coloproctology 2017 · 39:94–100
DOI 10.1007/s00053-016-0136-x
Published online: 19 January 2017

H. M. Schardey · S. Rogers · S. K. Schopf · T. von Ahnen · U. Wirth

Allgemein, Viszeral- und Gefäßchirurgie, Krankenhaus Agatharied, Lehrkrankenhaus der Ludwig-Maximilians – Universität München, Agatharied, Germany

Are gut bacteria associated with the development of anastomotic leaks?

A review of experimental and clinical studies

Introduction

Substantial experimental and clinical evidence from the past 60 years demonstrates the role of bacteria in the pathogenesis of anastomotic leak (AL) and the prevention of AL with topical antibiotics, even in the presence of ischemia [26]. The fact that this knowledge has not found its way into clinical practice might have to do with the fact that most surgeons are convinced that AL is caused by poor surgical technique either leaving gaps, traumatizing intestinal tissue, causing poor blood supply or tension on the suture line [27]. Even though, the evidence for these mechanical factors is neither really that convincing nor particularly conclusive [24], the idea that AL always has a mechanical cause triggered many investigations searching for the perfect anastomotic technique [27, 30]. Two arguments support the mechanical hypothesis, namely that experienced surgeons have a lower rate of AL since they are technically better and that those anastomoses which leak within the first 48 hours after surgery unsually do so for technical reasons [27]. On the other hand, even a perfectly fashioned anastomosis in a young and otherwise healthy patient treated in a high-volume department by the most experienced surgeon can leak [27], and unfortunately, far too many perfectly fashioned anastomoses do leak. So there must be something essential going wrong during the complex process of anastomotic wound healing. What could it be? In this review, we examine the experimental and clinical evidence concerning the role of intestinal bacteria in the pathogenesis of AL, present molecular mechanisms explaining how they can interfere with anastomotic healing, and point out present as well as innovative future ways to deal with this problem.

The German version of this article can be found under doi:10.1007/s00053-017-0145-4

Historical studies

Experimental data suggesting bacteria play a major role in development of anastomotic leak

Although Poth pioneered intestinal asepsis [15], it was Cohn and Rives in 1955 [5] who first carried out an animal experimental trial in dogs studying the combined challenge of ischemia and bowel anastomosis in colonic wound healing. They showed that locally applied tetracycline can prevent AL, even in the presence of gross ischemia caused by tying all blood vessels within 5 cm of the anastomoses. Those animals that received enteral antibiotics directly to the anastomotic site via an indwelling catheter demonstrated complete anastomotic healing, whereas those administered saline developed major leakage, peritonitis, and death. They thus concluded that superior results can be achieved in colon surgery, even in the presence of ischemia, by adding antibiotics to the lumen of the bowel.

Le Veen considered AL to result from an adverse influence exerted by the colonic bacteria [11]. He demonstrated that addition of erythromycin and kanamycin to the preoperative bowel preparation significantly ($p < 0.001$) improved the mean tensile strength of colonic anastomosis. Continuing this medication for one week postoperatively almost doubled the mean tensile strength and changed the mode of healing from that of secondary to healing by first intention. The wide antimicrobial spectrum of topical antibacterial activity and continuous application throughout the postoperative period seem to improve healing.

» Antibiotics applied to the bowel lumen achieve superior results in colon surgery, even with ischemia

Cohen [4] evaluated the relative effects of ischemia with and without topical antibiotic bowel preparation versus systemic parenteral antibiotics on colonic wound healing in a rat model. Anastomotic healing was severely impaired after tying all major vessels to the left colon in rats receiving parenteral or no antibiotics, with a 66 or 83% AL rate, respectively (**Table 1**). In the colons prepared with neomycin and erythromycin, which were continued into the postoperative period, no adverse effect of the in induced ischemia and no AL was found [4]. These results lend support to the results of Cohn [5] and Le Veen [11], and,

Table 1 Animal experimental trials testing the effect of ischemia, bacteria, and systemic and topical antibiotics on anastomotic healing

