Selective decontamination of the digestive tract in elective gastrointestinal surgery
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Systematic review of perioperative selective decontamination of the digestive tract in elective gastrointestinal surgery

ABSTRACT

Background
Studies on selective decontamination of the digestive tract (SDD) in elective gastrointestinal surgery have shown decreased rates of postoperative infection and anastomotic leakage. However, the prophylactic use of perioperative SDD in elective gastrointestinal surgery is not generally accepted.

Methods
A systematic review of randomized clinical trials (RCTs) was conducted to compare the effect of perioperative SDD with systemic antibiotics (SDD group) with systemic antibiotic prophylaxis alone (control group), using MEDLINE, Embase and the Cochrane Central Register of Controlled Trials. Endpoints included postoperative infection, anastomotic leakage, and in-hospital or 30-day mortality.

Results
Eight RCTs published between 1988 and 2011, with a total of 1668 patients (828 in the SDD group and 840 in the control group), were included in the meta-analysis. The total number of patients with infection (reported in 5 trials) was 77 (19.2%) of 401 in the SDD group, compared with 118 (28.2%) of 418 in the control group (odds ratio 0.58, 95% confidence interval 0.42 to 0.82; \( P = 0.002 \)). The incidence of anastomotic leakage was significant lower in the SDD group: 19 (3.3%) of 582 patients versus 44 (7.4%) of 595 patients in the control group (odds ratio 0.42, 0.24 to 0.73; \( P = 0.002 \)).

Conclusion
This systematic review and meta-analysis suggests that a combination of perioperative SDD and perioperative intravenous antibiotics in elective gastrointestinal surgery reduces the rate of postoperative infection including anastomotic leakage compared with use of intravenous antibiotics alone.
INTRODUCTION

Gastrointestinal (GI) surgery, and especially colorectal surgery, has been associated with a high rate of postoperative infection, longer subsequent hospital stay and higher costs. The cause of postoperative infection is multimodal. There are several risk factors for anastomotic leakage, including low preoperative albumin levels, intraoperative blood loss and a prolonged operating time (more than 3 h). Apart from optimization of the patient's condition and disease-related factors, preoperative parenteral antibiotics are administered to decrease the rate of postoperative infections after elective GI surgery. Antibiotic administration, 30–60 min before surgery, is standard treatment if contamination during surgery is expected. The addition of oral antibiotics that selectively target potentially pathogenic Gram-negative microorganisms, yeasts and Staphylococcus aureus, initiated before surgery and continued until normal passage of food and/or stool, seems to decrease further the incidence of infection. However, the use of selective decontamination of the digestive tract (SDD) in elective GI surgery is not generally accepted. In the Netherlands, only approximately 6% of surgeons use prophylactic SDD in elective GI surgery. Different oral decontamination protocols are applied. Some consist of a single antibiotic and others use combinations of antibiotics; some use antibiotics for only 1 day before surgery, whereas others continue antibiotic administration after surgery. Furthermore, protocols differ in antimicrobial selectivity. Some of the oral antimicrobials are absorbed (such as co-trimoxazole and quinolones), others are not. However, despite absorption, oral ciprofloxacin gives a constant drug concentration in faeces and therefore also has a good decontaminating effect. The most frequently used SDD protocol consists of a combination of three non-absorbable antibiotics (polymyxin E, tobramycin and amphotericin B), which are applied as an oral paste and administered orally and via the gastric tube, if present. These drugs are active against a broad spectrum of the potentially pathogenic aerobic Gram-negative rods, S. aureus, yeasts and fungi, while sparing the less pathogenic anaerobes and Gram-positive flora. Several meta-analyses have shown that SDD reduces the morbidity and mortality of critically ill patients. In surgical patients treated in an intensive care unit (ICU), postoperative SDD reduces the duration of mechanical ventilation, ICU and hospital stay, and mortality. No reviews have been published on the use of preoperative SDD in elective GI surgery. Therefore, a systematic review and meta-analysis was performed of studies reporting the effect of perioperative SDD in elective GI surgery to prevent postoperative infection and anastomotic leakage.

