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ORIGINAL ARTICLE

Prevention of anastomotic leak in rectal cancer surgery with local antibiotic decontamination: a prospective, randomized, double-blind, placebo-controlled single center trial

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Abstract

Purpose Anastomotic leak and other infectious complications are septic complications of rectal cancer surgery caused by bacteria. Data from registry analysis show a beneficial effect of local antimicrobial administration on anastomotic leaks, but data are inconsistent in recent clinical trials. Therefore, our aim was to study the efficacy of topical antibiotic treatment on the incidence of anastomotic leaks in rectal cancer surgery.

Methods A prospective, randomized, double-blind and placebo-controlled, single center trial was conducted. Patients received either placebo and amphotericin B or decontamination with polymyxin B, tobramycin, vancomycin, and amphotericin B four times per day starting the day before surgery until postoperative day 7. If a protective ileostomy was created, a catheter was placed transanally and the medication was administered locally to the anastomotic site. All patients received an intravenous perioperative antibiotic prophylaxis.

Results The trial had to be stopped for ethical reasons after first interim analysis with 80 patients instead of the initially planned 280 patients. Of the 40 patients randomized to receive placebo, eight (20%) developed anastomotic leak compared to only 2 (5%) in the treatment group of 40 patients (decontamination) with significant difference in the χ^2 test ($p = 0.0425$). Twenty percent of the placebo group and 12.5% in the treatment group developed infectious complications not associated with anastomotic leak ($p = 0.5312$). One patient (2.5%) in the placebo group died ($p = 0.3141$).

Conclusion Local decontamination with polymyxin, tobramycin, vancomycin, and amphotericin B is safe and effective in the prevention of anastomotic leak in rectal cancer surgery.

Keywords SDD · Oral antibiotic bowel decontamination · Local antibiotic therapy · Anastomotic leak · Rectal cancer surgery · Bowel preparation

Introduction

Colorectal anastomotic leak (AL) following low anterior resection is a frequent and serious complication after surgery of rectal cancer [1, 2]. Despite great advances in medicine in general, AL rates have not changed relevant during the last 30 years [1] with reported incidences of about 10 and ranging up to 30% [1–5]. Mortality rates of 0.5–30% are described [4–7], and it has an adverse influence on the results of cancer surgery regarding tumor recurrence and overall survival [1, 5, 8–11].

Although the pathophysiology of AL is still not completely understood, there is actually quite a bit of experimental and clinical evidence from the past 60 years, demonstrating the

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role of bacteria in the pathogenesis of AL as well as the prevention of AL with the use of topical antibiotics [12–16]. For the first time in humans, we were able to prove the safety and efficacy of local antibiotic decontamination using non-resorbable topical antimicrobial substances to prevent esophago-intestinal AL following total gastrectomy for gastric cancer in a prospective, double-blind, placebo-controlled, multi-center clinical trial [17]. Meanwhile, a systematic review has supported the concept of preventing anastomotic leakage in gastrointestinal surgery by the use of topic antibiotics [18].

Our randomized trial was conducted between 1999 and 2004, but data were not presented at that time due to high rate of AL in control group and low interest in this topic. The interest has change over the past decade; furthermore, two randomized controlled trials (RCTs) and a meta-analysis were published in 2019 emphasizing the importance of oral antibiotics in colorectal surgery [6, 19, 20].

It was the aim of this study to explore whether the same medication that effectively prevented AL following total gastrectomy also can prevent AL in colorectal anastomoses.

Therefore, we conducted a prospective randomized double-blind placebo-controlled single center trial in patients undergoing rectal cancer surgery using tobramycin, polymyxin B, and vancomycin in the treatment group and tested it against placebo (lactulose).

Patients and methods

Patient selection

All patients undergoing anterior and low anterior rectal resections at the Department of Surgery of the Ludwig-Maximilians-University, Munich, Germany for UICC I-IV rectal adenocarcinoma were screened for eligibility for the study. Rectal cancer was defined as tumor localization between 0 and 16 cm from anal verge measured with rigid rectoscopy. Patients younger than 18 years of age, mentally immature patients, patients for planned or conversion to abdomino-perineal rectal excision, patients participating in another study, patients with previous rectal surgery or cancer, pregnant patient, or patients with known allergies to the study medication were not eligible for the trial.

Patients eligible for this trial were enrolled by their surgeon and randomly assigned to either receive decontamination (treatment) or placebo. Patients automatically dropped out of the study, if no anastomosis was created (technical drop out). Patients with secondary withdrawal of consent or major protocol violation were excluded from analysis. All randomized patients stayed in the study for intention to treat analysis.

