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Original Article

Outcome of a 3-day vs 7-day selective digestive tract decontamination–based regimen for oral antibiotic bowel decontamination in left-sided colorectal surgery: A noninferiority study

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ABSTRACT

Background: Colorectal surgery still experiences high rates of infectious complications, such as anastomotic leakage (AL) and surgical site infections (SSIs). Therefore, oral antibiotic bowel decontamination (OABD) has experienced a renaissance. However, data on perioperative selective digestive tract decontamination (SDD)–based regimens or combined bowel preparation are inconsistent. Nonetheless, with widespread use of Enhanced Recovery After Surgery concepts, the ideal length for perioperative SDD treatment has to be reconsidered.
Methods: Perioperative outcome was analyzed in a cohort of patients undergoing minimally invasive surgery for left-sided colorectal cancer in a retrospective study. Additional to usual perioperative outcome measures, including AL, SSIs, and overall infectious complications, the efficacy of a shortened 3-day perioperative OABD treatment was compared with the efficacy of a 7-day perioperative OABD treatment based on a noninferiority analysis.
Results: Overall, 256 patients were included into analysis, of whom 84 and 172 patients were treated by 3-day and 7-day perioperative OABD regimens, respectively. AL occurred in 1.2% of patients in the 3-day group and 5.2% of patients in the 7-day group, and SSIs occurred in 3.6% of patients in the 3-day group and 5.8% of patients in the 7-day group, without significant difference. The shortened 3-day perioperative SDD-based regimen was noninferior to the regular 7-day perioperative SDD-based regimen concerning the rates of AL, SSIs, and infectious complications.
Conclusion: Our data demonstrated noninferiority of a shortened 3-day SDD-based treatment vs a 7-day SDD-based treatment for AL, SSIs, and overall infectious complications.

Introduction

Despite advancements in minimally invasive surgical techniques, along with the implementation of "Enhanced Recovery After Surgery" (ERAS) principles, colorectal surgery still faces high rates of infectious complications, notably anastomotic leakage (AL) and surgical site infections (SSIs) [1–4]. In particular, AL is known to adversely affect long-term oncologic outcomes after colorectal cancer surgery [5,6].

Over recent decades, the influence of the microbiota on the development of SSI and AL has been proven and even unraveled at the molecular level [7–10]. Concurrently, the practice of combined bowel preparation with oral antibiotics or selective digestive tract decontamination (SDD)–based perioperative oral antibiotic bowel

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decontamination (OABD) has seen a resurgence. Several registry data, single-center analyses, certain high-quality randomized controlled trials (RCTs), and meta-analyses have shown a positive effect of combined bowel preparation and OABD regimens on perioperative outcomes in colorectal surgery [11–17]. However, the data are not uniformly consistent. There is a wide range of different antibiotic regimens and pre- and perioperative concepts for use [11,13,16–20]. Although the use of SDD-based regimes is more widespread in Europe, other preoperative combined bowel preparation concepts are more common in the United States [13,18–22]. The preoperative administration of glycoside antibiotics (such as neomycin and kanamycin) and/or metronidazole as part of combined bowel preparation has been found to be less effective than perioperative SDD-based regimens [13,18–22]. Although Abis et al. [11] could only report a significant reduction in SSI and not AL in the SELECT trial, Roos et al. [23] and Schardey et al. [16] reported significant reductions in SSI and AL using a perioperative SDD-based regimen for OABD. Recently, Koskenvuo et al. [17] were able to demonstrate a similar effect using a preoperative combined bowel preparation regimen using neomycin and metronidazole.

These SDD-based regimens, which involve combinations of orally nonabsorbable antibiotics covering all relevant gram-negative and gram-positive bacteria, have been proven effective not only in colorectal surgery but also in gastrointestinal (GI) surgery [11,16,23]. These SDD treatments were initially used in intensive care units (ICUs) to reduce the rate of ventilator-associated lung infections [24,25]. Later, they were adopted in GI surgery for the prevention of bacteria-caused perioperative infectious complications, such as AL and SSIs [11,16,23]. However, all concepts using oral antibiotics for the prevention of perioperative infectious complications have a negative effect on the gut microbiome and gut microbial diversity [7,8]. Recent microbiome data from Alverdy et al. [7] revealed a decline in gut microbiome diversity because of prolonged perioperative antibiotic therapy. Furthermore, after surgery and antibiotic use, the healthy gut microbiome requires time to recover [7]. During this vulnerable period, it is susceptible to suppression by a detrimental “pathobiome,” increasing the risk of other infectious complications [7,8].

To prevent infectious complications in colorectal surgery, the SDD-based typically regimen begins preoperatively and continues until the seventh postoperative day (POD) [16,26]. However, patients undergoing colorectal surgical procedures using minimally invasive techniques and following ERAS regimens are often discharged well before this 7-day mark.

Considering these factors, the SDD regimen described above was shortened to 3 PODs. However, the effectiveness of this shortened regimen in preventing SSI and AL compared with the established and scientifically evaluated 7-day postoperative protocol remains uncertain. Our study aimed to analyze the effectiveness of the shortened 3 PODs vs 7 PODs perioperative SDD-based regimen in preventing AL and other infectious complications.

Materials and methods

Study population

We conducted an analysis of a cohort of patients undergoing minimally invasive surgery for left-sided colorectal cancer to compare the effects between a 3 PODs vs a 7 PODs perioperative SDD-based regimen for OABD using a noninferiority analysis. The study included patients from 2 regional hospitals who underwent SDD-based antibiotic bowel decontamination. We analyzed data from 118 patients at Agatharied Hospital (AH) and data from 138 patients at Neumarkt Hospital (NH). For the patients at NH in which data were collected prospectively, informed consent was obtained from all participants. The study protocol received approval from the local review board (the ethics committee of the Faculty of Medicine, Ludwig Maximilian University of Munich) and adhered to the guidelines of good clinical practice following the Declaration of Helsinki.