METHODS

Search strategy

A systematic literature search was conducted independently by two authors. The checklist of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was used in order to include all items for this review. Because the term 'selective decontamination of the digestive tract' (SDD) is commonly used, this term was used as a keyword in the search strategy.
decontamination of the digestive tract’ had not been introduced in earlier studies, the terms non-absorbable antibiotics including single or combined antibiotics, if administered orally, were also searched. In the present review, the term ‘SDD’ is used for all oral regimens, whereas ‘control’ is used for the group receiving intravenous antibiotics only. The search was performed using medical subject headings (MeSH) as well as free text words, such as “gastrointestinal diseases/surgery”[MeSH] and “gastrointestinal surgery” combined with “decontamination”[MeSH] or SDD.

The searched databases, MeSH and free text words used for the search are shown in Appendix S1 (supporting information). All articles identified by the search were assessed by title and abstract. The references of retrieved articles were checked to identify other relevant trials. Only randomized clinical trials (RCTs) assessing the efficacy of SDD or the prevention of postoperative infection, in adult patients undergoing elective GI surgery, compared with no oral regimen or placebo, were included.

Inclusion criteria
RCTs that compared the effect of the preoperative use of SDD in addition to intravenous antibiotics with intravenous antibiotics alone for the prevention of infections after elective GI surgery in adult patients were included in the study. Parenteral antibiotics had to be similar in both groups of patients. Postoperative infections were defined as wound infections, pneumonia, urinary tract infections, intra-abdominal abscesses and anastomotic leakage.

Exclusion criteria
Exclusion criteria were: studies evaluating SDD in emergency surgery; animal studies; studies of SDD in children; liver, bone marrow and small bowel transplantation; burns; and pancreatitis. Studies on the use of SDD in patients treated in the ICU were also excluded.

Selection of studies
Two reviewers independently assessed studies for eligibility based on titles and abstracts. The full text of the potentially relevant studies was obtained and also assessed by the two authors. In case of disagreement, the subject was discussed or reviewed by an independent researcher until consensus was achieved.

Endpoints
The primary clinical endpoint analysed was 30-day postoperative infections, including surgical-site infections (SSIs), urinary tract infections, pneumonia and anastomotic leakage. The secondary endpoint was mortality, defined as in-hospital death or death within 30 days after surgery.

Methodological quality
The two reviewers independently assessed the methodological quality of the studies according to the Jadad score. Disagreements were resolved by consensus. Studies with a Jadad score below 3 were not included.
Data extraction and management
The two reviewers independently extracted data from each outcome for the published results of included trials. Baseline characteristics of the study, and number of patients randomized and analysed, were retrieved. Study endpoints were extracted as numbers (with percentages) or as mean(s.d.) values where appropriate. The numbers of patients with complications were also counted. When data were extracted from graphical plots, or studies reported the number of complications rather than the number of patients with complications, or when numbers of a specific endpoint were not provided in the article, an attempt was made to contact the authors to clarify details and/or to request missing data on outcome.

Unit of analysis issues
Some studies compared three groups of patients: one group receiving oral therapy alone, a second group receiving perioperative systemic antibiotics, and a third group that had combined oral and systemic therapy. Data for the group receiving oral therapy alone were not included for these studies.

Statistical analysis
Outcomes were analysed as continuous or dichotomous variables, using standard statistical techniques available in the Review Manager program RevMan version 5.1 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). For continuous outcomes, the weighted mean difference and 95% confidence intervals (c.i.) were calculated. For dichotomous outcomes, the odds ratio (OR) was calculated with 95% c.i.
Heterogeneity of trial results was tested with the Higgins $\chi^2$ test, and the $I^2$ statistic was calculated to give an estimate of the degree of heterogeneity. $I^2$ values over 50% indicate considerable heterogeneity. 14

RESULTS
The search identified 1660 potentially relevant abstracts. Of these studies, 38 were evaluated based on title and abstract. Nineteen studies were excluded after full-text examination. Eleven studies with a Jadad score lower than 3 were excluded. A total of eight publications were eligible for inclusion in the systematic review, which included a total of 1668 participants (Figure 1).