An independent coordinating center (Institute for Medical Information Processing, Biometry, and Epidemiology, Ludwig-Maximilians-University, Munich, Germany) was responsible for creating the treatment allocation code for the study, auditing the data for consistency and accuracy, and conducting the interim analysis after 80 of the initially planned 280 patients were included into the trial. The coordinating center installed a Safety and Efficacy Monitoring Committee to monitor the trail. The protocol was approved by the Institutional Review Board of the Ludwig-Maximilians-University, Munich, Germany, and informed consent was obtained from all participants according to the principles of the institution.

Treatment

The study medication (treatment or placebo) was prepared by the pharmacy at university hospital of the Ludwig-Maximilians-University, Munich, Germany containing 31 dosages for each individual patient. The medication could not be distinguished between placebo and treatment in shape, color, or taste due to its preparation in capsules. It was assigned according to the treatment allocation code. Patients enrolled in the trial were randomized to receive preoperative, intraoperative, and postoperative placebo (lactulose 305 mg) or a combination of polymyxin B (100 mg), tobramycin (80 mg), and vancomycin (125 mg) (treatment). Amphotericin B (500 mg) was given in both groups to control for potential superinfections with fungi in the presence of antibiotic prophylaxis. Lactulose was chosen as a placebo as a substance proven to be harmless and qualified for oral and topical use. Lactulose was used in a subclinical dosage at which no relevant influence on gut microbiota and homeostasis was to be expected [21–23]. The same placebo drug had already been used in our previous clinical trial [17].

This specific combination of antibiotics expanding the SDD ("selective digestive tract decontamination") regimen by vancomycin was chosen to have a double coverage of gram-positive and negative-germs. Especially bacterial overgrowth with gram-positive cocci species following an elimination of gram-negative commensal and potential pathogenic species was thought be a problem. We therefore intended a double coverage of gram-positive cocci like staphylococci and enterococci species when adding vancomycin to the already potent regimen of SDD. Amphotericin B was used in both, intervention and placebo groups, as no adequate placebo medication was available and no relevant beneficial or adverse effect on anastomotic healing had to be expected based on our experience from our previously performed trial in gastric cancer surgery [17].

Placebo and study medication were dissolved in distilled water to a final volume of 20 ml at time of application. Amphotericin solution was present in liquid form (Amphomoronal®, Dermapharm AG, Munich, Germany). Study medication was administered four times per day at 6-hrs

interval. The day before surgery, mechanical bowel preparation was performed using 3–6 l of colonoscopy solution (KLEAN-PREP®, Norgine GmbH, Germany). Encapsulated either placebo or study medication were swallowed with the last liter of bowel cleansing solution given on the evening before surgery. It is of note that the doses of both, placebo and study medication were doubled at this single time point in order to achieve relevant intraluminal concentration and effects of the drugs despite the laxative effects of the bowel cleansing solution. Thereafter, only single doses were given every 6 hrs starting at 6 a.m. on the day of surgery until postoperative day 7. The first postoperative application was given as close as possible to the next 6-hrs mark after surgery. The route of drug administration depended on whether patients underwent creation of a protective ileostomy during surgery or not. While patients without ileostomy and all patients preoperatively received the drugs orally enclosed in capsules, patients with an ileostomy received the drugs dissolved in distilled water and administered directly to the anastomosis via a transanal placed Foley catheter. The catheter was placed at the end of surgery and secured with a stay suture. In total, each patient received 31 individual doses of either placebo or treatment medication.

Decisions regarding the use of additional antibiotics, intravenous fluids, cardiovascular and respiratory support, and surgical or other interventions were made by the attending surgeon during perioperative course and were not determined by the study protocol.

Rectal surgery was carried out in a standardized fashion with early infra-pancreatic transection of the inferior mesenteric vein and inferior mesenteric artery, mobilization of the splenic flecture, and total mesorectal excision as described by Heald and coworkers [24]. Anastomotic technique and pouch formation were at the decision of the operating surgeon.

Patients evaluation

Patients were observed until hospital discharge or death. Demographic, tumor related, and surgery-related data were recorded according to a standardized data sheet. In addition, from the day before surgery until postoperative day 7 leucocyte counts, c-reactive protein (CRP) and interleukin 6 (IL-6) were recorded for each patient. If AL was suspected, endoscopy, radiologic contrast enema, and thin layer-computed tomography (CT) were performed in order to verify or exclude the diagnosis. Routine hematologic, clinical chemistry, and bacteriological tests were not determined by the protocol.

Endoscopy with a rigid rectoscope was carried out at least twice in every patient of both groups: once prior to surgery in order to determine the distance of the tumor from the anal verge and once prior to discharge in order to diagnose or exclude AL as this was the primary end point for this clinical trial.

