ANNALS OF SURGERY
Vol. 225, No. 2, 172–180

The Prevention of Anastomotic Leakage After Total Gastrectomy with Local Decontamination

A Prospective, Randomized, Double-Blind, Placebo-Controlled Multicenter Trial

Hans M. Schardey, M.D.,* Uwe Joosten, M.D.,† Ulrich Finke, M.D.,‡
Karl H. Staubach, M.D.,§ Rolf Schauer, M.D.,‖ Alexander Heiss, M.D.,‖
Albert Kooistra, M.D.,§ Horst G. Rau, M.D.,* Reinhard Nibler, M.D.,*
Susanne Lüdeling, M.D.,* Klaus Unertl, M.D.,¶ Gotthardt Ruckdeschel, M.D.,#
Helmut Exner, Ph.D.,** and Friedrich W. Schildberg, M.D.*

From the Department of Surgery, Klinikum Grosshadern, Ludwig-Maximilians-University, Munich, Germany; the Department of Surgery,† Marienhospital Ruhr University Bochum, Herne, Germany; the Department of Surgery,‡ St. Josef Hospital Ruhr University Bochum, Bochum, Germany; the Department of Surgery,§ Medical University of Lübeck, Lübeck, Germany; the Department of Surgery II,‖ Zentralklinikum Augsburg, Augsburg, Germany; the Institut of Anesthesiology,¶ University Tübingen, Tübingen, Germany; and the Institut of Hygiene and Microbiology# and the Department of Medical Informatics, Biometry und Epidemiology,** Ludwig-Maximilians-University, Munich, Germany*

Objective
A prospective, randomized, double-blind, placebo-controlled multicenter trial was undertaken in 205 patients treated with total gastrectomy for gastric malignancies to evaluate whether local antimicrobial measures reduce the incidence of esophagojejunal anastomotic leakage.

Summary Background Data
Anastomotic leakage of the esophagojejunostomy is always a septic complication of total gastrectomy for gastric malignancies, but it never has been attempted to prevent this complication with the administration of topical antimicrobial agents during the critical phase of anastomotic wound healing.

Methods
To evaluate the efficacy and safety of topical decontamination, the study was carried out as a prospective, randomized, double-blind and placebo-controlled clinical multicenter trial in patients with total gastrectomy for gastric cancer. 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. Other interventions, including the administration of antibiotics and fluids, were not affected by the study protocol.

Results

Of 260 patients who were randomized, total gastrectomy was not carried out in 55 patients. They dropped out of the study. Patients receiving an esophagojejunostomy were observed until day 42, when they were discharged from the clinic or died. An intention-to-treat analysis of the data was carried out. Among the 103 recipients of placebo, there were 11 (10.6%) with an anastomotic leakage of the esophagojejunostomy, and among the 102 recipients of decontamination, there were 3 (2.9%) with an anastomotic leakage of the esophagojejunostomy ($p = 0.0492$). Pulmonary infections were observed in 23 patients (22.3%) receiving placebo and in 9 patients (8.8%) who were decontaminated ($p = 0.02$). There were 11 deaths (10.6%) among the recipients of placebo and 5 deaths (4.9%) among the recipients of decontamination ($p = 0.1$).

Conclusions

Decontamination with polymyxin, tobramycin, vancomycin, and amphotericin B during anastomotic wound healing is safe and effective in the prevention of esophagojejunal anastomotic leakage after total gastrectomy.

Leakage at the esophageal–intestinal anastomosis is a frequent and most serious complication after total gastrectomy for gastric malignancies. The reported incidences in recent European prospective multicenter trials vary between 7.2% and 12.3%.[1,2] The rate of this complication seems to be influenced by the localization and extent of the tumor disease, the extent of the surgical resection, and the experience of the surgeon.[1,2] Despite surgical reinterventions, the use of potent antibiotics, and intensive supportive care, the mortality among patients with anastomotic insufficiency may be as high as 45%.[3]

Poor surgical technique either leaving gaps or impairing blood supply to the anastomosis, resulting in necrosis at the suture line, as well as foreign body reaction to suture material generally are accepted reasons for anastomotic leakage.[4–6] The consequences of anastomotic insufficiency, however, are septic in nature. Exogenous or endogenous potentially pathogenic micro-organisms colonizing the digestive tract therefore also may play a causative role in the pathogenesis in addition to microcirculatory or other disturbances.