Quality assessment
All studies stated that the treatment allocation was random. Only three of the trials described the method and the concealment of randomization. The Jadad score varied between 3 and 5. Four studies were reported to be double-blind. 7,15–17 Withdrawals and drop-outs were accounted for in all included papers. Of 1668 patients, 828 received preoperative SDD with perioperative intravenous antibiotics, and 840 patients received perioperative intravenous antibiotics alone, with or without an oral placebo. Two trials
compared three groups of patients: only intravenous antibiotics, only oral antibiotics, and a combination of intravenous antibiotics. These trials were included in the pooled analysis, by including only the data for the two groups providing information with regard to the research question. Only four studies mentioned a placebo. This was described as a ‘placebo solution’\textsuperscript{15}, ‘complementary placebo’\textsuperscript{17}, ‘identical placebo’\textsuperscript{18} or ‘identical placebo with full recipe’.\textsuperscript{7} SDD was initiated between 12 and 48 h before surgery and included one to eight administrations of antibiotics. Mechanical bowel preparation before surgery was used in all patients undergoing colorectal surgery.\textsuperscript{7,17–21} Two studies\textsuperscript{15,16} included patients undergoing upper GI surgery (such as oesophagectomies and gastrectomies) and did not use mechanical bowel preparation, except when oesophagogastrrectomy with coloplasty or total gastrectomy with (partial) colectomy was planned.\textsuperscript{15} The type of bowel preparation varied between studies and consisted of clear liquid diets starting 2 days

\begin{figure}
\centering
\includegraphics[width=\textwidth]{PRISMA_diagram.png}
\caption{PRISMA diagram of selection of articles for systematic review. RCT, randomized clinical trial; i.v., intravenous.}
\end{figure}
before surgery\textsuperscript{17,21} polyethylene glycol\textsuperscript{19,20} or Klean-Prep\textsuperscript{®} (Helsinn, Lugano, Switzerland).\textsuperscript{7} In some studies, rectal enemas were used.\textsuperscript{17,18,21} Characteristics of the studies are summarized in Table 1.

**Antibiotic therapy**

The antibiotic regimens are shown in Table 2. In all trials, systemic antibiotics were given at an adequate dose before surgery. The regimen varied, but consisted mostly of a cephalosporin, sometimes combined with metronidazole. All trials used, at least, antibiotics with Gram-negative coverage. The intravenous antibiotics were continued for 24 h,\textsuperscript{7,15,17,21} or for 2 days\textsuperscript{19} or 3 days,\textsuperscript{20} in two trials, the systemic therapy was given only before surgery and at the end of the procedure during closure of the wound.\textsuperscript{16,18} In all trials, the systemic antibiotics used were the same in both groups of patients.

The oral prophylactic regimen differed between trials. Two oral antibiotics were given before surgery in five trials.\textsuperscript{17–21} The combination of polymyxin, tobramycin and amphotericin was used in the trials of Roos and colleagues\textsuperscript{7} and Schardey and co-workers.\textsuperscript{16} In the study of Schardey et al.,\textsuperscript{16} oral vancomycin was added to the SDD, thereby covering methicillin-resistant \textit{S. aureus} (MRSA).