Author	Animal	Organ	Challenge (CH)	Systemic antibiotics (SA)	Topical antibiotics (TA)	Controls (C)	Results	*p*-value
Cohn, 1955 [5]	Dogs	Colon anastomoses	Gross ischemia all groups	Both groups	tetracycline *N* = 7 AL 14%	Saline *N* = 10 AL 100%	TA superior	–
Le Veen, 1976 [11]	Dogs	Colon anastomoses	No	No	Erythromycin, kanamycin *N* = 11 TS 70%	Water *N* = 11 TS 20%	TA superior	0.001
Cohen, 1985 [4]	Rats	Colon anastomoses	Gross ischemia all groups	Clindamycin, gentamycin *N* = 6 AL 50%	Neomycin, erythromycin *N* = 6 AL 0%	Water *N* = 6 AL 83%	TA superior SA no effect	0.01
Schardey, 1994 [20]	Rats	Esophagoduodenal anastomoses	*Pseudomonas* *N* = 20 AL 95%	No group	Polymyxin B, tobramycin, vancomycin, amphotericin *N* = 17 AL 6%	Water *N* = 20 AL 80%	TA superior *P. aeruginosa* caused more leaks and a lower bursting pressure	0.0001
Schardey, 1997 [21]	Rats	Esophagoduodenal anastomoses	Germfree rats *N* = 30 AL 30%	None	None	Water *N* = 30 AL 76%	Germfree superior	0.0002

AL anastomotic leak, *TS* tensile strength

in addition, clearly reveal that systemic antibiotics have no protective effect on anastomotic healing.

» Beside poor surgical technique and impaired blood supply, bacteria play a major role in AL pathogenesis

We carried out the first animal experiments examining the protective effect of topical antibiotic prophylaxis following upper gastrointestinal surgery and were the first to suggest that *P. aeruginosa* might play a causative role in AL [20]. In the latter trial, rats undergoing total gastrectomy were orally inoculated with *P. aeruginosa* on postoperative day 1, in order to contaminate the anastomoses. In addition to to a control group, a treatment group was given oral antibiotic treatment (polymyxin B, tobramycin, vancomycin) starting on preoperative day 7, which was continued for the remainder of the experiment. We demonstrated that the anastomosis bursting pressure was significantly lower in animals that were inoculated with *P. aeruginosa*. AL was observed to be most frequent and severe in the group exposed to *P. aeruginosa* and least in rats treated with oral nonabsorbable antibiotics. Antibiotics directed against Gram-positive and Gram-negative potential pathogens had a protective effect, since only 6% of rats receiving antibiotics demonstrated anastomotic disruption compared to 95% of rats whose anastomoses were seeded with *P. aeruginosa* ($p < 0.0001$). When the topical antibiotics were started after surgery, their protective effect was less effective (AL 26%; $p = 0.0012$). It therefore seems important to start topical antibiotics before surgery. Germfree rats also had highly significantly lower AL rates than normal controls using topical antibiotics ($p = 0.0002$) [21]. We concluded that in addition to poor surgical technique and impaired blood supply to the intestinal anastomosis, bacteria play a major role in the pathogenesis of AL [20].

Clinical data indicating that topical decontamination prevents of anastomotic leak

Based on results of animal experiments, the first clinical study to test the preventive effect of topical antibiotics (decontamination) on upper gastrointestinal AL was designed [22]. To evaluate the efficacy and safety of topical decontamination, the study was carried out as a prospective, randomized, double-blind, placebo-controlled, multicenter clinical trial in patients with total gastrectomy for gastric cancer in six academic surgical centers in Germany. Patients received either placebo or decontamination with polymyxin B (100 mg), tobramycin (80 mg), vancomycin (125 mg), and amphotericin B (500 mg) four times per day orally, from the day before the operation until the seventh postoperative day. All patients received a perioperative intravenous prophylaxis with cefotaxime (2 × 2 g).

An "intention-to-treat analysis" of the data was carried out. Among the 103 recipients of placebo, there were 11 cases (10.6%) with anastomotic leak of the esophagojejunostomy, whereas there were only 3 (2.9%) cases of anastomotic leak of the esophagojejunostomy ($p = 0.0492$) among the 102 recipients of decontamination. Decontamination therefore reduced the AL rate by a factor of 3.6. The number of pulmonary infections was significantly reduced and mortality rate was cut in half. Patients' compliance was a problem in this trial, but the clinical leak rate of those patients who really took their medication was actually zero. Treatment costs for patients

with decontamination were 20% lower than for patients of the control group [23].