By topical application of nonresorbable bactericidal antibiotics,[7,8] the colonizing microflora of the oropharynx and upper gastrointestinal tract can be manipulated easily. It has been shown in an experimental study that bacteria are one of the major pathogenic factors for anastomotic insufficiency after gastrectomy in the rat, by using deliberate colonization with pathogenic bacteria or topical decontamination with tobramycin, polymycin B, and vancomycin.[9] By reducing colonizing bacteria in the upper alimentary tract, anastomotic leakage of esophagointestinal anastomoses virtually could be eliminated.

With the exception of vancomycin, the topical nonabsorbable antibiotics tobramycin, polymyxin B, the antimycotic agent amphotericin B, and the intravenously administered cefotaxime used in the trial were the substances applied by Stoutenbeek et al.[7] for infection prevention to patients in intensive care units. At that time, the concept of decontamination represented a profound shift in traditional infection control policy based on the restricted use of narrow-spectrum antibiotics only if infection, not colonization, occurred.[10] Vancomycin was added to the topical antibiotic cocktail to prevent infection of the suture line with colonizing *Staphylococcus aureus* as well as to prevent mixed infection with anaerobes and aerobes with an ability to cause abscess formation, as described by Onderdonk et al.[11]

To determine the efficacy of decontamination with tobramycin, polymyxin B, vancomycin, and amphotericin B in reducing the leakage rate of esophagointestinal anastomoses, we conducted a prospective, multicenter, randomized, double-blind, placebo-controlled clinical trial in patients undergoing total gastrectomy for gastric malignancy.

METHODS

The efficacy and safety of decontamination with tobramycin, polymyxin B, vancomycin, and amphotericin B was assessed in a double-blind fashion and analyzed according to a prospectively developed plan that used definitions adopted before the treatment allocation code was broken. The analysis focused only on the patients with an esophagointestinal anastomosis after total gastrectomy for gastric malignancy.

An independent coordinating center (Department of

Supported by Hoechst A.G.; Bristol-Myers Squibb, Germany, and Dragenopharm, Traunreut, Germany.

Address reprint requests to Hans M. Schardey, M.D., Department of Surgery, Klinikum Grosshadern, Ludwig-Maximilians-University, Marchioninistr. 15, 81377 Munich, Germany.

Accepted for publication February 21, 1996.

Medical Informatics, Biometry und Epidemiology, Ludwig-Maximilians-University, Munich, Germany) was responsible for creating the treatment allocation code for each site, auditing the data for consistency and accuracy, and conducting the interim analysis. Before the trial was started, the study medication for 260 patients (treatment, n = 130; placebo, n = 130) was packaged into vials and labeled according to the treatment allocation code. (Antibiotics and corresponding placebo were prepared by Dragenopharm and amphotericin B as well as corresponding placebo by Bristol-Myers Squibb, München, Germany). After the medication was distributed to the study centers, the trial began. It ended after the study medication had been used up. The coordinating center appointed a Safety and Efficacy Monitoring Committee to oversee the trial, which was undertaken at six academic surgical centers in Germany. The protocol was approved by the Institutional Review Board of the Ludwig-Maximilians-University, Munich, and informed consent was obtained from all participants according to the principles of each institution.

Patient Selection

On the day before surgery, patients with a malignant tumor of the stomach who were to be treated with total gastrectomy and subsequent esophagointestinal anastomosis were enrolled in this clinical trial by their surgeon and assigned randomly to receive decontamination or placebo. The indication for total gastrectomy was seen for large lymphomas and sarcomas, as well as for all carcinomas of the stomach, with the exception of the small intestinal-type lesions in the distal one third.

Patients were not eligible for the trial if they were younger than 18 years of age, mentally immature, or if there were expected adverse reactions to the study medication, such as allergies.

Patients automatically dropped out of the study with discontinuation of study medication if total gastrectomy and esophagointestinal anastomosis were not carried out intraoperatively. Patients with secondary withdrawal of consent before the end of the 4th postoperative day or the 21st dosage of study medication remained in the study for the intention to treat analysis.

Treatment

Patients enrolled in the trial were assigned randomly to receive preoperative, intraoperative, and postoperative oral placebo or polymyxin B (100 mg), tobramycin (80 mg), vancomycin (125 mg), and amphotericin B (500 mg). The contents of each vial with antibiotics or placebo were diluted to a final volume of 20 mL. Amphotericin B and corresponding placebo were present in liquid form. Study medication was administered four times per day at 6-hour intervals. Each patient was to receive 31 individual dosages. The first dosage was applied at 6 P.M. on the day before surgery. In none of the patients was oral medication continued beyond the seventh postoperative day. All patients received two intravenous infusions of cefotaxime, the first one during the induction of anesthesia and the second one before closure of the abdomen.

