this analysis was low, limiting its conclusions. An RCT by Tetteroo and colleagues[18] had different reporting of complications and was outdated and thus not included in the analysis. Overall morbidity was reported in only one study[16]. The type of resection varied, although most of the included patients underwent oesophagectomy or gastrectomy. The studies cover the time period for the introduction of minimal-access approaches in upper gastrointestinal surgery. These operations are associated with a reduced risk of postoperative infectious morbidity. Of the included studies, only Roos and co-workers[10] reported on the use of minimally invasive surgery, although the percentage of a specific procedure (e.g. gastric resection) was not apparent. Conversely, increasingly aggressive therapies for upper gastrointestinal cancers expose patients to increased risk of infection[21].

In this analysis, three of the four included studies were underpowered with regard to their primary endpoint. Only the study of Roos *et al.*[10] was of sufficient size for analysis of infectious complications. Based on the metadata, analysis of anastomotic leakage would need 548 patients (13 per cent placebo *versus* 6 per cent SDD), pneumonia 278 patients (25 *versus* 12 per cent) and mortality 1276 patients (9 *versus* 5 per cent) to reach a power of 80 per cent with an α error of 5 per cent. As detrimental side-effects and selection of resistant bacteria by SDD are uncommon, further well designed RCTs should investigate the impact of SDD in upper gastrointestinal surgery[22]. Hepatopancreatobiliary resections would be of particular interest, as preoperative biliary stenting is a known risk factor for postoperative infectious complications[8].

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.