» Decontamination decreased AL by a factor of 3.6, reduced pulmonary infections, and halved mortality

The same study design was employed to test the preventive effect of topical antibiotics on lower colorectal AL following rectal surgery for rectal cancer [24]. The day before surgery, bowels were washed, and medication was started and continued at 6 h intervals until postoperative day 7. After low anterior resection and because of protective ileostomy in 90% of the patients, medication was applied via a transanally positioned Foley catheter. The other 10% continued to take the medication orally. The trial had to be stopped for ethical reasons after the first interim analysis of 80 patients. The results of this single-center trial show that local decontamination with polymyxin B 100 mg, tobramycin 80 mg, vancomycin 125 mg, and amphotericin B 500 mg combined with a perioperative systemic prophylaxis with cefotaxime reduced the rate of anastomotic leaks by a factor of 4, from 20% (control group) to 5% (decontamination group; χ^2; $p = 0.0425$), [24]. This is similar to the reduction by a factor of 3.6 in the gastrectomy trial. The mean treatment costs for one patient in the decontaminated group were reduced by 5551 Euro or 37.36% in comparison to those receiving placebo [25].

Selective decontamination of the digestive tract (SDD) is a concept originally developed in the Netherlands to prevent pulmonary infections of patients in the intensive care unit. In a different prospective randomized clinical trial, perioperative SDD [17] in elective gastrointestinal surgery of the upper and lower gastrointestinal tract combined with standard intravenous antibiotics were compared to placebo. Topical medication was given four times per day from 48 h before surgery until at least the third postoperative day.

Abstract · Zusammenfassung

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Are gut bacteria associated with the development of anastomotic leaks? A review of experimental and clinical studies

Abstract

It has been proven in experimental and clinical studies that combined perioperative systemic antibiotic prophylaxis and prolonged nonresorbable topical antibiotics directed against common intestinal Gram-negative and Gram-positive pathogens in a mechanically cleaned bowel are effective in preventing intestinal anastomotic leak (AL). For 60 years, evidence has been accumulating that AL is caused by microbial pathogenicity. Examples are *E. faecalis* and *P. aeruginosa*, which develop the ability to breakdown collagen and/or cleave host Matrix metalloproteinase 9 (MMP9). The surgical trauma seems to trigger such complex reactions as gentotypical and phenotypical changes in commensal microbiota, turning them into tissue-destroying, leak-inducing pathogens. Investigations of further molecular mechanisms and clinical studies are ongoing. The use of antibiotics disrupts the endogenous microbiome and causes antibiotic resistance. It is therefore important to find therapies that leave the microbiome intact and target microbial virulence expression. One such approach to avoid indiscriminate elimination of all potential pathogens with simultaneous damage to protective microbiota is represented by phosphate-loaded polyethylene glycopolymers.

Keywords

Anastomotic leak · Decontamination · Topical antibiotics · Phosphate · Collagenase

Sind Darmbakterien an der Entstehung der Anastomoseninsuffizienz beteiligt? Eine Übersicht über experimentelle und klinische Arbeiten

Zusammenfassung

Es ist experimentell und klinisch erwiesen, dass eine präoperativ begonnene und in die erste postoperative Phase der Wundheilung hinein fortgesetzte lokale antimikrobielle Prophylaxe mit nichtresorbierbaren Antibiotika zur Prävention der Anastomoseninsuffizienz (AI) bei einem gereinigten Darm wirksam ist. Diese Antibiotika sollten gegen intestinale gramnegative und grampositive Pathogene gerichtet sein und mit einer perioperativen systemischen Antibiotikaprophylaxe kombiniert werden. Die Fakten verdichten sich seit 60 Jahren dahingehend, dass der AI eine primär mikrobielle Pathogenese zugrunde liegt. Sie wird durch potenziell pathogene Mikroorganismen verursacht, wie beispielsweise *E. faecalis* und *P. aeruginosa*, die die Fähigkeit erworben haben, Kollagene und intestinale Matrix-Metalloproteinase 9 (MMP9) zu spalten. Das chirurgische Trauma, aber auch operativ verursachte Ischämien scheinen genotypische und phänotypische Veränderungen der kommensalen Darmbakterien zu induzieren, wodurch diese in gewebezerstörende und dadurch insuffizienzverursachende Krankheitserreger mutieren. Weiterführende Untersuchungen und klinische Studien werden aktuell durchgeführt. Antibiotika schädigen das schützende endogene Mikrobiom und fördern die Resistenzentwicklung. Deshalb muss es Ziel sein, Therapien zu finden, die das Mikrobiom nicht zerstören und bei der mikrobiellen Virulenzexpression ansetzen. Einen Ansatz in diese Richtung bieten möglicherweise nichtmikrobizide Arzneimittel, wie phosphatbeladene Polyethylenglykolpolymere, welche die mikrobielle Virulenzexpression potenziell pathogener Mikroorganismen bei gleichzeitigem Erhalt des schützenden Mikrobioms unterbinden können.