Nasointestinal tubes were used in all patients perioperatively. Although the time for removal of the nasointestinal tubes was not dictated by the study protocol, it was standard practice in five of the six participating centers to choose the earliest possible time, preferably the first postoperative day. The remaining center routinely removed them on the fifth postoperative day.

Decisions regarding the use of antibiotics, intravenous fluids, cardiovascular and respiratory support, and surgical or other interventions were made by each patient's attending surgeon and were not dictated by the study protocol.

Patient Evaluations

Patients were observed for 42 days. Patients not having left the hospital by day 42 or having been readmitted before the 42nd postoperative day were observed until discharge or death. All patients were controlled by independent radiologists not involved in the study for anastomotic insufficiency of the esophagointestinal anastomosis. A Gastrografin swallow (Schering, Berlin, Germany) was carried out when esophagointestinal leakage was suspected or routinely on the seventh postoperative day. If postoperative complications rendered the patient unable to cooperate, a bedside test with Gastrografin or indigo carmine blue in the intensive care unit, endoscopic proof with radiologic Gastrografin documentation, or an intraoperative test with indigo carmine blue was carried out during emergency operation to detect or exclude esophagointestinal leakage.

Routine hematologic, clinical chemistry and bacteriologic tests were not dictated by the study protocol. Forty-two patients had daily bacteriologic examinations of oropharynx.

Definitions and Criteria

In the study, the terms "anastomotic insufficiency" or "anastomotic leakage" were defined as a complete intestinal wall defect at the anastomotic suture line detected with radiologic contrast medium study or positive color test. Pulmonary infections were assumed if four of the five following criteria were fulfilled: 1) clinical auscultation positive for rales, 2) signs of lung infiltration on chest x-ray, 3) positive bacteriology, 4) body tempera-

Table 1. DEMOGRAPHIC CHARACTERISTICS OF THE PATIENTS WITH ESOPHAGOINTESTINAL ANASTOMOSES

Characteristics	Study Group* Placebo (n = 103)	Decontamination (n = 102)
Age (yrs)	62.6 ± 11.9†	63.7 ± 11.4†
Sex (% male)	57.3	58.8
Karnofsky score on admission	82.9 ± 7†	83.7 ± 7.5†
Coronary heart disease	21	24
Cardiac insufficiency	20	20
Arrhythmia	9	8
Hypertension	25	30
Pulmonary disease	15	13
Renal insufficiency	0	2
Liver disease	1	2
CNS disease	5	3
Diabetes	8	7
Miscellaneous	9	16

CNS = central nervous system.
* Differences between study groups were not significant.
† Values are ± standard deviation.

Table 2. LOCALIZATION, STAGE, AND TYPE OF TUMOR DISEASE

Characteristics	Study Group* Placebo (N = 103)	Decontamination (n = 102)
Tumor localization (N)		
Cardia	32	25
Corpus	41	51
Antrum	25	22
Stump	5	4
Carcinoma stage (UICC 1987) (N)		
0	1	1
IA	11	17
IB	19	11
II	21	27
IIIA	22	21
IIIB	16	15
IV	9	8
Lymphoma	6	1
Sarcoma	1	0

UICC = Union International Contre le Cancer (International Union Against Cancer).
* Differences between study groups were not significant.

ture above 38.5 C, and 5) leukocytosis $> 10^4$ or $< 5 \times 10^3$.

Statistical Analysis

The sample was calculated to detect a 70% reduction in anastomotic insufficiency rate of the esophagointestinal anastomoses at the end of the study. For the calculation, we assumed a leakage rate of 10% for the placebo group, an alpha error of 0.05, and a beta error of 0.2 to 0.3. Two interim analyses were conducted by the coordinating center.

Groups were compared by Pearson's chi square test with Yates correction, Fisher's exact test, t test, or the Mann–Whitney *U* test. All tests for significance were two-tailed. A p value < 0.05 was considered significant.

RESULTS

Two hundred sixty patients were randomized during a 31-month period (August 1991–March 1994). In 55 cases (21.1%), total gastrectomy had not been carried out, so that these patients did not receive an esophagointestinal anastomosis and could not be evaluated. They dropped out of the study immediately, and study medication was discontinued. The analysis of efficacy of oral decontamination in this report is based on 205 patients with esophagointestinal anastomoses. Information was available on all of them through day 42, with discharge coming after the 42nd day or death.