The costs for decontamination (200 €), other medication, surgery, additional endoscopy, and radiology-related costs, as well as costs for ICU or normal ward were calculated in € for each patient of both groups.

Primary endpoints were AL; secondary endpoints were all other septic complications and mortality. All data in this trial were collected prospectively.

Definitions and criteria

In the study, the terms AL was defined as a complete intestinal wall defect at the anastomotic suture line allowing the intra and extraluminal spaces to communicate being detected by means of endoscopy, radiologic contrast enema, thin layer CT, or surgery [25].

The severity of leaks was classified according to the classification suggested by our group 1995, which was later adopted by the International Study Group of Rectal Cancer Surgery [25]:

- Grade A: without change in patient management,
- Grade B: requiring antibiotic and endoscopic intervention but not needing re-laparotomy, and
- Grade C: requiring re-relaparotomy.

In order to improve the quality of our data, we clearly defined subjective findings that need to be met in order to diagnose other common postoperative septic complications such as pneumonia, urinary tract infection, and wound infections:

Pneumonia was assumed when four of the five criteria were fulfilled: (1) clinical auscultation positive for rales, (2) signs of lung infiltration on chest x-ray, (3) positive bacteriology, (4) body temperature above 38.5 °C, and (5) leukocytosis $> 10^4$ or $< 5 \times 10^3$. Urinary tract infection was defined as positive urine bacteriology and symptoms. Infection of central venous line was defined as positive bacteriology. Wound infections were defined according to the definitions for surgical site infections of Centers for Disease Control and Prevention [26]. Rectal cancer was graduated in cancer stages depending on pathohistologic report and preoperative clinical staging for distant metastases according to UICC classification [27].

Statistical analysis

The sample size was calculated to detect a 70% reduction in AL rates of the colorectal anastomosis as primary endpoint according to our previous performed trial using a similar antibiotic regimen in gastric cancer surgery [17]. For the sample size calculation, we assumed a leak rate of 12% in the placebo group, an alpha error of 0.05, and a beta error of 0.2. Based on these measures, a total of 280 patients was calculated to be required in order to show significant differences between

groups. Interim analysis was planned and conducted as specified in the study protocol by the coordinating center after randomization of 80 patients. Groups were compared by χ^2 test with Yates Correction, Fisher's exact test, Log-Rank-test, Student's t test or variance analysis (ANOVA). All tests for significance were two-tailed. A p value < 0.05 was considered significant.

Results

From December 1999 to February 2004, patients undergoing surgery for rectal cancer with primary anastomosis were screened ($n = 234$), and 80 patients had been enrolled in this clinical trial and randomized into treatment ($n = 40$) and control ($n = 40$) group (Fig. 1). According to the definitions in the study protocol, the first interim analysis had to be carried out after 80 of the 280 initially planned patients had been enrolled into the trial. As the interim analysis demonstrated a significantly lower rate of AL in the treatment compared to the placebo group, the study had to be terminated in accordance with the study protocol. Therefore, the analysis of efficacy of local decontamination reported here is based on 80 patients with colorectal anastomosis after low anterior resections (90%) and anterior rectal resections (10%) for rectal cancer included and randomized in this trial before interim analysis was performed. Clinical information was available on all of these patients until discharge from the hospital or death. Due to the limited number of patients available for analysis in this study, only primary and secondary endpoints as well as treatment costs were evaluated.

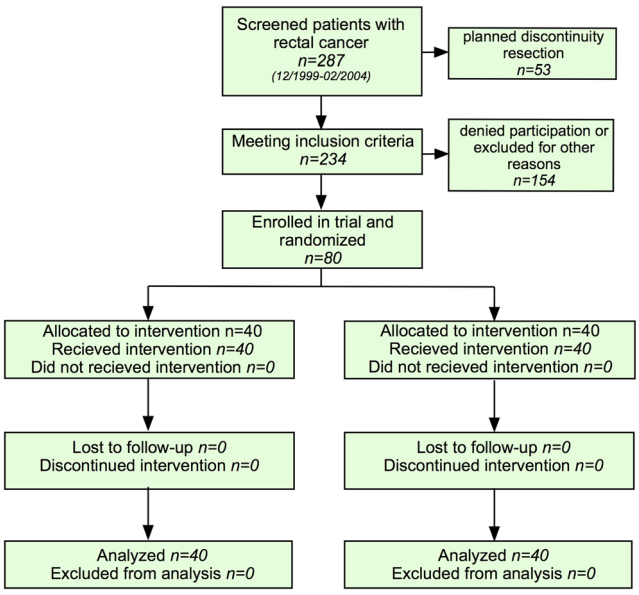

Fig. 1 CONSORT diagram for the clinical trial

Comparison between study groups

Among the patients with colorectal anastomoses, 40 received treatment and 40 received placebo. In both groups, there were no patients who discontinued medication during the postoperative course. There was no secondary withdrawal of consent. No allergies or intolerances concerning the study medication were observed. There were no randomized patients receiving abdomino-perineal rectal excision.