Perioperative management

An SDD-based regimen, composed of polymyxin B (100 mg), gentamicin (80 mg), vancomycin (125 mg), and amphotericin B (500 mg), hereafter referred to as OABD, was used as previously described [16,26]. The OABD medication was administered 4 times daily, starting in the evening before surgery, and was typically given in capsule form orally (Fig. 1). In cases of rectal cancer surgery involving the creation of a diverting loop ostomy, after anastomosis, a Foley catheter was inserted transanally. Through this catheter, the OABD medication, dissolved in distilled water, was applied topically, as described previously [16]. At both centers, OABD was started the day before surgery and continued until the seventh POD. All patients underwent surgery between 2003 and 2022. NH later changed the OABD regimen for shortened use only for the first 3 days postoperatively in May 2019, and all subsequently operated patients received the shortened 3-day regimen. The adherence to the OABD regimen was monitored in all patients. In addition to OABD, all patients undergoing rectal cancer surgery received mechanical bowel preparation, whereas patients undergoing other left-sided colorectal surgery received a mild laxative bowel preparation. Systemic single-shot antibiotic prophylaxis, usually cefuroxime and metronidazole, was administered before surgery according to the guidelines and recommendations [27,28]. The general recommendations and guidelines for preventing SSIs were followed [27–29]. The most important aspect in the prevention of SSIs is avoiding preoperative skin injuries because of, for example, shaving, adequate preoperative skin disinfection with an alcohol-based disinfectant, change of surgical gloves and instruments before abdominal wall closure, use of ringed wound protectors, and preoperative single-shot intravenous antibiotic prophylaxis [29]. All patients who received perioperative OABD and who started the OABD regimen on the day before surgery were included in the analysis (on-treatment protocol), regardless of whether perioperative OABD therapy was stopped earlier in the postoperative course than intended.

Minimally invasive rectal cancer surgical procedures were performed according to the latest technical standards, usually laparoscopically, including total mesorectal excision technique for all low anterior rectal resections. In patients with sigmoid cancer, oncologic resections were performed with complete mesocolic excision and central ligation of the inferior mesenteric artery. Circular double-row staplers (Ethicon Circular Stapler; Ethicon Endo-Surgery, Johnson & Johnson) of various sizes were used to create anastomoses in a double-stapling technique. Intraoperative leak testing using Patent Blue solution (Guerbet GmbH, Sulzbach, Germany) was routinely performed in all surgical procedures. As all operations were elective procedures, the surgical field can be considered clean contaminated.

Outcome measures

Patient demographic information, including age and sex; the American Society of Anesthesiologists (ASA) score; the Charlson Comorbidity Index [30]; specific diagnoses; TNM staging; and Union Internationale Contre le Cancer (UICC) classification for colorectal cancer, were recorded. In addition, perioperative details, such as type of procedure and conversion to open surgery, were documented. All perioperative complications within 30 days, including overall infectious complications (such as AL, SSI according to the Centers for Disease Control and Prevention definition [27], urinary tract infection, or pulmonary infection), general complications (such as cardiovascular complications), and mortality, were monitored. Despite SSI and

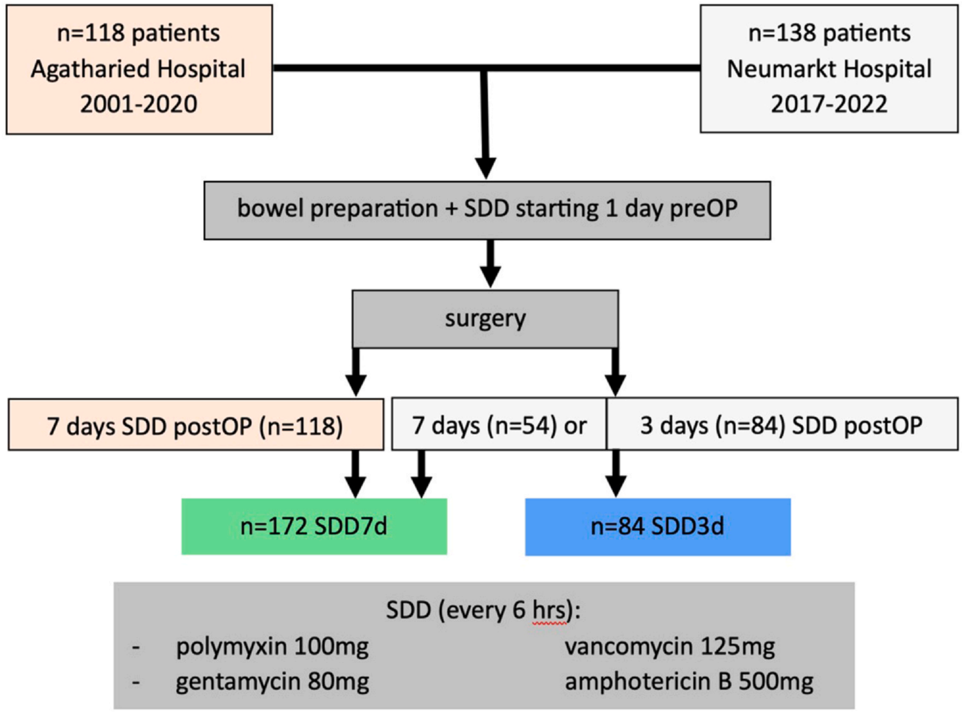

Figure 1. Flowchart for study design and SDD treatment. SDD, selective digestive tract decontamination.

AL, surgical complications, which occurred in single cases (intraoperative complications, such as ureter or urinary bladder injury, early incisional hernias, and bleeding complications), are summarized as "other surgical complications." All complications were classified according to the Clavien-Dindo classification [31], and in addition, the Comprehensive Complication Index was calculated [32]. Laboratory values, including white blood cell (WBC) count and C-reactive protein (CRP) levels, were monitored perioperatively. The complete administration of OABD medication was evaluated along with any reasons for discontinuing the medication. All potential adverse events associated with OABD treatment were recorded. Furthermore, all available microbiologic reports were checked for infections caused by *Clostridium difficile* or multiresistant bacteria. AL was defined and classified according to the International Study Group of Rectal Cancer as a defect of the intestinal wall at the anastomotic site requiring no change in patient management (grade A), needing therapeutic intervention but no revision surgery (grade B), or requiring revision surgery (grade C) [33]. AL was typically diagnosed using computed tomography scans, endoscopy, or revision surgery. However, because of missing routine anastomotic evaluation, only clinically apparent AL could be detected.

The primary endpoint of the study was the noninferiority of the shortened 3 PODs OABD perioperative regimen compared with the 7 PODs OABD regimen regarding AL. The secondary endpoints included the noninferiority of the 3-day OABD regimen for SSIs and overall infectious complications.

Statistical analysis

Statistical analysis was performed using SPSS (version 29; IBM) and GraphPad Prism (version 7; GraphPad Software Inc). Patient characteristics and perioperative data were summarized using adequate measures of location and dispersion. The Mann-Whitney *U* test (MW) for nonnormally distributed values and the Student *t* test (t) for normally distributed values were used for exploratory comparisons between groups. The normal distribution of mean differences was tested using the Kolmogorov-Smirnov test. The Fisher exact test and $\chi 2$ test were used to compare data between subgroups based on nominal or categorical data. Laboratory values of WBC count and CRP were compared between the 3-day SDD and 7-day SDD groups and between groups with and without complications. Receiver operating characteristic (ROC) curve analysis was used to investigate whether a renewed increase in CRP or WBC count could discriminate between cases with/without AL and cases with/without overall infectious complications. The area under the curve (AUC) was calculated to assess the discriminatory ability of the ROC curve analysis. A *P* value of $\leq .05$ was defined to indicate statistical significance.