**Oral decontamination**

Preoperative oral decontamination was given by mouth. Only three trials described the use of oral decontamination after surgery.\textsuperscript{7,15,16} If a patient had a nasogastric tube after surgery, the trial medication was given both through the tube and orally in only one trial.\textsuperscript{7}

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### Table 1 | Characteristics of studies included in the meta-analysis.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Study design</th>
<th>Jadad score</th>
<th>No. of patients</th>
<th>Type of surgery</th>
<th>Mechanical bowel preparation</th>
<th>Duration of oral decontamination (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lau et al.\textsuperscript{21}</td>
<td>1988</td>
<td>RCT</td>
<td>3</td>
<td>65 67</td>
<td>Colorectal</td>
<td>Yes</td>
<td>Preop. 1 Postop. -*</td>
</tr>
<tr>
<td>Stellato et al.\textsuperscript{17}</td>
<td>1990</td>
<td>RCT</td>
<td>4</td>
<td>51 51</td>
<td>Colorectal</td>
<td>Yes</td>
<td>Preop. 1 Postop. -*</td>
</tr>
<tr>
<td>Schardey et al.\textsuperscript{16}</td>
<td>1997</td>
<td>RCT</td>
<td>5</td>
<td>102 103</td>
<td>Gastrectomy</td>
<td>No</td>
<td>Preop. 1 Postop. 7</td>
</tr>
<tr>
<td>Ishida et al.\textsuperscript{19}</td>
<td>2001</td>
<td>RCT</td>
<td>3</td>
<td>72 71</td>
<td>Colorectal</td>
<td>Yes</td>
<td>Preop. 2 Postop. -*</td>
</tr>
<tr>
<td>Lewis\textsuperscript{18}</td>
<td>2002</td>
<td>RCT</td>
<td>4</td>
<td>109 106</td>
<td>Colorectal</td>
<td>Yes</td>
<td>Preop. 0.5 Postop. -*</td>
</tr>
<tr>
<td>Kobayashi et al.\textsuperscript{20}</td>
<td>2007</td>
<td>RCT</td>
<td>3</td>
<td>246 245</td>
<td>Colorectal†</td>
<td>Yes</td>
<td>Preop. 1 Postop. -*</td>
</tr>
<tr>
<td>Farran et al.\textsuperscript{15}</td>
<td>2008</td>
<td>RCT</td>
<td>5</td>
<td>40 51</td>
<td>Gastrectomy and oesophagectomy</td>
<td>No</td>
<td>Preop. 0.5 Postop. 5</td>
</tr>
<tr>
<td>Roos et al.\textsuperscript{7}</td>
<td>2011</td>
<td>RCT</td>
<td>5</td>
<td>143 146</td>
<td>Upper GI, HPB and colorectal</td>
<td>Yes</td>
<td>Preop. 2 Postop. ≥ 3‡</td>
</tr>
</tbody>
</table>

*Postoperative oral decontamination was not applied or not mentioned in the publication. †With occasional cholecystectomy. ‡Selective decontamination of the digestive tract (SDD) was continued for at least 3 days after surgery or until normal bowel movements/stool and intake were achieved. RCT, randomized clinical trial; GI, gastrointestinal; HPB, hepatopancreatico-biliary.
Primary outcome

The data are summarized in Table 3. Infectious complications were reported in five studies; infections occurred in 77 (19.2%) of 401 patients in the SDD group versus 118 (28.2%) of 418 patients in the control group. Wound infections were found in 35 (5.1%) of 686 patients in the SDD group versus 74 (10.8%) of 686 patients in the control group, with missing data in two trials. Anastomotic leakage was found in 19 (3.3%) of 582 patients in the SDD group versus 44 (7.4%) of 595 in the control group. SSIs were described in only three trials, with or without anastomotic leakage. Two studies supplied exact data for all types of infectious complication. Incomplete data on outcome were found in six of the eight trials. Missing data were obtained in only one instance.