The treatment and placebo groups were well balanced with respect to demographic characteristics and associated underlying diseases (Table 1). There were some minor, statistically nonsignificant differences between the groups for the cancer stages according to the UICC classification (Table 2). The other clinical variables regarding surgical approaches, duration of surgery, number of required blood transfusions, tumor localization, neoadjuvant radio-chemotherapy, R1 residual tumor, pouch formation, suture techniques, and stoma formation (Table 3) were comparable between groups. In both groups, $n = 36$ patients underwent low anterior rectal resection with creation of a protective loop ileostomy (90%); anterior rectal resection without ileostomy was performed in $n = 4$ patients (10%) of each group only (Table 3).

Efficacy of oral decontamination

Decontamination significantly reduced the rate of AL by the factor four. While only two patients (5%) in the decontamination group developed an AL, eight (20%) patients with AL were identified in the placebo group. All patients with AL underwent low anterior rectal resections and had a protective loop ileostomy. None of the patients without protective loop ileostomy ($n = 4$ in control and $n = 4$ in treatment group) suffered from AL. For the occurrence of AL, χ^2 test revealed a statistically significant difference between groups ($p = 0.043$) (Table 4). When excluding patients without a protective loop ileostomy and only comparing patients undergoing low anterior rectal resections, who received an ileostomy ($n = 36$ in control and $n = 36$ in treatment group), the difference in leak rate is still significant in χ^2 test ($p = 0.041$). Statistical analysis revealed no relevant difference between patients with ($n = 8$) or without ileostomy ($n = 72$) regarding AL (χ^2; $p = 0.260$).

In the treatment group, one patient with grade C leak required emergency reoperation; there was an extensive ischemia so that a rectum amputation with an end colostomy was required. The other case was a grade B AL that could be treated successfully with endoscopic lavage and negative pressure wound therapy system (EndoSponge®, B. Braun, Melsungen, Deutschland).

Of the eight patients with AL in the control (placebo) group, there was one patient with a grade C leak requiring emergency reoperation and creation of a Hartmann's situation with an end colostomy. All other cases were classified as

Table 1 Patient demographic data

Characteristics	Placebo $n = 40$	Decontamination $n = 40$	p value
Age (years) (median)	64.58 (65)	64.1 (65)	n.s.
Sex (n (%) male)	24 (60%)	28 (73%)	n.s.
ASA–score (± SD)	2.2 (± 0.5)	2.2 (± 0.4)	n.s.
BMI [kg/m^2] (± SD)	26.3 (± 3.7)	25.5 (± 3.9)	n.s.
Pre-OP albumin [g/dl] (± SD)	3.9 (± 0.9)	3.6 (± 1.6)	n.s.

SD, standard deviation; *n.s.*, not significant

grade B leaks that could be treated successfully with endoscopic lavage and negative pressure wound therapy (EndoSponge®, B. Braun, Melsungen, Deutschland).

Postoperative infection not related to leakage was encountered in eight (20%) patients in the placebo group and five (12.5%) receiving decontamination (Table 4). The difference was not statistically significant. All of these infections were minor complications not requiring surgery or intensive care treatment. However, when AL is also considered to be an infectious complication, the total number of infections was significantly higher in the placebo ($n = 15$; 38%) compared to the treatment group ($n = 7$; 18%; $p = 0.045$).

A side effect of the lower leak rate of colorectal anastomoses in the decontaminated group was a shorter in-hospital stay of 22 ± 12 days compared to 29 ± 17 days in the placebo group with the log-rank test revealing a significant difference between groups ($p = 0.0206$; Table 4).

The mean treatment costs of one patient in the placebo group were € 14.985 (range € 3.306–€ 110.915) in comparison to only € 9.308 (range € 3.506–€ 46.288) in the decontamination group. The prophylaxis with local decontamination (total costs: € 200 per patient) reduced the overall mean treatment costs by € 5.551 or 37%. The increase of costs in patients of the placebo group was generated by the prolonged in hospital stay caused by AL ($p = 0.026$). Further factors contributing to increased costs secondary to higher leak rates in the placebo group are an increase in the number of endoscopies performed per patient, number of days spent on ICU per patient, as well as days treated with antibiotics (Table 4.).