Comparisons Between Study Groups

Among the patients with esophagointestinal anastomoses, 102 received decontamination and 103 received placebo. In each group, there were 12 patients who discontinued medication early during the postoperative course. One additional female patient in the treatment group took the medication only discontinuously, however, during the entire postoperative period. Such behavior had not been anticipated in the protocol, so that it was not possible to sort her out on the basis of secondary withdrawal of consent. The treatment and placebo groups were well balanced with respect to demographic characteristics and associated underlying diseases (Table 1). Although there were more lymphomas and one sarcoma in the control group, the differences were statistically not significant. There were minor, statistically nonsignificant differences between the groups for the tumor stages (International Union Against Cancer [UICC] 1987[12]) (Table 2), tumor localizations (Table 3), surgical approaches (Table 4), extension of the resections onto other organs, lymphadenectomies, duration of anesthesia, number of required blood transfusions, reconstructions, and suture tech-

Table 3. PERIOPERATIVE DATA

Parameter	Study Group* Placebo (N = 103)	Decontamination (N = 102)
Duration of anesthesia (min)	314.8 ± 107†	301.6 ± 87.7†
Blood transfusions (RBC; units)	1.8 ± 1.9†	1.8 ± 1.8†
Lymphadenectomy (N)		
N1	7	10
N2	85	83
N3	11	9
Additional organ resection (N)		
Distal esophagus	15	15
Spleen	56	50
Tail of pancreas	5	11
Colon segment	3	3
Small bowel segment	1	1
Kidney	1	1
Liver segment	5	0
Gallbladder	8	6
Common bile duct	1	0
Miscellaneous	7	3
Compeletness of resection (N)		
R0	90	90
R1	3	6
R2	10	5
Reconstruction (N)		
Roux-en-Y	101	101
Longmire	2	1
Suture technique (N)		
Circular stapler (3 types)	72	72
Manual suture (3 techniques)	31	30
Surgeons (N)	43	43
Noncompliance	12	12

RBC = red blood cell (count).
* Differences between study groups were not significant.
† Values are ± standard deviation.

niques. There was no pouch construction carried out in any patient. In patients of the placebo group, nasointestinal tubes were removed after a mean of 2.87 (standard deviation, 3.94) days and in recipients of decontamination of 2.58 (standard deviation, 2.86) days after surgery. There was no statistical difference between the groups. The procedures were carried out by 43 surgeons in both groups.

Efficacy of Oral Decontamination

Decontamination significantly reduced esophagointestinal insufficiency rate by 7.7%. In 102 patients receiving decontamination, esophagojejunal anastomotic insufficiency developed in 3 (2.9%), whereas among the 103 patients receiving placebo, 11 (10.6%) esophagojejunal anastomotic insufficiencies were detected. The two-tailed Fisher's exact test indicated that this difference was significant ($p = 0.0492$; power = 0.7631).

Of the 11 patients with esophagojejunal anastomotic insufficiency receiving placebo, peritonitis developed in 5 patients, who died with the signs of septic multiple organ failure. A total of 35 surgical reinterventions, 1 puncture drainage, and 6 treatments with fibrin sealant were carried out in an attempt to save this subgroup of patients. The mean postoperative survival of these participants was 32.6 days (range, 13–63 days). All received intensive care treatment and systemic broad-spectrum antibiotics. The other six patients were treated successfully with parenteral nutrition, local drainage, and antibiotic therapy, and one was treated in addition with puncture drainage. They were discharged after a mean postoperative hospitalization of 28.5 days (range, 15–42 days).

Of the three patients with esophagojejunal anastomotic insufficiencies receiving oral decontamination, one had a merely radiologically detectable blind-ending fistula without systemic signs of infection. This patient was discharged after a prolonged observation period without any specific therapy on the 21st postoperative day. The second patient had discontinued the study medication on the third postoperative day and an enterocutaneous fistula developed on postoperative day 8. He was discharged on the 41st postoperative day. The third patient had compliance problems in the sense that the study medication was taken during the entire observation period, however only discontinuously, so that on most days, fewer than four applications actually were received by the patient. An enterocutaneous fistula developed on day 7. The patient could be discharged on postoperative day 39. Both insufficiencies healed under drainage, parenteral nutrition, and antibiotic therapy, and the latter, in addition, was treated with fibrin sealant. There was no morbidity or mortality due to anastomotic insufficiency in any patient who actually ingested the decontamination orally from the day before surgery until at least the end of the fifth postoperative day.