Meta-analysis

Meta-analysis of the RCTs showed a significant difference in postoperative infections in favour of the SDD group (OR 0.58, 95% c.i. 0.42 to 0.82; \( P = 0.002 \)). The incidence of anastomotic leakage was significant lower in the SDD group (OR 0.42, 0.24 to 0.73; \( P = 0.002 \)). The risk of wound infection (OR 0.44, 0.29 to 0.67; \( P < 0.001 \)) and pneumonia (OR 0.45, 0.27 to 0.74; \( P = 0.004 \)) were also significantly lower in the SDD group.

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**Table 2** Oral and systemic antibiotic regimens in the included studies.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Oral antibiotics</th>
<th>Oral doses before surgery</th>
<th>Systemic antibiotics</th>
<th>Duration of systemic antibiotics after surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lau et al.</td>
<td>Neomycin 1 g + erythromycin 1 g</td>
<td>3 daily doses 1 day before surgery</td>
<td>Metronidazole 500 mg + gentamicin 2 mg/kg *</td>
<td>3 doses in 24 h</td>
</tr>
<tr>
<td>Stellato et al.</td>
<td>Neomycin 1 g + erythromycin 1 g</td>
<td>3 daily doses 1 day before surgery</td>
<td>Cefoxitin 2 g *</td>
<td>3 doses in 24 h</td>
</tr>
<tr>
<td>Schardey et al.</td>
<td>Polymyxin B 100 mg + tobramycin 80 mg + amphotericin B 500 mg + vancomycin 125 mg</td>
<td>4 daily doses, 20 ml, 1 day before surgery</td>
<td>Cefotaxime, 2 ‘infusions’ *</td>
<td>2 doses before and during closure</td>
</tr>
<tr>
<td>Ishida et al.</td>
<td>Kanamycin 500 mg + erythromycin 400 mg</td>
<td>4 daily doses, started 2 days before surgery</td>
<td>Cefotiam 1 g *</td>
<td>2 daily doses, for 48 h</td>
</tr>
<tr>
<td>Lewis et al.</td>
<td>Neomycin 1 g + metronidazole 1 g</td>
<td>2 daily doses, evening before surgery</td>
<td>Amikacin 1 g + metronidazole 1 g *</td>
<td>No antibiotics after surgery</td>
</tr>
<tr>
<td>Kobayashi et al.</td>
<td>Kanamycin 1 g + erythromycin 400 mg</td>
<td>3 daily doses, 1 day before surgery</td>
<td>Cefmetazol 1 g *</td>
<td>2 daily doses, 72 h</td>
</tr>
<tr>
<td>Farran et al.</td>
<td>Erythromycin 500 mg + gentamicin 80 mg + nystatin sulphate 100 mg</td>
<td>4 daily doses, 20 ml, 1 day before surgery</td>
<td>Amoxicillin 2 g + clavulanic acid 200 mg *</td>
<td>According to hospital guidelines</td>
</tr>
<tr>
<td>Roos et al.</td>
<td>Polymyxin B sulphate 100 mg + tobramycin 80 mg + amphotericin B 500 mg</td>
<td>4 daily doses, 10 ml, started 2 days before surgery</td>
<td>Cefuroxime 1500 mg + metronidazole 500 mg *</td>
<td>3 doses in 24 h</td>
</tr>
</tbody>
</table>

*Both groups (oral and systemic antibiotic versus systemic antibiotics alone) received the same systemic antibiotics.
0.52, 0.30 to 0.89; \( P = 0.018 \) was also decreased in the SDD group, although only three RCTs\(^7,15,16\) provided data on pneumonia (Figure 2). The incidence of urinary tract infection did not differ between the treatment groups (OR 0.51, 0.23 to 1.13; \( P = 0.099 \)), but data were provided in only two trials.\(^7,16\) Four of the eight studies presented data on mortality.\(^7,15–17\)