To evaluate the effectiveness of the 3 PODs vs 7 PODs OABD regimen (3-day SDD vs 7-day SDD groups) in terms of AL prevention, we assessed the noninferiority based on the risk difference (RD). The RD was calculated as the difference in AL rates between the 3-day SDD and 7-day SDD groups: $RD = p_{3dSDD} - p_{7dSDD}$. The null hypothesis was that the 3-day OABD regimen is inferior to the 7-day OABD regimen ($RD > \Delta$). Noninferiority for the 3-day OABD regimen required an RD less than a prespecified noninferiority margin ($RD \leq \Delta$). Noninferiority was regarded as established if the predefined noninferiority margin Δ was greater than the upper limit of the 2-sided 95% CI of the RD [34,35].

Based on our previous findings and existing literature, we predefined the noninferiority margin to $\Delta = 2.5\%$ RD for AL. This decision is based on the understanding that a rate of approximately 5.0% ± 2.5% for AL is considered an acceptable outcome in left-sided colorectal resections, in line with the data currently available [5,11–13,16,17,21–23]. The noninferiority margin for SSIs and general infectious complications was predefined to $\Delta = 5.0\%$ (5.0% ± 5.0%) for the RD based on similar considerations and currently available data [5,11–13,16,17,21–23].

Results

Patient characteristics

A total of 256 left-sided minimally invasive colorectal surgical procedure were included in this study, 84 using a 3 PODs OABD

Table 1
Patients characteristics.

Characteristic		Groups		All cases (N = 256)	P values
		3-d SDD (n = 84)	7-d SDD (n = 172)		
Age (y), mean ± SD		61.6 ± 11.5	66.7 ± 10.2	65.0 ± 10.9	.001[a,b]
Sex	Female	29 (34.5%)	78 (45.3%)	107 (41.8%)	.099[c]
	Male	55 (65.5%)	94 (54.7%)	149 (58.2%)	
ASA score	1	13 (15.5%)	16 (9.3%)	29 (11.3%)	.458[c]
	2	39 (46.4%)	84 (48.8%)	123 (48.1%)	
	3	32 (38.1%)	71 (41.3%)	103 (40.2%)	
	4	0 (0%)	1 (0.6%)	1 (0.4%)	
	5	0 (0%)	0 (0%)	0 (0%)	
Charlson Comorbidity Index		4.7 ± 2.0	4.9 ± 1.8	4.8 ± 1.9	.102[a]
UICC stage	0	2 (2.4%)	5 (2.9%)	7 (2.7%)	.599[c]
	I	27 (32.1%)	60 (34.9%)	87 (34.0%)	
	II	14 (16.7%)	40 (23.3%)	54 (21.1%)	
	III	27 (32.1%)	42 (24.4%)	69 (27.0%)	
	IV	14 (16.7%)	25 (14.5%)	39 (15.2%)	

ASA, American Society of Anesthesiologists; SDD, selective digestive tract decontamination; UICC, Union Internationale Contre le Cancer.
[a] Mann-Whitney *U* test.
[b] Statistically significant difference.
[c] χ^2 test.

regimen (3-day SDD) and 172 using a 7 PODs OABD regimen (7-day SDD). The patient characteristics are summarized in Table 1. The 2 groups were quite homogeneous regarding the following confounders: ASA score (χ^2: *P* = .458), Charlson Comorbidity Index (MW: *P* = .102), UICC stage (χ^2: *P* = .599), and sex (χ^2: *P* = .099) (Table 1). Only for age, there was a significant difference between the 2 groups, with older patients included in the 7-day SDD group (MW: *P* = .001).

Perioperative data

The perioperative data are presented in Table 2. There was no significant difference in the distribution between rectal cancer surgery and left-sided colorectal cancer surgery (χ^2: *P* = .110) between the 2 groups, but the rate of ostomies was significantly higher in the 3-day SDD group (χ^2: *P* = .002). OABD treatment was mostly complete in both groups (χ^2: *P* = .098) and was terminated prematurely in only a few cases with nausea (n = 8) or prolonged postoperative ileus (n = 7). Only 1 case of *C difficile* infection occurred in the 7-day SDD group in a patient who otherwise had an unremarkable course and was treated with oral metronidazole therapy (χ^2: *P* = .484). There were no infections or infectious complications caused by multiresistant bacteria. The rate of patients being treated in an ICU or intermediate care unit after surgery was not different between the groups (χ^2: *P* = .069).

Perioperative outcome measures

The perioperative outcome is summarized in Table 3. There was no significant difference between the 3-day SDD and 7-day SDD groups regarding overall complication rate (χ^2: *P* = .334), rate of overall infectious complications (χ^2: *P* = .204), SSI (χ^2: *P* = .279), AL (χ^2: *P* = .117), or other surgical complications (χ^2: *P* = .961). In addition, for other general complications, such as urinary tract infections (χ^2: *P* = .484), pneumonia (χ^2: *P* = .391), myocardial infarction (χ^2: *P* = .737), or stroke (no cases in both groups), there was no significant difference between the 2 groups. The distribution of complications was distributed equally between the groups according to the Clavien-Dindo classification (χ^2: *P* = .665) and the Comprehensive Complication Index (MW: *P* = .637). There was no significant difference between the groups concerning the rates of postoperative interventions (χ^2: *P* = .771) and revision surgical procedures (χ^2: *P* = .204). Overall, 30-day mortality was comparable between groups (χ^2: *P* = .985). Mortality was not associated with severe surgical complications, such as AL, but was associated with cardiovascular events. Of note, 1 patient died of myocardial infarction, and another patient died of consecutive pneumonia after myocardial infarction. Moreover, 1 patient died of a fulminant pulmonary embolism.

Noninferiority analysis of the main perioperative outcome measures

The 3 PODs perioperative OABD treatment was found to be noninferior compared with the 7 PODs OABD treatment in terms of AL (upper limit of the 95% CI for RD, 0.003; Δ_{AL} = 2.5%), SSI (upper limit of the 95% CI for RD, 0.031; Δ_{SSI} = 5.0%), and infectious complications (upper limit of the 95% CI for RD, 0.018; Δ = 5.0%).