Table 2 Clinical data regarding rectal cancer

Characteristics	Placebo $N = 40$	Decontamination $N = 40$	p value
T1	9 (22%)	5 (13%)	n.s.
T2	13 (32%)	14 (35%)	n.s.
T3	15 (38%)	17 (43%)	n.s.
T4	3 (8%)	4 (10%)	n.s.
N0	27 (67%)	22 (55%)	n.s.
N1	7 (18%)	12 (30%)	n.s.
N2	6 (15%)	6 (15%)	n.s.
M0	32 (80%)	28 (70%)	n.s.
M1	8 (20%)	12 (30%)	n.s.
UICC1	18 (45%)	12 (30%)	n.s.
UICC2	9 (23%)	8 (20%)	n.s.
UICC3	5 (13%)	9 (23%)	n.s.
UICC4	8 (20%)	11 (28%)	n.s.
Grade 1	3 (8%)	3 (8%)	n.s.
Grade 2	23 (58%)	25 (63%)	n.s.
Grade 3	14 (35%)	12 (30%)	n.s.

UICC, Union International Contre le Cancer (International Union against Cancer); *n.s.*, not significant

Discussion

The results of this clinical trial show that local decontamination with polymyxin B, tobramycin, and vancomycin started preoperatively and continued until postoperative day 7 reduces the rate of AL significantly in patients undergoing (low) anterior resection and TME with colorectal anastomoses for rectal cancer. Due to the profound benefit of decontaminated patients, this trial had to be stopped for ethical reasons after the first interim analysis including only 80 patients. The results of this clinical trial are similar to the results of a previous RCT using the identical prophylactic medication with a similar protocol in patients with total gastrectomy for gastric cancer [17].

After this methodologic solid trial was performed between 1999 and 2004, the data have never been published because at this time, the surgical world opposed against the use of mechanical bowel preparation [28, 29] as well as its combination with oral antibiotic therapy as enhanced recovery regimens became popular [30, 31]. At that time, mechanical bowel preparation was abandoned from clinical practice due to various studies, which showed no or even negative impact of mechanical bowel preparation on perioperative outcome [28, 29]. Despite its significant result with a fourfold decrease of anastomotic leakage and a relevant decrease in surgical site infections, this trial was forgotten, until the concept of preoperative bowel preparation and use of perioperative local antibiotic prophylaxis experienced a renaissance in the past few years. Therefore, after a careful review and interpretation of our data with international experts, this manuscript was prepared for publication. This was the first clinical trial ever performed to show beneficial effects of topical antibiotic use on

Table 3 Perioperative data

Parameter	Placebo $n = 40$	Decontamination $n = 40$	p value
Duration of surgery min (± SD)	275 (± 91)	246 (± 85)	n.s.
Patients receiving transfusions [RBC units/patient] (± SD)	2 [2,12] (± 0.37)	1 [2](± 0.16)	n.s.
Tumor distance from anal verge in cm (± SD)	8.4 (± 3,5)	8.7 (± 3.9)	n.s.
Neoadjuvant radiochemotherapy (%)	16 (40%)	18 (45%)	n.s
R1 resection (%)	4 (10%)	2 (5%)	n.s.
Pouch (%)	2 (5%)	1 (3%)	n.s.
Stapled anastomosis (%)	34 (85%)	36 (90%)	n.s
Protective stoma (%)	36 (90%)	36 (90%)	n.s.

SD, standard deviation; *R1 resection*, microscopic evidence of residual tumor; *n.s.*, not significant; *RBC*, red blood cells

anastomotic healing in colorectal surgery. As this manuscript reports the results of a randomized, placebo-controlled, double-blind clinical trial, its impact on the topic of combined bowel preparation justifies its late publication to some extent.

The concept of local antibiotic prophylaxis in gastrointestinal surgery for the prevention of anastomotic leakage was first performed by Cohn about 60 years ago. His first animal experimental trial in dogs showed that locally applied topical antibiotics can prevent leaks even in the presence of ischemia [12]. Interestingly, Cohen was able to demonstrate that in contrast to local application, the systemic treatment with antibiotics did not have any protective effect on anastomotic healing in a rat model [14].