Schlüsselwörter

Anastomoseninsuffizienz · Dekontamination · Topische Antibiotika · Phosphat · Kollagenase

Table 2 Clinical trials examining the protective effect of perioperative systemic antibiotics plus pre- and prolonged postoperative topical antibiotics on anastomotic leak

Author	Trial	Surgery	Perioperative systemic antibiotics (both groups)	Topical agent (control group)	Topical medication (treatment group)	Duration of topical application (OP day = 0)	*p*-value
Schardey, 1997 [22]	RCT Multicenter	Total gastrectomy	Cefotaxime	Placebo *N* = 103 AL 10.6%	PTV + A *N* = 102 AL 2.9%	Days –1 until 7	0.049
Roos, 2009 [16]	Retrospective cohort	Colectomy	Cefotaxime	None *N* = 86 AL 26%	PT + A *N* = 76 AL 11%	Days –2 until 3 + X	0.014
Roos, 2011 [17]	RCT	Gastrointestinal surgery	Cefotaxime	None *N* = 146 AL 15.1%	PT + A *N* = 143 AL 6.3%	Days –2 until 3 + X	0.016
Schneider, 2016 [24]	RCT Stopped at first interim analysis	Low anterior rectal resection	Cefotaxime	Placebo *N* = 40 AL 20%	PTV + A *N* = 40 AL 5%	Days –1 until 7	0.042
Wirth, 2016 [31]	Retrospective cohort Crossover comparison with [7]	Anterior and low anterior rectal resection	Control not standardized Treatment group cefotaxime	None *N* = 17,867 AL 11.9%	PT + A *N* = 206 AL 5.3%	Days –1 until 7	0.00106
Roos, 2013 [18]	Meta-analysis of 8 RCTs	Upper and lower gastrointestinal surgery	Various	Placebo or nothing *N* = 582 AL 7.4%	Various nonresorbable antibiotic agents *N* = 595 AL 3.0%	Pre- and postoperative for various duration	0.002

RCT randomized controlled trial, *P* polymyxin B, *T* tobramycin, *V* vancomycin, *A* amphotericin B, *AL* anastomotic leak, *OP* operation, *X* X days means that some patients received the SDD medication for a longer period after surgery among those all patients receiving treatment in the ICU

SDD reduced the rate of postoperative infectious complications and AL (from 9.6 to 4.8%, respectively) following intestinal surgery significantly ($p = 0.0115$) compared to standard intravenous antibiotics alone. The authors conclude that perioperative SDD should be considered for patients undergoing gastrointestinal surgery [17]. The rate of anastomotic leak was reduced by a factor of 2, which is less than we observed in both of our trials. Whether this had to do with the combination of substances administered remains unclear. The medication tested in this trial is the same as the one used in our trial, except for vancomycin, which was not part of the antibiotic strategy in the SDD regimen.

In addition to the broad antibiotic spectrum of the decontaminating drugs, mechanical bowel preparation seems to play a role in preventing AL. Mechanical bowl preparation alone can significantly reduce the overall complication rate and infectious complications in rectal cancer surgery, but (without topical antibiotics) does not reduce the rate of AL, as has been shown in an excellent randomized clinical trial (RCT) [2]. Stool inactivates topical antibiotics, such that it makes sense to apply them after mechanical bowl preparation. After finishing our randomized trial, we stopped giving vancomycin as part of our decontamination concept in order to reduce the total amount of antibiotics, and, in line with the fast-track rehabilitation concepts of Kehlet [9], stopped performing mechanical bowl preparation. When looking at a series of 206 patients retrospectively, we found 1 % technical leaks which were repaired within the first 48 h and a 4.3% failure rate of topical medication to prevent leaks [31]. Even though this was better than the rate of 11.9% from a German quality assurance program not including stage IV patients [8], we went back to mechanical bowl preparation [2] and to vancomycin [24]. We wanted to use this potential for improving results.

A meta-analysis of randomized clinical trials (RCTs) was conducted again by the same Dutch researchers comparing the effect of perioperative SDD with systemic antibiotics (SDD group) against systemic antibiotic prophylaxis alone (control group) in gastrointestinal surgery. Eight RCTs with a total of 1668 patients (828 in the SDD group and 840 in the control group) were included in this meta-analysis. In addition to a significant reduction of systemic infections, the incidence of anastomotic leakage was significantly 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, 0.24–0.73; $p = 0.002$) [18].