Pulmonary infections were observed in 23 (22.3%) patients of the placebo group and in 9 (8.8%) patients of the decontaminated group. This difference was significant ($p = 0.0115$ by two-tailed Fisher's exact test). There was no influence of decontamination on the occurrence of urinary tract infections, duodenal stump leakage, intraabdominal abscesses, and pancreatic fistulas (Table 4). The total number of patients in whom complications developed was 46 (44.7%) among the recipients of placebo and 31 (30.4%) among the recipients of decontamination. The Yates-corrected chi square test indicated this difference to be significant ($p = 0.0494$).

The difference in mortality was not significant ($p = 0.1000$ by Fisher's exact test), although death occurred in 11 (10.6%) patients from the placebo group and only

Table 4. RESULTS (INTENTION-TO-TREAT ANALYSIS)

Parameter	Study Group: Placebo (N = 103)	Study Group: Decontamination (N = 102)	p Value
Complications		3 (2.9%)	
Esophagointestinal insufficiency	11 (10.6%)		0.0492
Pulmonary infection	23 (22.3%)	9 (8.8%)	0.0115
Urinary tract infection	8 (7.7%)	7 (6.8%)	1.0000
Duodenal insufficiency	1 (0.9%)	1 (0.9%)	1.0000
Abscess	4 (3.8%)	5 (4.9%)	1.0000
Pancreatic fistula	5 (4.8%)	5 (4.9%)	1.0000
Miscellaneous	9 (87.3%)	9 (88.2%)	1.0000
Total	46 (44.7%)	31 (30.4%)	0.0494
Mortality	11 (10.6%)	5 (4.9%)	0.1000
Condition		75 ± 19*	
Karnofsky score on day 42	68 ± 25*		0.0600
Therapeutic interventions		14 (13.7%)	
Intensive care therapy†	26 (25.2%)		0.0518
Antibiotic therapy	41 (39.8%)	26 (25.4%)	0.0289
Surgical reintervention	10 (9.7%)‡	5 (4.9%)§	0.2833

* Values are ± standard deviation.
† Patients with a postoperative intensive care unit stay of more than 4 days or emergency admission to the intensive care unit were included.
‡ 35 interventions.
§ 13 interventions.

5 (4.9%) from the decontaminated group. The condition of patients as evaluated by the Karnofsky index on the 42nd postoperative day, however, showed a trend in favor of patients receiving decontamination with 75 ± 19 points compared to patients receiving placebo 68 ± 25 points ($p = 0.0600$ by t test).

More patients in the placebo group required additional therapeutic interventions than in the decontaminated group. Antibiotic therapy showed the most pronounced difference (Table 4).

Decontamination caused a reduction, but not a complete elimination of potentially pathogenic bacteria and yeast from the oropharynx (Table 5). The selection or development of resistant strains was not increased under decontamination.

Safety

There were no serious adverse reactions in 130 patients given oral decontamination. One patient had postoperative facial flushing and mild hypotension. After detailed examinations, an allergic or toxic reaction to the study medication could be ruled out. The most common report was directed against the poor taste of the orally applied medication. This also was the reason for 12 patients in each group to withdraw consent before the conclusion of the 4th postoperative day.

Discontinuation of oral decontaminating antimicrobial drugs early in the postoperative course, during the initial phase of anastomotic wound healing, proved disadvantageous. Among the recipients of decontamination, the sub-

Table 5. BACTERIOLOGIC SAMPLES FROM THE OROPHARYNX OF 40 PATIENTS

	Study Group: Placebo	Study Group: Decontamination	p Value
No. of patients	20	20	
No. of samples	120	120	
Gram-negative	26	9	0.0030
Staphylococcus aureus	40	9	0.0001
Candida and yeast	64	50	0.07

group of 12 patients who withdrew consent and the 1 patient with compliance problems who only took the oral medication discontinuously had a disproportionately high complication rate. There were two anastomotic insufficiencies of the esophagojejunostomy, one duodenal stump leakage causing death on postoperative day 180, one pulmonary infection, and one death associated with postoperative hemorrhage in the presence of thrombopenia. Discontinuation of placebo by 12 patients in the control group did not lead to an increase in the rate of infectious complication. The complications involved one fatal anastomotic leakage, two nonfatal pulmonary infections, one fatal pulmonary infection, and one death of unknown cause on postoperative day 5 after discontinuation of placebo medication on day 4.

A cost–benefit analysis, which will be published elsewhere, showed a postoperative reduction in treatment cost of 20% for the decontaminated group compared to that of the control group. This effect was calculated despite the fact that more patients in the control group died and those who died did so earlier during the postoperative course, which actually reduced the hospital costs for this group.