Comparisons between groups

Data comparing rectal resections with other left-sided resections are presented in Table 4. Comparing rectal resections with other left-sided resections, there is no significant difference between groups for age (MW: *P* = .894), sex (χ^2: *P* = .526), ASA score (χ^2: *P* = .479), Charlson Comorbidity Index (MW: *P* = .296), and UICC stages (χ^2: *P* = .572). Many more diverting ostomies have been created in rectal resections than in left-sided colonic resections (χ^2: $P < .001$). Overall complication rates (χ^2: *P* = .099), SSI rates (χ^2: *P* = .776), AL rates (χ^2: *P* = .197), overall infectious complication rates (χ^2: *P* = .641), and mortality rates (χ^2: *P* = .081) were similar between groups. The complications according to the Clavien-Dindo classification were distributed without significant difference (χ^2: *P* = .144). There was no significant difference in the rates of reintervention (χ^2: *P* = .099) or

Table 2
Perioperative data.

Variable		Groups		All included cases (N = 256)	P values
		3-d SDD (n = 84)	7-d SDD (n = 172)		
Surgery	Sigmoid resection/left hemicolectomy	36 (42.9%)	92 (53.5%)	128 (50.0%)	.110[a]
	Rectal resection	48 (57.1%)	80 (46.5%)	128 (50.0%)	
	MIS	82 (97.6%)	164 (95.3%)	246 (96.1%)	.379[a]
	Conversion to open surgery	2 (2.4%)	8 (4.7%)	10 (3.9%)	
Diverting ostomy		44 (52.4%)	55 (32.0%)	99 (38.7%)	.002
Complete OABD treatment		82 (97.6%)	159 (92.4%)	241 (94.1%)	.098[a]
Postoperative inhospital stay (d), mean ± SD		9.2 ± 4.7	11.3 ± 8.0	10.6 ± 7.1	.012[c]
ICU/IMC stay		75 (89.3%)	138 (80.2%)	213 (83.2%)	.069[a]
ICU/IMC duration (d), mean ± SD		1.0 ± 0.6	1.7 ± 2.2	1.5 ± 1.8	.002[c]

ICU, intensive care unit; IMC, intermediate care unit; MIS, minimally invasive surgery; OABD, oral antibiotic bowel decontamination; SDD, selective digestive tract decontamination.
[a] χ^2 test.
[b] Statistically significant difference.
[c] Mann-Whitney *U* test.

revision surgery (χ^2: $P = .352$). Only postoperative inhospital stay was significantly shorter in left-sided colonic resections than in rectal resections (MW: $P < .001$).

Comparison of laboratory values

Between the 2 groups, 3-day SDD and 7-day SDD, WBC count, and CRP levels were not significantly different (MW: $P > .05$) in the postoperative course, except for CRP level on the first POD, which was significantly lower in the 3-day SDD group (Fig. 2A and Supplementary Table 1). Comparing rectal resections with left-sided colonic resections, WBC count and CRP levels showed no significant differences (MW: $P > .05$), except for WBC count on POD4 (MW: $P = .014$) and CRP level on POD1 (MW: $P = .002$) (Fig. 2B and Supplementary Table 1).

In cases with AL vs cases without AL, WBC count showed no significant differences between preoperative values and POD1 to POD7 values (MW: $P > .05$), whereas CRP levels showed significant differences between preoperative values and POD2 to POD7 values (MW: $P < .05$) (Fig. 2C and Supplementary Table 2). In cases with infectious complications vs cases without overall infectious complications, the WBC count was significantly different on POD2 (MW: $P = .024$). CRP levels were significantly higher in cases with infectious complications preoperatively and between POD1 and POD7 (MW: $P < .05$) (Fig. 2C and Supplementary Table 2). The mean duration to occurrence of AL was 6.5 ± 3.3 days.

Furthermore, we used ROC curve analysis to investigate whether a renewed increase in CRP level or WBC count could indicate the occurrence of AL or overall infectious complications. For AL, the AUCs were 0.52 for WBC count and 0.77 for CRP level increase after the fifth POD (Fig. 3A). Regarding overall infectious complications, the AUCs were 0.61 for WBC count and 0.80 for CRP level increase after the fifth POD (Fig. 3B).

Discussion

We present the first analysis comparing a 7 PODs perioperative OABD regimen with a shortened 3 PODs perioperative OABD regimen based on a noninferiority approach in minimally invasive colorectal cancer surgery. In both groups, perioperative bowel decontamination seemed to have an overall beneficial effect on perioperative outcome, especially AL, SSIs, and overall infectious complications [5,11,13,16,23,36].

The distributions of surgical procedures for left-sided colon cancer and rectal cancer were similar between the groups, with no significant higher number of rectal resections in the 3-day SDD group and a significant higher rate of protective ostomies. In addition, the significant higher rate of protective stomas may have influenced the lower rate of AL in the 3-day SDD group. In contrast, the groups were quite homogeneous regarding the Charlson Comorbidity Index, ASA score, and UICC stages. The overall complication rate was similar between the groups, as was the rate of SSIs, AL, pneumonia, and overall infectious complications. Mortality rates were quite low in both groups, with all cases of 30-day mortality occurring in left-sided colonic resections but none in the rectal resection subgroup. Mortality was not associated with severe surgical morbidity and AL; however, mortality was associated with cardiovascular events.

Overall, perioperative SDD-based bowel decontamination was well tolerated and completed in most of the cases. It is noteworthy that, despite the difference in postoperative length of OABD treatment, the OABD regimen was completed in both groups in most of the patients without significant differences between groups. Infectious complications with rates between 14% and 20% have been described in previous RCTs in the SDD treatment group [11,16,23] or in other retrospective or registry studies [6,14,15,18,19,36]. Recently published data demonstrate persistently high rates of SSI (3%–20%) and AL (4%–6%) in colorectal surgery using a perioperative SDD-

Table 3
Perioperative outcome.