» Perioperative SDD should be considered for patients undergoing gastrointestinal surgery

The evidence concerning the effectivity of topical antibiotics in the prevention of intestinal anastomotic leak, with much experimental data and 10 RCTs, is meanwhile rather plentiful (**Table 2**). Still missing are studies dealing with the question of whether SDD plus vancomycin is more effective than the classical SDD reg-

Table 3 Effect of different bowl preparations on anastomotic leak rate in elective colectomy

Author	Trial	*N*	No BP AL %	MBP AL %	OABP AL %	MBP + OABP AL %	*p*-value
Althumairi, 2016 [1]	Retrospective cohort	19,686	4.38	3.60	2.81	2.33	<0.001
Kiran, 2015 [10]	Retrospective cohort	8442	4.6	3.5	–	2.1	0.0001
Scarborough, 2015 [19]	Retrospective cohort	4999	5.7	–	–	2.8	0.001

No BP no bowl preparation, *MBP* mechanical bowl preparation, *OABP* oral antibiotic bowl preparation, *MBP + OABP* Mechanical bowl preparation plus oral bowl preparation, *AL* anastomotic leak

imen and which duration of prophylactic treatment delivers the best results.

Clinical data for prevention of anastomotic leak by mechanical and antibiotic bowl preparation before surgery

Mechanical bowel preparation in various combinations with oral and or systemic antibiotic prophylaxis is mostly used before colorectal procedures. Of course, colon or ileocolic anastomoses are low-risk anastomoses, and many trials in the past were not sufficiently powered to detect small improvements of 2 or 3% in such patient groups. On the other hand, many trials show the benefit of adding oral antibiotics to mechanical bowl preparation to prepare their patients for gastrointestinal surgery in order to prevent infections and anastomotic leak. Most surgeons in the recent past did not routinely follow this concept [6, 7].

» Mechanical bowl preparation plus oral antibiotics halve SSI, anastomotic leak, and ileus rates

Very recently, more data from different studies and meta-analyses have become available. These data now clarify the nearly 50-year debate surrounding the question of whether bowel preparation improves outcomes after colorectal resection. Mechanical bowel preparation in conjunction with oral antibiotics reduces surgical site infections (SSI), anastomotic leak, and ileus—the most common and troublesome complications after colorectal surgery—by nearly half [10]. There is high-quality evidence that antibiotics covering aerobic and anaerobic bacteria, delivered orally and intravenously prior to elective colorectal surgery, reduce the risk of surgical wound infection even as much as 75% [13]. We now know that the colon should be empty, so that the antibiotic preparations have contact to the bowl mucosa where they can deliver their action without being inactivated by the presence of stool [1, 3, 10, 19, 31]. Very recent retrospective studies reporting the results of register databases with very large numbers of patients show a significant reduction of anastomotic leak under this regimen in comparison to no or only mechanical bowel preparation alone [1, 10, 19]. The reported leak rates of 2.1–2.8% are quite acceptable (**Table 3**). These results again lend more weight to the concept of preventing AL with topical antibiotics.

Recent experimental data

Molecular mechanisms of bacteria causing anastomotic leak

Current data published by a group of surgeon scientists around J. Alverdy from the University of Chicago, USA, shed light on the molecular mechanisms used by some intestinal bacterial pathogens to break down anastomotic tissue and reverse what the body has synthesized during the healing process. They reported that exposure of anastomotic tissues to pathogenic bacteria, such as *P. aeruginosa*, resulted in selection of a more virulent phenotype caused by a single nucleotide point mutation (SNP). This phenotype is characterized by high collagen-degrading activity against collagen types I and IV, which is associated with anastomotic leak [14]. The surgical procedure of cutting and reuniting intestinal tissue is apparently the trigger for this complex reaction.

The latter authors hypothesized that the capacity of intestinal bacteria to degrade collagen may be an important mechanism underlying anastomotic leak [14]. To identify additional and perhaps more common bacteria with collagen-degrading activity that might colonize anastomotic tissue after surgery, they examined the microflora associated with anastomotic tissues in rats after anastomotic surgery [28]. Using 16S rRNA amplicon sequencing of samples collected on the day of surgery and the sixth day following surgery, they analyzed the changes in luminal versus tissue-associated microbiota at anastomotic sites created in the colon of rats. Results indicate that anastomotic injury induced significant changes in the anastomotic tissue-associated microbiota, with minimal differences in the luminal microbiota. The most striking differences were 500- and 200-fold increases in the relative abundance of *Enterococcus* and *Escherichia*/*Shigella*, respectively. Functional profiling predicted the predominance of bacterial virulence-associated pathways in post-anastomotic tissues, including production of hemolysin, cytolethal toxins, fimbriae, invasins, cytotoxic necrotizing factors, and coccolysin. Taken together, their results suggest that compositional and functional changes accompany anastomotic tissues and may potentially accelerate or complicate anastomotic healing [28].