DISCUSSION

The results of this clinical trial show that decontamination with polymyxin B, tobramycin, vancomycin, and amphotericin B four times per day from the day before the operation until the seventh postoperative day combined with a perioperative systemic prophylaxis with cefotaxime reduces the rate of anastomotic insufficiencies significantly in patients undergoing total gastrectomy for gastric malignancy. Because of the simultaneous significant reduction of pulmonary infections, the overall postoperative complication rate after total gastrectomy of the recipients of decontamination could be reduced significantly.

The results of this clinical trial are similar to the results of a previous animal experimental trial, proving bacteria to be a major pathogenic factor for anastomotic insufficiency in the rat.[9] The two studies provide convincing evidence that nonresorbable bactericidal antibiotics directed against potentially pathogenic bacteria, which may colonize the upper alimentary tract, confer substantial protection from anastomotic leakage.

A concurrent control group was essential in this trial to show that the surgical standard in carrying out total gastrectomy by the study centers involved is comparable to that of other international centers. The results obtained in our control group with respect to the rate of anastomotic insufficiency after total gastrectomy, overall complication rate, and mortality after total gastrectomy and N2 (UICC)[12] lymph node dissection are similar to the results obtained in recent European multicenter studies. In the Dutch trial, the leakage rate was 9%, the overall complication rate was 42%, and the mortality rate was 11.1%.[1] In the German trial, the leakage rate in R0[12] patients who were resected varied between 7.2% and 12.7% for total gastrectomies and extended total gastrectomies, respectively, the overall complication rate was 37.8%, and the 90-day mortality was 11%.[2,3] These figures compare well with those of the control group in our study of 10.6% anastomotic insufficiencies, 44.7% overall complication rate, and 10.6% mortality. Although better clinical results have been reported in the literature, they could not be confirmed by multicenter studies. We decided that the trial of most value would be one that determined whether adding decontamination to conventional therapy would improve the anastomotic insufficiency rate.

It might be viewed critically that for the fashioning of esophagojejunostomies, 3 types of circular staplers and 3 types of manual suture techniques were used by 43 surgeons, who had a varying degree of experience in gastric surgery. However, in addition to the fact that during the planing phase, participating surgeons would not agree to using only one technique, this type of standardization was not chosen for two reasons:

1. There are no data from clinical trials available that would prove one suture technique or stapler superior to other available methods.
2. The experience of the surgeon could be identified as a significant factor for the occurrence of anastomotic leakage.[3] We thought that the best results may be obtained by the individual surgeon if he or she uses the technique trained in.

The esophagojejunostomy is an ideal model to study the effect of decontamination on anastomotic wound healing, because the leakage rate is rather high, decontaminating drugs after being applied orally reach the anastomosis quickly and unaltered, and the radiologic control of the anastomosis with Gastrografin for insufficiency is standard clinical practice in Germany. This suggests a good quality of evaluation by independent radiologists.

Poor surgical technique either leaving gaps or causing an impaired blood supply to the anastomosis resulting in necrosis at the suture line is the generally accepted reason for anastomotic insufficiency. We propose that an additional factor also may be of major importance. The presence of bacteria, which produce endotoxins or exotoxins, may interfere with wound healing of the anastomosis in the sense that they cause macrophage-mediated downregulation of fibroblast proliferation as could be shown *in vitro*.[13,14] In addition, bacterial invasion and proliferation in necrotic tissue at the suture line may, in the mere absence of local defense mechanisms, cause direct infection with intramural abscess formation resulting in anasto-

motic leakage. Although microcirculatory disturbances are the probable cause of necrosis,[5] necrosis may promote local infection in the presence of bacteria. The severity of local infection associated with the release of bacterial toxins at the suture line may in turn determine the extent of necrosis and influence the occurrence of anastomotic leakage.

Decontamination has proved to be an effective measure for the prevention of infection by eradicating and preventing carriage of aerobic potentially pathogenic microorganisms from the oropharynx, stomach, and intestine in 22 independent, randomized, controlled trials.[15] Because bacterial pathogens of the upper alimentary tract have been implicated to be the causative organisms of postoperative infections after gastric surgery,[16–18] irrespective of whether they are acquired[7] or endogenous, it was our idea to use decontamination to ensure anastomotic wound healing in the mere absence of infectious thread.