Variable			Groups		All cases (N = 256)	P values
			3-d SDD (n = 84)	7-d SDD (n = 172)		
All complications			17 (20.2%)	44 (25.6%)	61 (23.8%)	.334[a]
Overall infectious complications			4 (4.8%)	16 (9.3%)	20 (7.8%)	.204[a]
Surgical site infections			3 (3.6%)	10 (5.8%)	13 (5.1%)	.279[a]
		Superficial	3 (3.6%)	5 (2.9%)	8 (3.1%)	
		Deep	0 (0%)	0 (0%)	0 (0%)	
		Organ space	0 (0%)	5 (2.9%)	5 (2.0%)	
Anastomotic leakage			1 (1.2%)	9 (5.2%)	10 (3.9%)	.117[a]
		A	0 (0%)	1 (0.6%)	1 (0.4%)	
		B	0 (0%)	1 (0.6%)	1 (0.4%)	
		C	1 (1.2%)	7 (4.1%)	8 (3.1%)	
Other surgical complications			6 (7.1%)	12 (7.0%)	18 (7.0%)	.961[a]
Urinary tract infections			0 (0%)	1 (0.6%)	1 (0.4%)	.484[a]
Pneumonia			1 (1.2%)	5 (2.9%)	6 (2.3%)	.391[a]
Myocardial infarction			1 (1.2%)	3 (1.7%)	4 (1.6%)	.737[a]
Stroke			0 (0%)	0 (0%)	0 (0%)	N/A
Other nonsurgical complications			8 (9.5%)	14 (8.1%)	22 (8.6%)	.711[a]
Mortality (30 d)			1 (1.2%)	2 (1.2%)	3 (1.2%)	.985[a]
Clavien-Dindo class	I		5 (6.0%)	12 (7.0%)	17 (6.6%)	.665[a]
	II		3 (3.6%)	4 (2.3%)	7 (2.7%)	
	IIIa		4 (4.8%)	6 (3.5%)	10 (3.9%)	
	IIIb		4 (4.8%)	13 (7.6%)	17 (6.6%)	
	IVa		1 (1.2%)	3 (1.7%)	4 (1.6%)	
	IVb		0 (0%)	0 (0%)	0 (0%)	
	V		1 (1.2%)	2 (1.2%)	3 (1.2%)	
Comprehensive Complication Index			5.8 ± 14.7	6.9 ± 15.9	6.5 ± 15.5	.637[b]
Reintervention			4 (4.8%)	10 (5.8%)	14 (5.5%)	.771[a]
Revision surgery			4 (4.8%)	16 (9.3%)	20 (7.8%)	.204[a]

N/A, not available; SDD, selective digestive tract decontamination.
[a] χ^2 test.
[b] Mann-Whitney U test.

Table 4
Perioperative data and outcome for rectal resections vs left-sided colonic resections.

Variable		Rectal resections (n = 128)	Left-sided colonic resections (n = 128)	All cases (N = 256)	*P* values
Age (y), mean ± SD		64.4 ± 10.8	65.6 ± 11.0	65.0 ± 10.9	.894[a]
Sex	Female	51 (39.8%)	56 (43.8%)	107 (41.8%)	.526[b]
	male	77 (60.2%)	72 (56.2%)	149 (58.2%)	
ASA score	1	15 (11.7%)	14 (10.9%)	29 (11.3%)	.479[b]
	2	66 (51.6%)	57 (44.5%)	123 (48.1%)	
	3	47 (36.7%)	56 (43.8%)	103 (40.2%)	
	4	0 (0%)	1 (0.8%)	1 (0.4%)	
	5	0 (0%)	0 (0%)	0 (0%)	
Charlson Comorbidity Index		4.74 ± 1.70	4.96 ± 2.00	4.80 ± 1.90	.296[a]
Diverting ostomy		91 (71.1%)	8 (6.3%)	99 (38.7%)	< .001[b]
UICC stage	0	2 (1.6%)	5 (3.9%)	7 (2.7%)	.572[b]
	I	47 (36.7%)	40 (31.3%)	87 (34.0%)	
	II	29 (22.7%)	25 (19.5%)	54 (21.1%)	
	III	33 (25.8%)	36 (28.1%)	69 (27.0%)	
	IV	17 (13.3%)	22 (17.2%)	39 (15.2%)	
All complications		36 (28.1%)	25 (19.5%)	61 (23.8%)	.099[b]
Overall infectious complications		11 (8.6%)	9 (7.0%)	20 (7.8%)	.641[b]
Surgical site infections	Superficial	7 (5.5%)	1 (0.8%)	8 (3.1%)	.776[b]
	Deep	0 (0%)	0 (0%)	0 (0%)	
	Organ space	0 (0%)	5 (3.9%)	5 (2.0%)	
Anastomotic leakage		7 (5.5%)	3 (2.3%)	10 (3.9%)	.197[b]
Postoperative inhospital stay (d), mean ± SD		11.6 ± 7.5	9.6 ± 6.7	10.6 ± 7.1	< .001[a,ba,c]
Mortality (30 d)		0 (0%)	3 (2.3%)	3 (1.2%)	.081[b]
Clavien-Dindo class	I	11 (8.6%)	6 (4.7%)	17 (6.6%)	.144[b]
	II	4 (3.1%)	3 (2.3%)	7 (2.7%)	
	IIIa	6 (4.7%)	4 (3.1%)	10 (3.9%)	
	IIIb	9 (7.0%)	8 (6.3%)	17 (6.6%)	
	IVa	4 (3.1%)	0 (0%)	4 (1.6%)	
	IVb	0 (0%)	0 (0%)	0 (0%)	
	V	0 (0%)	3 (2.3%)	3 (1.2%)	
Comprehensive Complication Index		6.8 ± 13.2	6.3 ± 17.6	6.5 ± 15.5	.172[a]
Reintervention		10 (7.8%)	4 (3.1%)	14 (5.5%)	.099[b]
Revision surgery		8 (6.3%)	12 (9.4%)	20 (7.8%)	.352[b]

ASA, American Society of Anesthesiologists; UICC, Union Internationale Contre le Cancer.
[a] Mann-Whitney *U* test.
[b] χ^2 test.
[c] Statistically significant difference.

based treatment or combined bowel preparation regimens [6,11,13,16–18,23,36]. The same clinical trials reported complication rates of 10% to 20% for SSI and 10% to 15% for AL in colorectal surgery without the use of pre- or perioperative oral antibiotics [11,14,17,18,23,26]. Therefore, our previous and current presented data are consistent with other registry-based data on rectal cancer surgery [6,11,14–16,23,26]. As we now report on left-sided colorectal cancer surgical procedures, the rates of AL are lower in left-sided colorectal cancer surgical procedures than in rectal cancer surgical procedures [6,11,16,23,26]. The overall positive effect of perioperative SDD-based treatment in colorectal surgery and in GI surgery has been demonstrated by several studies [11,16,18,23,26,36].

However, the question of whether a 3 PODs perioperative OABD treatment is sufficient to prevent all kinds of infectious complications cannot be answered, as the mere absence of a significant difference does not mean that the perioperative outcome is the same in both groups. Therefore, we performed a noninferiority analysis for the main outcome measures of AL, SSI, and infectious complications based on the relative difference and Wald method [34,35]. Apart from the data from Bogner et al. [36] reporting a favorable outcome in colorectal surgery using a similar 3 PODs SDD-based regimen compared with a historic control group, no data are available on this shortened OABD regimen or a comparison with a regular 7 PODs perioperative OABD regimen [16,26]. In our study, we can prove noninferiority of the 3-day perioperative OABD regimen over the 7 PODs perioperative OABD regimen concerning AL, SSIs, and overall infectious complications for the first time.