Meta-analysis showed that the mortality rate (in-hospital death or death within 30 days after surgery) did not differ between the treatment groups (OR 0.64, 0.32 to 1.29; \( P = 0.215 \)). Separate analysis of subgroups for upper and lower GI surgery was performed. For overall infectious complications, a meta-analysis of 387 patients having upper GI surgery and 432 having lower GI surgery was conducted. SDD reduced infectious complications in both subgroups (OR 0.59, 0.38 to 0.91 and OR 0.55, 0.32 to 0.95; \( P = 0.862 \)) (Figure 3). For anastomotic leakage, 387 patients having upper GI surgery and 790 having lower GI surgery were analysed. SDD reduced the risk of anastomotic leakage in both subgroups, with no difference in effect between upper and lower GI surgery: OR 0.36 (0.16 to 0.79) versus 0.45 (0.20 to 1.01) (\( P = 0.699 \)) (Figure 4). Subgroup analysis of other endpoints could not be performed owing to low numbers of patients.

### Table 3.1 Postoperative infectious complications in patients receiving oral and intravenous antibiotics (selective decontamination group) versus intravenous antibiotics alone (control group).

<table>
<thead>
<tr>
<th>Reference</th>
<th>SDD group</th>
<th>Control group</th>
<th>Postop. infectious complications</th>
<th>Wound infection</th>
<th>Abscess</th>
<th>Pneumonia</th>
<th>Urinary tract infection</th>
<th>Anastomotic leakage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lau et al.(^21)</td>
<td>65</td>
<td>67</td>
<td>8 vs 8</td>
<td>3 vs 5</td>
<td>2 vs 2</td>
<td>n.r.</td>
<td>n.r.</td>
<td>1 vs 2</td>
</tr>
<tr>
<td>Stellato et al.(^17)</td>
<td>51</td>
<td>51</td>
<td>4 vs 6</td>
<td>3 vs 2</td>
<td>1 vs 5</td>
<td>n.r.</td>
<td>n.r.</td>
<td>1 vs 3</td>
</tr>
<tr>
<td>Schardey et al.(^16)</td>
<td>102</td>
<td>103</td>
<td>31 vs 46</td>
<td>n.r.</td>
<td>5 vs 4</td>
<td>9 vs 23</td>
<td>7 vs 8</td>
<td>3 vs 11</td>
</tr>
<tr>
<td>Ishida et al.(^19)</td>
<td>72</td>
<td>71</td>
<td>n.r.</td>
<td>8 vs 17</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>1 vs 2</td>
</tr>
<tr>
<td>Lewis et al.(^18)</td>
<td>109</td>
<td>106</td>
<td>n.r.</td>
<td>5 vs 17</td>
<td>1 vs 2</td>
<td>n.r.</td>
<td>n.r.</td>
<td>3 vs 1</td>
</tr>
<tr>
<td>Kobayashi et al.(^20)</td>
<td>246</td>
<td>245</td>
<td>n.r.</td>
<td>6 vs 14</td>
<td>11 vs 12</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
</tr>
<tr>
<td>Farran et al.(^15)</td>
<td>40</td>
<td>51</td>
<td>6 vs 13</td>
<td>n.r.</td>
<td>n.r.</td>
<td>5 vs 10</td>
<td>n.r.</td>
<td>1 vs 3</td>
</tr>
<tr>
<td>Roos et al.(^7)</td>
<td>143</td>
<td>146</td>
<td>28 vs 45</td>
<td>10 vs 19</td>
<td>n.r.*</td>
<td>8 vs 9</td>
<td>3 vs 11</td>
<td>9 vs 22*</td>
</tr>
</tbody>
</table>

Some patients had more than one complication. *All intra-abdominal abscesses in this study were caused by anastomotic leakage, and reported in that column. n.r., Not reported.
Figure 2.1 Forest plot of all postoperative infectious complications, anastomotic leakage, wound infections and pneumonia in patients having selective decontamination of the digestive tract with oral antibiotics plus intravenous antibiotics (SDD group) versus those receiving intravenous antibiotics alone (control group). A fixed-effect Mantel–Haenszel model was used for meta-analysis. Odds ratios are shown with 95% confidence intervals.
### Review of SDD in GI Surgery