Current data being published from a group of surgeon scientists around J. Alverdy is unraveling the molecular mechanisms used by intestinal bacterial pathogens to breakdown anastomotic tissue and reverse what the body has synthesized during the healing process [1, 16, 32–35]. They reported that exposure of anastomotic tissues to pathogenic bacteria such as *Pseudomonas aeruginosa* resulted in selection of a more virulent phenotype by single nucleotide point (SNP) mutation characterized by high collagen-degrading activity, which was associated with AL [31]. They hypothesized that the capacity of intestinal bacteria like *Pseudomonas aeruginosa*, *Serratia marcescens*, and *Enterococcus faecalis* to degrade collagen may be an important mechanism underlying the

Table 4 Postoperative data and anastomotic leak rates

Parameter	Placebo $n = 40$	Decontamination $n = 40$	p value
Anastomotic leak (%)	8 (20%)	2 (5%)	0.0425*
Mortality (%)	1 (3%)	0 (0%)	n.s.
Pneumonia (%)	0 (0%)	2 (5%)	n.s.
Intra-abdominal abscess *n* (%)	0 (0%)	1 (3%)	n.s.
Sepsis central venous line *n* (%)	2 (5%)	1 (3%)	n.s.
Wound infection *n* (%)	3 (8%)	1 (3%)	n.s.
Urinary tract infection *n* (%)	2 (5%)	0 (0%)	n.s.
Infections complications other than AL (%)	7 (18%)	5 (13%)	n.s.
Infections complications including AL (%)	15 (38%)	7 (18%)	0.045*
Vulvitis *n* (%)	1 (3%)	0 (0%)	n.s.
Gastroenteritis *n* (%)	1 (3%)	0 (0%)	n.s.
Postoperative hospital stay days (± SD)	28.85 (± 17.22)	21.92 (± 11.72)	0.0206**
Mean ICU treatment in number of days /pat. (± SD)	1.55 (± 6.53)	0.625 (± 3.05)	n.s.
Endoscopies/pat. (± SD)	17.5 (± 24.8)	4.5 (± 6.2)	0.049
Nr. surgical reinterventions/pat. (± SD)	0.1 (± 0.304)	0.15 (± 0.425)	n.s.
Days of systemic antibiotic treatment/pat. (± SD)	0.65 (± 2.81)	0.2 (± 1.265)	n.s.

* Chi square test

** Log-rank test

*** *T* test (two-sided)

n.s., not significant; *AL* anastomotic leak

pathophysiology of AL [32–35]. Finally, they could demonstrate that among usual commensal microbiota, *Enterococcus faecalis* strains revealed enhanced collagen-degrading activity and the capacity to activate intestinal tissue matrix metalloproteinase 9 (MMP9) directly [34], but also by exploiting plasminogen [35]. Plasminogen is present in high concentrations also in healing colonic tissue; when activated to plasmin by bacterial enzymes, it causes hyperfibrinolysis and insofar contributes to the pathogenesis of AL [35]. These experimental data are shedding light on the molecular mechanisms' bacteria use when causing AL. Eliminating these commensal microbes from the surface of the intestinal mucosa with topical antibiotics eliminates these virulence factors and would be one way of preventing AL.

Over the past two decades, bowel preparation in colorectal surgery underwent alternating changes. It was abolished in the advent of the era of enhanced recovery regimens, as clinical trials showed no clear advantage of mechanical bowel preparation [28–31]. The concept of combined oral antibiotic and mechanical bowel preparation shows a great variety. Many combinations of different oral and systemic antibiotics as well as different regimens for mechanical bowel preparations were used, mostly before rectal surgery procedures. However, in 2010, the French GRECCAR III trial could demonstrate a clear advantage of mechanical bowel preparation versus no bowel preparation regarding the outcome overall and infectious morbidity, but not for anastomotic leakage, major morbidity, or mortality [36]. At the same time, Roos et al. were able to show the positive effect of the use of local decontamination (SDD) in gastrointestinal and hepatobiliary surgery as well as of combined bowel preparation in colorectal surgery [18, 37, 38]. In their RCT, they could show a decrease in overall postoperative complications, infectious complications, and anastomotic leakage [37]. Furthermore, in their meta-analysis of RCTs available at that time, they could demonstrate a decrease in rate of infectious complications as well as anastomotic leakage [18]. Between 2012 and 2016, this topic became "en vogue", and data from large registries from the USA were published; they all could demonstrate a strong effect of combined bowel preparation on the reduction of surgical site infections [39–42] and some even for the reduction of AL by about a factor of two [39, 41, 42]. These data are consistent with the data from RCTs using an SDD-like regimen with a twofold decrease in infectious complications and AL [18, 37]. These results seem to clarify the nearly 50 years of lasting debate, whether or not bowel preparation improves outcomes after colorectal resection. In all of these studies, the combination of mechanical bowel preparation and oral antibiotics leads to a significant reduction in morbidity thereby helping to prevent the most common and troublesome complications after colorectal surgery [39–42]. But in contrast to the previously published data, the 2019 published data from the "SELECT" and "MOBILE" RCTs showed contrary outcomes of combined bowel preparation [6, 19]. The SELECT trial using an SDD regimen was stopped after first interim analysis including 485 patients undergoing colorectal resections; the primary endpoint, a significant decrease in rates of AL, was going to be failed due to an all in all low rate of AL in the entire study population [6]. Nonetheless, it at least demonstrated a twofold decrease in infectious complications [6]. The MOBILE trial with 396 patients used only a single dose of neomycin and metronidazole preoperatively in combination with mechanical bowel preparation in the treatment group; it failed to show any relevant effect on surgical site infections or AL in comparison to controls [19]. Besides the fact that in both trials only a minor percentage of high-risk rectal resections were carried out, there are some major differences between the Dutch concept and the Finnish one. The first is using an SDD regimen, starting 2 days before surgery and continued until the 3rd postoperative day or even until the patient was discharged from ICU [6], and the latter is only using a single dose of neomycin and metronidazole preoperatively [19]. The most recent relevant publication on this topic is the meta-analysis by Rollins et al. analyzing 63,080 patients from 12 cohort studies and 6437 patients from 28 RCTs [20]. They could demonstrate a reduction in surgical site infections (RR 0.51; 0.46–0.51) and AL (0.62; 0.55–0.70) mostly based on the registry data. The RCTs alone could not show a relevant reduction of AL (RR 0.69; 0.43–1.11; $p = 0.13$) [20]. The number of patients included in RCTs is small compared to the large number of patients in the registry analyses, and all studies are inconsistent regarding the duration and regimen of topical antibiotics, mechanical bowl preparations, as well as the site of colonic or rectal resections [20].