The actual available data on this topic are inconsistent in terms of the duration of perioperative OABD or combined bowel preparation only, the type of GI and colorectal surgical procedures, and the regimen of oral antibiotic drugs [11–13,16–19,22,23,26,36,37]. The use of a perioperative SDD-based regimen was highly effective in reducing SSI, AL, and other infectious complications compared with other concepts using combined bowel preparation with other antibiotic regimens [11–13,16,22,23,36,37]. Despite additional costs of the SDD medication, previous analyses have shown the cost-effectiveness of perioperative SDD-based treatment by reducing the duration of inhospital stay, days in the ICU, and the number of surgical or interventional procedures [16,36]. An increase in perioperative morbidity not only can be unpleasant for our patients and expensive for the healthcare system but also can have a negative effect on the oncologic outcome [4,38,39]. Therefore, strategies to prevent these complications are urgently needed, and the various concepts of combined bowel preparation are becoming increasingly established in colorectal surgery.

Conversely, the use of additional oral antibiotics should be approached with caution, particularly in an era marked by increasing instances of multidrug-resistant bacteria [40]. However, current data suggest that the regular use of topical antibiotics, such as the SDD regimen in ICUs, primarily reduces colonization by certain bacteria, such as enterococci, and is safe concerning the increasing microbial resistance to antibiotics [24,25]. In our experience with the use of OABD regimens, we did not detect any adverse reactions to the medication or an increase in the incidence of multidrug-resistant bacterial infections [6,16,26,41]. The growing knowledge of gut microbiome dysbiosis related to colorectal surgery and the use of antibiotics might be advantageous for an individualized approach to the prevention of infectious perioperative complications [7,8]. Therefore, more data on perioperative microbiome signatures are necessary to stratify patients according to intrinsic microbiome-

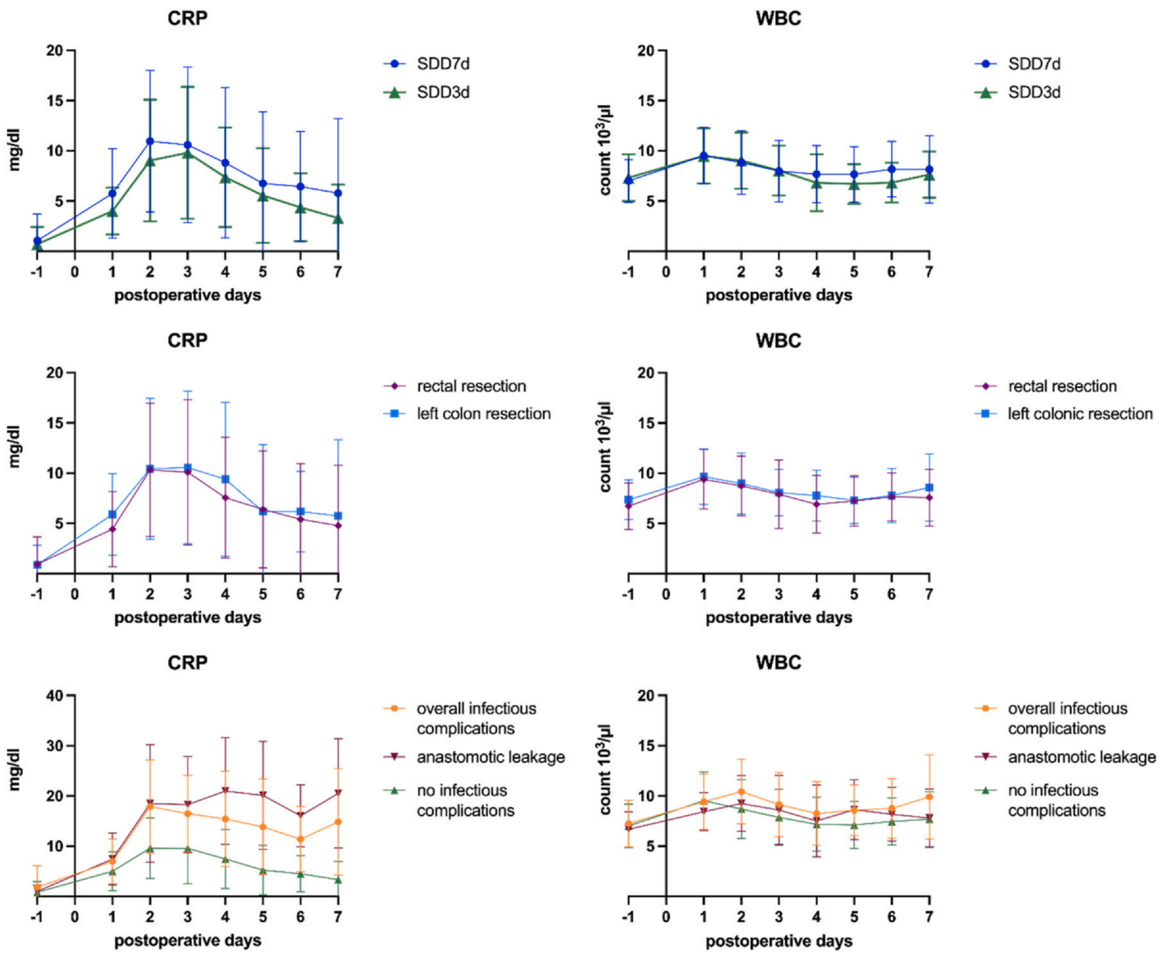

Figure 2. Comparison of laboratory values (WBC count and CRP levels) between 3-day SDD and 7-day SDD groups (A). for cases with left-sided colon resection vs rectal resections (B), and for cases with/without anastomotic leakage and with/without overall infectious complications (C). CRP, C-reactive protein; SDD, selective digestive tract decontamination; WBC, white blood cell.

based risk of surgical complications. This approach might enable the customization of antibiotic treatments to meet the specific needs of individual patients, but the effects of SDD-based treatment and surgical intervention on changes in the gut microbiome and its reconstitution remain to be clarified in further prospective studies.

This study has certain limitations, notably because of the retrospective characteristics of the included 7-day SDD group. This approach might have led to the underreporting of minor complications, such as superficial SSIs, which could occur after discharge without requiring a hospital return. Because of the retrospective nature of this study, no prospective 30-day follow-up data of the patients are available. However, for serious complications and significant morbidity, this retrospective bias is likely to be negligible, as these usually occur during hospitalization or lead to readmission for