#### Figure 3.1 Forest plot of postoperative infectious complications following upper and lower gastrointestinal (GI) surgery in patients having selective decontamination of the digestive tract with oral antibiotics plus intravenous antibiotics (SDD group) versus those receiving intravenous antibiotics alone (control group). A fixed-effect Mantel–Haenszel model was used for meta-analysis. Odds ratios are shown with 95% confidence intervals.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>IV + oral Events</th>
<th>IV only Events</th>
<th>Total Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Upper</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farran 2008</td>
<td>6</td>
<td>40</td>
<td>13</td>
<td>51</td>
<td>18.1%</td>
</tr>
<tr>
<td>Roos 2011, upper</td>
<td>16</td>
<td>48</td>
<td>17</td>
<td>43</td>
<td>22.3%</td>
</tr>
<tr>
<td>Schardey 1997</td>
<td>31</td>
<td>102</td>
<td>46</td>
<td>103</td>
<td>59.5%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>190</td>
<td>197</td>
<td>100.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>53</td>
<td>76</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Ch² = 0.50, df = 2 (P = 0.78); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.41 (P = 0.02)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>IV + oral Events</th>
<th>IV only Events</th>
<th>Total Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lower</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lau 1988</td>
<td>8</td>
<td>65</td>
<td>8</td>
<td>67</td>
<td>19.2%</td>
</tr>
<tr>
<td>Roos 2011, lower</td>
<td>12</td>
<td>95</td>
<td>28</td>
<td>103</td>
<td>65.4%</td>
</tr>
<tr>
<td>Stellato 1990</td>
<td>4</td>
<td>51</td>
<td>6</td>
<td>51</td>
<td>15.4%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>211</td>
<td>221</td>
<td>100.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>24</td>
<td>42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Ch² = 2.31, df = 2 (P = 0.32); I² = 13%</td>
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<td>Test for overall effect: Z = 2.15 (P = 0.03)</td>
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Test for subgroup differences: Ch² = 0.03, df = 1 (P = 0.86), I² = 0%
DISCUSSION

The present meta-analysis shows that the perioperative use of SDD in addition to standard intravenous antibiotics decreases postoperative infections and anastomotic leakage. Mortality was not reduced. However, the number of studies reporting mortality was low. The full regimen of SDD, topical polymyxin, tobramycin and amphotericin, eradicates the colonization and overgrowth of potentially pathogenic Gram-negative microorganisms, S. aureus and yeasts from oral cavity to rectum and prevents the translocation of endotoxin, microorganisms and subsequent infections. The addition of vancomycin additionally protects against MRSA, but is not advocated for standard SDD, because Gram-positive flora plays an important role in the resistance to colonization. Other regimens have a smaller Gram-negative spectrum and do not cover yeasts. Yeasts, especially Candida species, may account for about 20% of abdominal pathogens, especially after upper GI surgery.
In addition to a reduction in organ-site infections, perioperative SDD appears to diminish the risk of anastomotic leakage. Next to poor surgical technique and impaired blood supply to the intestinal anastomosis, bacteria play a major role in the pathogenesis of anastomotic insufficiency. They may cause local inflammation at the anastomosis, with intramural abscess formation and anastomotic dehiscence. Preoperative SDD may also reduce perioperative endotoxaemia, caused by the permeation of bacterial compounds through a diminished gut–blood barrier with a reduced systemic inflammatory response. However, perioperative endotoxaemia has been studied mostly during cardiac surgery and may be less prevalent during GI surgery, although it is sometimes reported. Systemic side-effects of SDD are few, because the antibiotics are administered orally and do not enter the bloodstream with most of the regimens used. Despite fear of resistance, long-term use of SDD in patients treated in the ICU is not associated with an increased acquisition of resistant bacterial flora. The reason for this may be that resistance occurs under conditions of a high concentration of microbes but a low antibiotic concentration, as in the gut when using intravenous antibiotics alone. Eradication of Gram-negative species with SDD decreases the risk of antibiotic resistance. However, careful microbial surveillance remains crucial.