In summary, the relevant RCTs in colorectal surgery at least show an advantage of the SDD regimen over controls regarding surgical site infections and inconsistently also for AL, therefore supporting the strategy of topical antibiotics in a reasoned combination [6, 20, 37–42]. This decrease in infectious complications including AL by about a factor of two is less than the factor of four we observed in our trials [6, 7, 17, 37]. Our concept for antibiotic decontamination using polymyxin B, tobramycin, amphotericin B, and vancomycin seems to be much more efficacious, and we cover a much larger spectrum of potentially pathogenic germs, most of them even twice. At least, the most relevant difference is the efficacy against *Enterococcus faecium* and other enterococci species (as long as they are not primarily resistant), since these bacteria are only insufficiently covered by a conventional SDD regimen. Recent experimental data suggests that they might play a significant role in development of AL [1, 13, 15–17, 32–35]. Furthermore, in contrast to the other available trials focusing a lot more on colonic than rectal resections, our clinical trial was including rectal resections only [6, 18, 19, 37,

39–42]. These have a higher risk for infectious complications as well as AL and therefore might benefit more from the use of topical antibiotics. We are aware that there are increasing numbers of vancomycin-resistant Enterococci species [43], but published data of routine use of topical antibiotics like SDD on intensive care units (ICU) show even a decrease in colonization with Enterococci species [44]. In more than 20 years the use of topical antibiotics in gastrectomy and colorectal surgery, no adverse events regarding multi-drug resistant germs including Enterococci species were observed [7]. Therefore, it might be possible that vancomycin, which is not absorbed by the human intestinal tract, might have made an important contribution in the prevention of AL in our trials by significantly improving the efficacy of topical antibiotic therapy. On the other hand, the widespread use of antibiotics is a major concern regarding the development of antimicrobial resistance. Presently, the beneficial effect of topical antibiotics in prevention of AL in our opinion outweighs the possible adverse side effects.

In this clinical trial as in our clinical trial on gastric cancer surgery published before [17], we used a regimen of combined bowel preparation in all patients and as described above started the topical antibiotics on the day before surgery and continued until the 7th postoperative day. In our RCT, 90% of the patients had a protective ileostomy created during surgery, and therefore the decontamination was delivered via a transanal catheter and only 10% of patients ($n = 8$) with intact intestinal continuity after anterior rectal resections received the study medication respectively placebo orally. The transanal catheter and the topical prophylaxis both were very well tolerated. In our study, no adverse events due to intake of study medication occurred.

For infectious complications including anastomotic leakage, there was a significant difference between the groups (38% vs. 18%, Table 4). With the exceptions of two cases of pneumonia, which responded well to the treatment with antibiotics, all other infections were minor. The average treatment cost per patient was 37% lower under decontamination in this trial despite the costs for the antibiotic medication. This was mainly due to a shorter in hospital stay and a lower number of diagnostic and interventional endoscopies in the treatment group. Based on our experience on local antibiotic decontamination on gastric and now rectal cancer surgery, a topic application appears to be safe and the effect as well as the dosage predictable, as high concentrations of the antibiotic mixture can be reached locally at the desired place of action, meaning at the anastomotic site. But the topic administration is limited to surgical sites in gastrointestinal tract, which are easily accessible like in gastric and rectal cancer surgery. But even other intestinal procedures like right colectomy or sigmoid resections, not only for cancer but also in diverticular disease, local antibiotic decontamination can be achieved safely by oral intake of non-absorbable antibiotics. In all cases of protective ileostomy or colostomy, topical decontamination can be achieved, e.g., via a transanal catheter due to the discontinuity of intestinal passage.