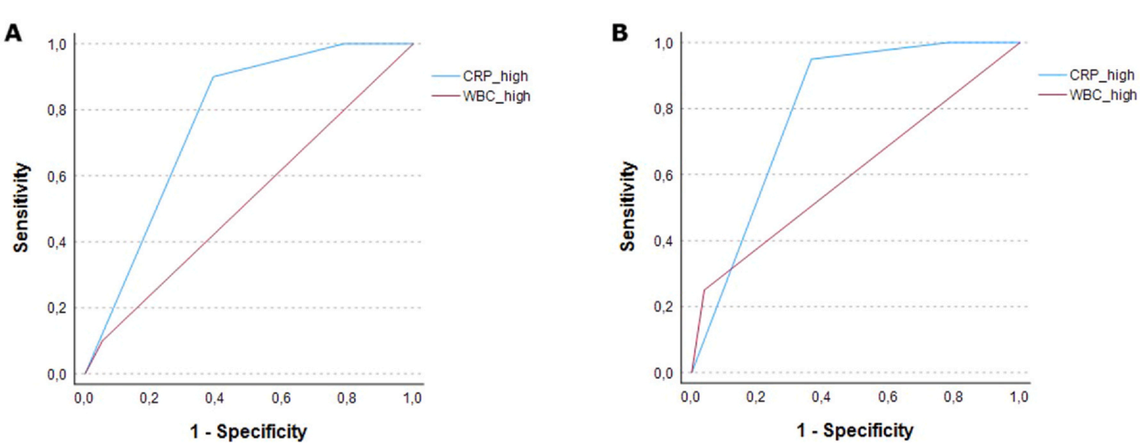

Figure 3. ROC curve analysis for renewed increase in CRP or WBC count after the fifth postoperative day for AL (A) and overall infectious complications (B). AL, anastomotic leakage; CRP, C-reactive protein; ROC, receiver operating characteristic; WBC, white blood cell.

treatment. Only left-sided resections for colorectal cancer were considered, as perioperative OABD treatment is not performed for other colorectal cancer surgical procedures in AH because of the much lower risk of AL and other infectious complications [5,11,13,23,36]. Overall, our results are consistent with those of other published data on colorectal cancer surgery [11–13,15,16,18,36]. The 7-day SDD group data span 2 decades, which may affect the accuracy of certain elements, such as the average hospital stay. The 3-day SDD group underwent surgery more recently, so other confounding factors might have affected the rates of AL, SSIs, and other perioperative complications. The groups had homogeneous comorbidities (ASA score and Charlson Comorbidity Index) and UICC stages. In contrast to most of the other available prospective data or data from RCTs, we also included patients with UICC stage IV in our analysis (15% in both groups) [5,11,13,16,23]. Overall, perioperative data are comparable between both OABD treatment groups, and prospective data comparing a shortened perioperative SDD treatment with a control are not available. Nevertheless, a potential bias because of intersite variation, which may affect the perioperative outcome parameters, could not be excluded. Despite these limitations, our study effectively reflects the realities of surgical practice and standard care in surgery for colorectal cancer.

Conclusion

According to the presented results, OABD is an effective and safe tool for the prevention of AL, SSI, and other infectious complications in left-sided colorectal surgery, even when used in a shortened 3 PODs perioperative regimen. In recent years, combined bowel preparation and OABD concepts have been increasingly used, as these have proven to be very effective in various RCTs and registry studies on the prevention of SSI, AL, and other infectious complications.

For the first time, we could prove noninferiority concerning AL, SSIs, and overall infectious complications for a 3 PODs perioperative OABD regimen compared with the established 7 PODs perioperative OABD regimen. More data from prospective and preferably randomized clinical trials are needed to provide even better evidence for a shortened 3 PODs perioperative OABD treatment in colorectal cancer surgery, as all these complications may affect the quality of life and oncologic outcome of our patients.

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Author contributions

U Wirth and J Schardey: project development, data management, data analysis, and manuscript writing; T von Ahnen: data collection, data analysis, and manuscript editing; A Crispin: data management, data analysis, and manuscript writing; A Kappenberger and P Zimmermann: data collection, data analysis, and manuscript editing; F Kühn: data collection and management, data analysis, and manuscript writing; JG D′Haese and J Werner: project development, data management, and manuscript editing; B Rau: project development, data collection and management, and manuscript writing. All authors commented on previous versions of the manuscript and read and approved the final manuscript.

Declaration of Competing Interest

The authors declare no competing interests.

Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.gassur.2024.07.031.