In a clinical setting, it never has been proved, to our knowledge, that antibiotics can reduce significantly the incidence of anastomotic insufficiency. Trials conducted with intravenous antibiotic applications in colorectal surgery mostly examined the question of septic complications in general.[19] One reason for failure of intravenous antibiotics in the prevention of anastomotic leakage might be the inability to prevent bacterial invasion of necrosis. In a randomized, clinical trial carried out by Tetteroo et al.,[20] selective decontamination also has failed to prevent anastomotic dehiscence in patients with esophagointestinal anastomoses after esophagectomy.[20] The influence of decontamination on the development of surgical complications or anastomotic leakage had, however, not been the aim of their study. These were, however, equally distributed in both groups. The reason for failure to prevent anastomotic leakage may be because of the circumstance that in several patients, the antibiotics bypassed the anastomosis via a nasogastric tube or needle jejunostomy and that no topical medication was given to prevent colonization with gram-positive bacteria. The latter accounted for 85% of infections in the decontaminated group, which had an overall infection rate of 32%.

We want to emphasize that in our study, oral vancomycin was given to prevent colonization with gram-positive bacteria and that the antibiotics in all cases passed over the anastomotic suture line to prevent bacterial contact with the anastomoses.

Compliance was a problem due to the poor taste of the medication, which occurred because of the bitter-tasting polymyxin. Because of the present lack of alternatives to polymyxin B, patient information needs to be complete and guidance by their surgeons needs to be firm to ensure regular oral uptake of the medication throughout the seventh postoperative day. The observation made in our trial that discontinuation of medication was followed by a disproportionately high incidence of severe septic complications implicates the inherent danger of this type of prophylaxis, if it is not continued until the primary phase of wound healing has ended and granulation tissue has reestablished the gut barrier at the suture lines. The colonizing resistance of the endogenous flora may be impaired by the decontaminating drugs, leaving the gastrointestinal tract defenseless against the invasion of microbial pathogens, as has been suggested by van der Waaij.[21] If the increase of septic complications in this subgroup of patients occurred for microbiologic reasons, the observed complication rate would lend support to our hypothesis that bacteria interfere with intestinal wound healing. This conclusion, however, is speculative. The medication itself is safe.

There is a large body of clinical evidence indicating that bacteria impair healing of tissue after surgical intervention. Among the multitude of factors influencing wound dehiscence of skin wounds after major abdominal surgery, the type of incision or type of closure was not found to be of significance.[22] A most highly significant factor, however, was the influence of systemic or local infection in the study conducted by Riou et al.,[22] including 2761 patients. There also is experimental evidence implicating the role of infection in the pathogenesis of colonic anastomotic leaks. LeVeen et al.[23] looked at the relation between bacteria-incited inflammation and wound healing by studying the effects of prophylactic antibiotics on colonic anastomoses. The addition of erythromycin and kanamycin to the bowel preparation in dogs increased significantly the tensile strength of colonic anastomoses 7 days after operation. Histologic examination results of these suture lines showed healing by first intention in groups treated with antibiotics and healing by second intention in groups not receiving antibiotics. Cohen et al.[24] found ischemic colonic anastomoses in the rat to heal without disruption in the presence of intraluminal antibiotic preparations. Control subjects treated with intravenous antibiotics and those treated without antibiotics had a significantly higher rate of disruption. Cohn[25] has stressed the role of infection in anastomotic leaks. In his review article, he wrote that intraluminal antibiotics, by diminishing the role of infection, can protect some technically inadequate anastomoses from disruption.

The results of our clinical trial indicate that decontamination, which is directed against the most common bacterial pathogens causing postoperative infections, effectively protects patients with an esophagojejunostomy against anastomotic leakage if the medication is taken regularly by the patient.

Acknowledgments

The authors thank Professor K. Überla from the Department of Medical Informatics, Biometry und Epidemiology, Ludwig-Maximilians-Uni-

versity, Munich, for his consulting during the planning phase, the development of the study protocol, his advisory supervision in the recruitment period of patients, and during the analysis of the data. The authors also thank the following departmental chairpersons: Professor Hans P. Bruch, the Medical University of Lübeck, Lübeck; Professor Gerd Hohlbach, the Department of Surgery, Marienhospital Ruhr University Bochum, Herne; Professor Victor Zumtobel, the Department of Surgery, St.-Josef-Hospital Ruhr University Bochum, Bochum; Professor Jens Witte, the Department of Surgery II, Zentralklinikum Augsburg, Augsburg; and Professor B. Günther, the Department of Surgery, Städtisches Krankenhaus, München-Neuperlach, München.