Regarding the placebo-medication, lactulose is an approved drug without serious side effects and has been safely used as a laxative for years [21–23]. Meanwhile, lactulose has been shown to be a prebiotic drug with beneficial effect on microbiota, but not in the herein applied subclinical dose. Lactulose in a daily dose of 2 g seems to have an effect on the levels of short-chain fatty acids in the intestinal content [21]; higher amounts of up to 5 g daily intake are needed "to exert the full beneficial prebiotic effect" [21] with impact on increasing the abundance of bacterial species like Bifidobacteria and Lactobacilli and decreasing the number of potential harmful bacterial species [21–23]. Therefore, no adverse effect on anastomotic healing or infectious complications needed to be expected using the widely accepted prebiotic lactulose. No adverse effect of prebiotics in general or lactulose in particular on anastomotic healing are described in literature. On the other hand, as the difference regarding anastomotic leakage rates was very clear with a fourfold decrease in treatment compared to control group receiving lactulose, no really beneficial effect on anastomotic healing can be stated for the use of lactulose as a prebiotic.

As a limitation of our study, in our control group, there is a high rate (20%) of AL, but available data show rates of up to 28% in single studies [3] and comparable rates of 15–20% in more recent clinical trials [36, 37]. Average rates of AL in rectal cancer surgery seem to lay at around 11% in literature as well as in a large German cohort study [1, 2, 5]. The level of anastomosis is depending on the tumor localization in rectal cancer surgery and is considered to be a risk factor for anastomotic leakage in different clinical trials and reviews available [5, 45, 46]. It has been reported before that the rate of AL was 15.0% vs. 8.9% depending on tumor height > 12 cm from anal verge and < 6 cm, respectively in a large German series of rectal cancer surgery on 17,867 patients [5]. In the work of Hamabe et al., the rate for AL was even 3.4 times higher in tumor localization < 7 cm from anal verge [46]. Also, in our data, the rate of AL was higher in low anterior rectal resections compared to anterior rectal resections. As AL was the primary endpoint in our clinical trial, all anastomoses have been controlled by endoscopy before patients' discharge, which could explain the higher rate of AL in our control group to some extent. All available registry analysis based on retrospective data and the other RCTs did not check the integrity of anastomoses at the time of discharge on a regular basis [5–7, 19, 36, 39–42, 47]. As in most published data, only clinically evident AL are reported and loop-ileostomy can decrease the rate of symptomatic AL; in clinical trials without protective loop-ileostomy, the rates of AL range up to 28% [3, 45]. Therefore, our rate for AL of 20% in control group with routine endoscopic control of every anastomosis after rectal cancer surgery are certainly comparable to other clinical trials in

colorectal surgery. In contrast to that, AL rates of around 10% were reported in other recently published clinical trials like the SELECT trial investigating local antibiotic decontamination, however, in about 80% colo-colonic and not colorectal anastomoses had been created [6, 19, 37].

Further limitations of the present study are the small number of patients available for analysis as the study had to be stopped after the first interim analysis due to the profound positive effect of the treatment on our patients' outcome. The mortality rate of 3% in the placebo group is also within the normal range [1–3, 5, 6, 19, 20, 36, 47] attesting a professional complication management.

The results of our RCT indicate that decontamination with polymyxin B, tobramycin, and vancomycin, which is directed against the most common pathogens causing postoperative infections, effectively protects patients with a colorectal anastomosis against AL. This regimen of combined mechanical bowel preparation and postoperative application of topic antibiotics is even feasible in routine use in elective colorectal surgery [7]. In the future, however, we might learn not only to target virulence expression of potential pathogens, preventing them from mutating or changing their phenotype with anti-virulence drugs but even select patients under risk for development of infectious complications and AL based on their individual microbiome composition as well as the presence of drug-resistant pathogens [32, 35, 48].

Conclusion

In our present study, we were able to demonstrate that perioperative local treatment with a mixture of three antibiotics (polymyxin B, tobramycin, and vancomycin) is able to effectively reduce AL rates and treatment costs. Together with the growing evidence demonstrating the positive effect of local decontamination in gastrointestinal surgery, this study supports the use of these regimens for patients undergoing rectal cancer surgery.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review board (Ethikkommission der Medizinischen Fakultät, LMU München) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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