References

[1] Cavallaro P, Bordeianou L. Implementation of an ERAS pathway in colorectal surgery. Clin Colon Rectal Surg 2019;32(2):102–8.
[2] Wind J, Polle SW, Fung Kon Jin PH, Dejong CH, von Meyenfeldt MF, Ubbink DT, et al. Systematic review of enhanced recovery programmes in colonic surgery. Br J Surg 2006;93(7):800–9.
[3] Andolfi C, Umanskiy K. Appraisal and current considerations of robotics in colon and rectal surgery. J Laparoendosc Adv Surg Tech A 2019;29(2):152–8.
[4] Bonjer HJ, Deijen CL, Abis GA, Cuesta MA, van der Pas MHGM, de Lange-de Klerk ESM, et al. A randomized trial of laparoscopic versus open surgery for rectal cancer. N Engl J Med 2015;372(14):1324–32.
[5] Jannasch O, Klinge T, Otto R, Chiapponi C, Udelnow A, Lippert H, et al. Risk factors, short and long term outcome of anastomotic leaks in rectal cancer. Oncotarget 2015;6(34):36884–93.
[6] Wirth U, Rogers S, Haubensak K, Schopf S, von Ahnen T, Schardey HM. Local antibiotic decontamination to prevent anastomotic leakage short-term outcome in rectal cancer surgery. Int J Color Dis 2018;33(1):53–60.
[7] Alverdy JC, Hyoju SK, Weigerinck M, Gilbert JA. The gut microbiome and the mechanism of surgical infection. Br J Surg 2017;104(2):e14–23.
[8] Alverdy JC, Schardey HM. Anastomotic leak: toward an understanding of its root causes. J Gastrointest Surg 2021;25(11):2966–75.
[9] Shogan BD, An GC, Schardey HM, Matthews JB, Umanskiy K, Fleshman JW, et al. Proceedings of the first international summit on intestinal anastomotic leak, Chicago, Illinois, October 4-5, 2012. Surg Infect 2014;15(5):479–89.
[10] Schardey HM, Rogers S, Schopf SK, von Ahnen T, Wirth U. Are gut bacteria associated with the development of anastomotic leaks?: A review of experimental and clinical studies. Coloproctology 2017;39(2):94–100.
[11] Abis GSA, Stockmann HBAC, Bonjer HJ, van Veenendaal N, van Doorn-Schepens MLM, Budding AE, et al. Randomized clinical trial of selective decontamination of the digestive tract in elective colorectal cancer surgery (SELECT trial). Br J Surg 2019;106(4):355–63.
[12] Rollins KE, Javanmard-Emamghissi H, Acheson AG, Lobo DN. The role of oral antibiotic preparation in elective colorectal surgery: a meta-analysis. Ann Surg 2019;270(1):43–58.
[13] Koskenvuo L, Lehtonen T, Koskensalo S, Rasilainen S, Klintrup K, Ehrlich A, et al. Mechanical and oral antibiotic bowel preparation versus no bowel preparation for elective colectomy (MOBILE): a multicentre, randomised, parallel, single-blinded trial. Lancet 2019;394(10201):840–8.
[14] Cannon JA, Altom LK, Deierhoi RJ, Morris M, Richman JS, Vick CC, et al. Preoperative oral antibiotics reduce surgical site infection following elective colorectal resections. Dis Colon Rectum 2012;55(11):1160–6.
[15] Morris MS, Graham LA, Chu DI, Cannon JA, Hawn MT. Oral antibiotic bowel preparation significantly reduces surgical site infection rates and readmission rates in elective colorectal surgery. Ann Surg 2015;261(6):1034–40.
[16] Schardey HM, Wirth U, Strauss T, Kasparek MS, Schneider D, Jauch KW. Prevention of anastomotic leak in rectal cancer surgery with local antibiotic decontamination: a prospective, randomized, double-blind, placebo-controlled single center trial. Int J Colorectal Dis 2020;35(5):847–57.
[17] Koskenvuo L, Lunkka P, Varpe P, Hyöty M, Satokari R, Haapamäki C, et al. Morbidity after mechanical bowel preparation and oral antibiotics prior to rectal resection: the MOBILE2 randomized clinical trial. JAMA Surg 2024;159(6):606–14.
[18] Ambe PC, Zarras K, Stodolski M, Wirjawan I, Zirngibl H. Routine preoperative mechanical bowel preparation with additive oral antibiotics is associated with a reduced risk of anastomotic leakage in patients undergoing elective oncologic resection for colorectal cancer. World J Surg Oncol 2019;17(1):20.
[19] Ghuman A, Kasteel N, Brown CJ, Karimuddin AA, Raval MJ, Wexner SD, et al. Surgical site infection in elective colonic and rectal resections: effect of oral antibiotics and mechanical bowel preparation compared with mechanical bowel preparation only. Colorectal Dis 2020;22(11):1686–93.
[20] Hansen RB, Balachandran R, Valsamidis TN, Iversen LH. The role of preoperative mechanical bowel preparation and oral antibiotics in prevention of anastomotic leakage following restorative resection for primary rectal cancer - a systematic review and meta-analysis. Int J Colorectal Dis 2023;38(1):129.
[21] Lei P, Jia G, Yang X, Ruan Y, Wei B, Chen T. Region-specific protection effect of preoperative oral antibiotics combined with mechanical bowel preparation before laparoscopic colorectal resection: a prospective randomized controlled trial. Int J Surg 2023;109(10):3042–51.
[22] Willis MA, Toews I, Soltau SL, Kalff JC, Meerpohl JJ, Vilz TO. Preoperative combined mechanical and oral antibiotic bowel preparation for preventing complications in elective colorectal surgery. Cochrane Database Syst Rev 2023;2(2):CD014909.
[23] Roos D, Dijksman LM, Oudemans-van Straaten HM, de Wit LT, Gouma DJ, Gerhards MF. Randomized clinical trial of perioperative selective decontamination of the digestive tract versus placebo in elective gastrointestinal surgery. Br J Surg 2011;98(10):1365–72.
[24] van der Bij AK, Frentz D, Bonten MJM. ISIS-AR Study Group. Gram-positive cocci in Dutch ICUs with and without selective decontamination of the oropharyngeal

and digestive tract: a retrospective database analysis. J Antimicrob Chemother 2016;71(3):816–20.
[25] Cuthbertson BH. Selective decontamination of the digestive tract in critical care: a teenage angst or coming of age issue? Crit Care 2018;22(1):296.
[26] Schardey J, von Ahnen T, Schardey E, Kappenberger A, Zimmermann P, Kühn F, et al. Antibiotic bowel decontamination in gastrointestinal surgery-a single-center 20 years' experience. Front Surg 2022;9:874223.
[27] Ban KA, Minei JP, Laronga C, Harbrecht BG, Jensen EH, Fry DE, et al. American College of Surgeons and Surgical Infection Society: surgical site infection guidelines, 2016 update. J Am Coll Surg 2017;224(1):59–74.
[28] Leaper DJ, Edmiston CE. World Health Organization: global guidelines for the prevention of surgical site infection. J Hosp Infect 2017;95(2):135–6.
[29] Strobel R, Kreis M, Lauscher JC. Postoperative Wundinfektionen – Vermeidungs- und Behandlungsstrategien. Chirurg 2021;92(4):385–94.
[30] Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol 1994;47(11):1245–51.
[31] Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240(2):205–13.
[32] Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien PA. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. Ann Surg 2013;258(1):1–7.
[33] Rahbari NN, Weitz J, Hohenberger W, Heald RJ, Moran B, Ulrich A, et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. Surgery 2010;147(3):339–51.
[34] Sidi Y, Harel O. Incomplete data analysis of non-inferiority clinical trials: difference between binomial proportions case. Contemp Clin Trials Commun 2020;18:100567.
[35] Sui J, Jiao J, Sun Y, Liu J, Bastero R, Koch G. Evaluation of alternative confidence intervals to address n ON-INFERIORITY through the stratified difference between proportions. Pharm Stat 2021;20(1):146–62.
[36] Bogner A, Stracke M, Bork U, Wolk S, Pecqueux M, Kaden S, et al. Selective decontamination of the digestive tract in colorectal surgery reduces anastomotic leakage and costs: a propensity score analysis. Lange Arch Surg 2022;407(6):2441–52.
[37] Suzuki T, Sadahiro S, Tanaka A, Okada K, Saito G, Miyakita H, et al. Usefulness of preoperative mechanical bowel preparation in patients with colon cancer who undergo elective surgery: a prospective randomized trial using oral antibiotics. Dig Surg 2020;37(3):192–8.
[38] Mirnezami A, Mirnezami R, Chandrakumaran K, Sasapu K, Sagar P, Finan P. Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak: systematic review and meta-analysis. Ann Surg 2011;253(5):890–9.
[39] Eberhardt JM, Kiran RP, Lavery IC. The impact of anastomotic leak and intra-abdominal abscess on cancer-related outcomes after resection for colorectal cancer: a case control study. Dis Colon Rectum 2009;52(3):380–6.
[40] Markwart R, Willrich N, Haller S, Noll I, Koppe U, Werner G, et al. The rise in vancomycin-resistant Enterococcus faecium in Germany: data from the German Antimicrobial Resistance Surveillance (ARS). Antimicrob Resist Infect Control 2019;8:147.
[41] Wirth U, Schardey J, von Ahnen T, Zimmermann P, Kühn F, Werner J, et al. Oral antibiotic bowel decontamination in open and laparoscopic sigmoid resections for diverticular disease. Int J Colorectal Dis 2021;36(8):1667–76.