References

1. Bonenkamp JJ, Songun I, Hermans J, et al. Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. Lancet 1995; 345:745–748.
2. Roder JD, Böttcher K, Siewert JR, et al. Prognostic factors in gastric carcinoma: results of the German Gastric Carcinoma Study 1992. Cancer 1993; 72:2089–2097.
3. Böttcher K, Siewert JR, Roder JD, et al. Risiko der chirurgischen Therapie des Magencarcinoms in Deutschland. Chirurg 1994; 65:298–306.
4. Halsted WS. Circular suture of the intestine: an experimental study. Am J Med Sci 1887; 94:436–461.
5. Schäfer K, Loeweneck H, Stanka H, Ernst R, Zumtobel V. Mikrozirkulations-störungen bei Colonanastomosen und ihre Bedeutung für die Pathogenese der Nahtinsuffizienz. Langenbecks Arch Chir 1990; 375:24–32.
6. Adams W, Ctercteko G, Bilous M. Effect of an omental wrap on the healing and vascularity of compromised intestinal anastomoses. Dis Colon Rectum 1992; 35:731–738.
7. Stoutenbeek CP, van Seane HKF, Miranda DR, Zandstra DF. The effect of selective decontamination of the digestive tract on colonisation and infection rate in multiple trauma patients. Intensive Care Med 1984; 10:185–192.
8. Unertl K, Ruckdeschel G, Selbman HK, et al. Prevention of colonization and respiratory infections in long-term ventilated patients by local antimicrobial prophylaxis. Intensive Care Med 1987; 13:106–113.
9. Schardey HM, Kamps T, Rau HG, et al. Bacteria: a major pathogenic factor for anastomotic insufficiency. Antimicrob Agents Chemother 1994; 38:2564–2567.
10. Van Saene HKF, Unertl KE, Alcock SR, et al. Emergence of antibiotic resistance during selective digestive decontamination? J Hosp Infect 1993; 24:158–162.
11. Onderdonk AB, Bartlett JG, Louie T, Sullivan-Seigler N, Gorbach SL. Microbial synergy in intra-abdominal abscess. Infect Immun 1976; 13:22–26.
12. Hermanek P, Sobin LH, eds. UICC TNM classification of malignant tumors. 4th ed. 2nd rev. Berlin: Springer; 1982.
13. Bankey P, Fliegel V, Singh R, Knighton D, Cerra F. Hypoxia and endotoxin induce macrophage mediated suppression of fibroblast proliferation. J Trauma 1989; 29:972–980.
14. Metzger Z, Hoffeld T, Oppenheim J. Suppression of fibroblast proliferation by activated macrophages: involvement of H_2O_2 and a non-prostaglandin E product of the cyclooxygenase pathway. Cell Immunol 1986; 100:501–514.
15. Selective Decontamination of the Digestive Tract Trialists Collaborative Group. Meta-analysis of randomised controlled trial of selective decontamination of the digestive tract. Br Med J 1993; 307:525–532.
16. Nichols RL, Smith JW. Intragastric microbial colonization in common disease states of the stomach. Ann Surg 1975; 182:557–565.
17. Sjöstedt S, Kager L, Heimdahl A, Nord CE. Microbial colonization of tumors in relation to upper gastrointestinal tract in patients with gastric carcinoma. Ann Surg 1988; 207:341–346.
18. Sjöstedt S, Levin P, Malmberg AS, Bergman U, Kager L. Septic complications in relation to factors influencing gastric microflora in patients undergoing gastric surgery. J Hosp Infect 1989; 13:191–197.
19. Baum ML, Anish DS, Chalmers TC, et al. A survey of clinical trials of antibiotic prophylaxis in colon surgery: evidence against further use of no-treatment controls. N Engl J Med 1981; 305:795–799.
20. Tetteroo GWM, Wagenvoort JHT, Castlein A, et al. Selective decontamination to reduce gram negative colonisation and infection after oesophageal resection. Lancet 1990; 335:704–707.
21. van der Waaij. Colonization resistance of the digestive tract: clinical consequences and implications. J Antimicrob Chemother 1982; 10:263–270.
22. Riou JPA, Cohen JR, Johnson H Jr. Factors influencing wound dehiscence. Am J Surg 1992; 163:324–330.
23. LeVeen HH, Wapnicks S, Falk D, et al. Effects of prophylactic antibiotics on colonic healing. Am J Surg 1976; 131:47–53.
24. Cohen SR, Cornell CN, Collins MH, et al. Healing of ischemic colonic anastomoses in the rat: role of antibiotic preparation. Surgery 1985; 97:443–446.
25. Cohn I Jr. Intestinal antisepsis. Surg Gynecol Obstet 1970; 130:1006–1014.