The present review excluded the methodologically less strong trials and thus provides a high quality of evidence. Furthermore, all trials used the same systemic antibiotic(s) in the SDD and control groups of patients, making the groups comparable. Heterogeneity of the included studies was low. However, five of the eight analysed trials included (exclusively) patients having colorectal surgery, with only three studies reporting on upper GI surgery, making the evidence for SDD in this subgroup of patients less robust. This review has several limitations. First, observer bias could have influenced the results in the studies without blinding. Second, there is concern regarding publication bias, because not all studies reported all infectious complications, nor mortality. Third, the definition of SSI was described in seven studies, but the definition of pneumonia and anastomotic leakage were described only in three. Fourth, one study accounted for half of all anastomotic leakages and also had the highest leakage rate (31 of 289, 10.7%). The literature reports leakage in up to 10% of patients. The largest study did not specifically report anastomotic leakage, and an attempt to obtain data on anastomotic leakage from the authors failed. Therefore, to confirm the present results, anastomotic leakage should be an endpoint in future trials. The majority of the studies in the present meta-analysis were conducted before 2007 and did not include enhanced recovery after surgery (ERAS) protocols. Implementation of ERAS protocols reduces hospital stay and appears to reduce the incidence of postoperative infection. A Cochrane analysis showed a reduction in length of stay and overall complications, whereas major complications were not reduced. Hospital stay was not an endpoint of the present review and meta-analysis, but could be of interest to study in the future, especially in the context of an ERAS protocol. The authors postulate, however, that preoperative SDD may reduce postoperative infections and anastomotic leakage further, because the full regimen of SDD specifically eradicates GI colonization with Gram-negative bacteria and yeast, which foreshadows postoperative infection. In the included
studies different types of antibiotic with different antimicrobial coverage and duration of treatment were used. However, all studies applied oral antibiotics with Gram-negative coverage, although only one trial assessed the degree of preoperative decontamination by taking rectal cultures in the operating room before surgery. This trial showed that SDD needs to be administered in a sufficient dosage and for at least 48–72 h before surgery to achieve effective decontamination of the intestinal tract. The present meta-analysis shows that the administration of perioperative SDD in elective GI surgery decreased postoperative infectious complication and anastomotic leakage rates for upper GI and colorectal surgery. Future trials are needed to confirm whether SDD has additive positive effects in addition to an ERAS protocol.
REFERENCES


SUPPLEMENTARY MATERIAL

Appendix S1

Search Strategy
MEDLINE (Jan 1980 until September 2012), the Cochrane Central Register of Controlled Trials (CENTRAL), and EMBASE were searched. The literature search was not restricted by language or year of publication. The following medical subject headings (MeSH) and free text words were used: ((“gastrointestinal diseases/surgery”[Mesh] OR gastrointestinal surgery OR gastro intestinal surgery OR “digestive system surgical procedures”[Mesh] OR (“gastrointestinal tract”[Mesh] AND (“surgical procedures, operative”[MeSH Terms] OR “general surgery”[Mesh]) OR (surgery AND (esophagus OR esophagectomy OR esophageal OR gastrectomy OR stomach OR liver OR pancreatitis OR pancreatectomy OR colectomy OR colon OR rectal))) AND (“decontamination”[Mesh] OR SDD OR decontaminat*[tiab] OR ((“anti-bacterial agents”[Mesh] OR antibiotic*) AND (prophylactic OR prophylaxis OR preventive OR oral OR parenteral OR preoperative OR nonabsorbable OR “non absorbable”))) AND (trial OR random* OR comparative OR “systematic review” OR meta-analysis OR vs[ti] OR versus[ti]) NOT (“animals”[Mesh] NOT “humans”[Mesh]).