» Collagen-degrading and MMP9-cleaving pathogens, e.g., *E. faecalis*, appear to be associated with AL

Finally these authors could demonstrate that among commensal microbiota, *Enterococcus faecalis* strains with enhanced collagen-degrading activity and the capacity to activate host intestinal tissue

matrix metalloproteinase 9 (MMP9) contribute to the pathogenesis of anastomotic leak [29]. Pathogens with the dual capacity to degrade collagen and cleave MMP9, such as *E. faecalis*, appear to be associated with anastomotic leak in a rat model [29]. Intestinal microbiota seem to contribute to the amplification of MMP9, hypoxia-inducible factor 1-alpha (HIF-1 alpha), and inflammation during anastomotic surgery [29]; an effect that is again amplified by devascularization [29]. Data demonstrate that MMP9 expression in tissues exposed to both anastomosis and devascularization can be attenuated when rats are exposed to a topical antibiotic solution (ciprofloxacin, metronidazole, and neomycin). This might be an explanation for what happens when intestinal microbes are eliminated by topical antibiotics from the surface of the intestinal mucosa. Either this or pharmacological suppression of intestinal MMP9 activation prevented AL in rats. A clinical trial investigating the role of microbes in anastomotic healing to the left colon and rectum has begun [29].

Perspective

Non-microbicidal anti-virulence drugs: a future way of dealing with potential pathogens

The use of non-microbicidal drugs to create microenvironmental conditions that suppress the virulence of pathogens is an attractive strategy to minimize the negative consequences of intestinal microbiome disruption caused by antibiotic use [14, 28, 29, 32, 33]. It has been shown previously that phosphate is depleted in the intestinal tract following surgical injury, that this depletion is a major "cue" that triggers bactericidal virulence, and that the maintenance of luminal phosphate abundance in the gut prevents virulence expression [12, 14, 32, 33]. Since inorganic phosphate is not a suitable agent for phosphate delivery to the site of host–pathogen interaction, because it is readily absorbed in the small intestine, other ways must be found [32]. A novel drug-delivery approach using polyphosphate-loaded polyethylene glycol hydrogel nanoparticles has now been reported. This allows for prolonged release of polyphosphates, which can be exploited as a target for virulence suppression of lethal pathogenic phenotypes in the gastrointestinal tract [32]. After all, phosphate bound to polyethylene glycol was able to reverse a *P. aeroginosa* destructive phenotype and prevent AL in the rat [14]. Maybe this or similar non-microbicidal drugs will prove to be clinically effective in the future to prevent AL.

Summary

Anastomotic leak is caused by microbial pathogenicity, although there are still some details to be clarified. Decontamination from day –1 before surgery until day +7 thereafter significantly reduces the rate AL of high-risk anastomoses to the rectum and esophagus. For colon resections, the one-time antibiotic bowl preparation seems sufficient. In colorectal surgery, mechanical bowel preparation should precede administration of topical nonresorbable antibiotics. The topical antibiotics tobramycin, polymyxin B, and amphotericin B with and without vancomycin have been examined in RCT's, the addition of vancomycin can improve the effectiveness against *Enterococci*. Perioperative systemic antibiotic prophylaxis is required for every intestinal procedure.

In the future, medication targeting bacterial virulence expression need to be further examined and drugs approved. These should then be tested for their efficacy in preventing anastomotic leak against decontamination, in order to be able to apply them in this context.

Corresponding address

H. M. Schardey
Allgemein, Viszeral- und Gefäßchirurgie, Krankenhaus Agatharied, Lehrkrankenhaus der Ludwig-Maximilians – Universität München
Norbert-Kerkel-Platz 1, 83734 Agatharied, Germany
Hans.Schardey@KHAgatharied.de

Compliance with ethical guidelines

Conflict of interest. H.M. Schardey, S. Rogers, S.K. Schopf, T. von Ahnen, and U. Wirth declare that they have no competing interests.

This article does not contain any studies with human participants or animals performed by any of the authors.

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