

Systemic Prophylaxis with Doxycycline in Surgery of the Colon and Rectum

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A prospective double-blind study on the effects of doxycycline as a prophylactic antimicrobial in elective colonic surgery is presented. One hundred-eighteen patients were evaluated. Fifty-eight were treated and 60 were controls. Two hundred milligrams, doxycycline or placebo (two capsules) were given orally four to six hours prior to surgery and 100 mg or placebo (one capsule) for five days postoperatively. Doxycycline levels in serum and tissues were determined and related to the MIC-values of the contaminants of the operative field. A significantly lower incidence of abdominal wound sepsis, intra-abdominal complications, and septicemia was recorded in the doxycycline group compared to the control group, 12.1 and 45% respectively. The prophylactic effect was most pronounced in patients with a negative wound culture upon closure. Macroscopical peritoneal contamination was associated with less severe consequences in the doxycycline group. Infections in the perineal field, 3/15 vs 8/17, appeared alone in the doxycycline group, whereas they were combined with abdominal sepsis in 6/8 among the controls. Treatment also reduced the incidence of repeat laparotomy due to septic complications, 0 vs 8. Thus systemic pre and postoperative prophylaxis with doxycycline significantly reduced both the incidence and the severity of postoperative sepsis in potentially contaminated elective colorectal surgery without any adverse reactions.

SURGERY ON THE COLON and rectum is accompanied by a great risk of developing postoperative surgical sepsis.³ As the organisms responsible for these infections usually are of intestinal origin, various attempts to reduce the colonic microflora with antimicrobials have been tried successively with most agents developed since the introduction of sulfaderivatives.¹¹ In the last decade a number of prospective and controlled studies on intestinal antisepsis, short-term systemic prophylaxis, and intraincisional instillation of antimicrobials, have demonstrated a significant reduction in postoperative surgical sepsis, especially abdominal wound sepsis.^{2,8}

Lately potent and potentially toxic agents, *i.e.* aminoglycosides and lincomycin, generally reserved for severe infections, have been used in prophylaxis.⁸ Doxycycline is a nontoxic tetracycline derivative with

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an antibacterial spectrum including both nonsporing anaerobes and intestinal aerobes, and a high affinity to intestinal tissue.⁶ Together with its observed effects in infectious complications to gastrointestinal surgery¹⁰ these properties make doxycycline an interesting alternative for systemic prophylaxis in colorectal surgery.

The aim of the present investigation was to study the validity of the following postulation. Could creation of an antimicrobial barrier in especially the intestinal wall and the peritoneal operative field environment, through systemic prophylaxis with doxycycline intra and postoperatively for five days, reduce the rate and magnitude of postoperative septic complications to colorectal surgery.

Material and Methods

Selection of Patients

This study was undertaken at the surgical clinic, University Hospital, Linköping, between January 1975 and April 1976. Patients scheduled for elective surgery on the colon and rectum were consecutively assigned, on a prospective, randomized, and double-blind basis to two groups: treatment with doxycycline (Vibramycin®) or placebo.

Patients over 16 years of age were included if resection or transection of the colon was contemplated. All patients on whom construction or closure of a colostomy was the sole operative procedure performed, were excluded. The protocol also excluded any patient with preoperative, or additional, antimicrobial therapy or who had been febrile within a week preoperatively.

The main part of this type of surgery is concentrated to two wards. Operations were performed by all surgeons skilled in colonic surgery or by registrars under supervision. No one surgeon operated on a dispropor-

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Submitted for publication: May 17, 1977.

tionate number of cases in either control or treatment groups.

Preoperative Preparation

Patients were admitted at least two days prior to surgery for mechanical and dietary preparation. The fecal mass in the colon was reduced, as follows, in both groups. *Day 1.* Low residue diet, 10 mg bisacodyl orally, and a water enema. *Day 2.* Liquid low residue diet, 10 mg bisacodyl orally, and a bisacodyl micro enema. *Day 3.* No further treatment. Surgery was performed according to the regular operative schedule.

Treatment

Oral administration of doxycycline was used to allow for a double-blind procedure as it was impossible to produce a placebo solution undistinguishable from the doxycycline solution for parenteral use. Each patient received a numbered box with seven capsules, the contents of which remained unknown to the patient, the staff, and the investigators until the study was completed. Two capsules (200 mg doxycycline or placebo) were given at 8:00 a.m. on the day of operation, normally four to six hours prior to surgery. Postoperatively one capsule (100 mg or placebo) was administered orally at 8:00 a.m. for five days.

All abdominal wounds were closed primarily and drainage was used when indicated. The perineal wound was also closed primarily with a drain, with a few exceptions. All drains, both abdominal and perineal, were closed and inserted through separate incisions.

Sampling Procedures

Blood samples for determination of serum levels of doxycycline were collected at the onset of operation. They were centrifuged after clotting and frozen at -80° until assay.

In the majority of patients tissue samples were taken on removal from the bowel wall and tumor tissue. Specimens from the subcutis, oment, and muscle for determination of doxycycline levels were taken in a separate group of patients. Blood and fecal matter were removed from the specimens with blotting paper, and they were then dissected to remove fatty and connective tissue, and blood extravasations. In many cases the bowel wall was dissected into its two main layers, one consisting of mucosa and the other of muscularis and serosa. All specimens were then cut into 3 mm \times 3 mm pieces and frozen at -80° until assay. Determination of the concentration of doxycycline was carried out with a standard cylinder plate method modified for doxycycline (Bacteriological Laboratory, Research Department, Pfizer Ltd, Sandwich, England).

Bacteriology

During surgery a cotton swab culture was taken from the surface of the completed anastomosis, colotomy, or the abdominal floor (proctectomies), and from the subcutis after peritoneal closure prior to skin closure. This procedure was followed in most of the patients. Each cotton bud was transported to the laboratory in a modified Stuart medium. Hematin, blood, and endo agar plates as well as nutrient broth were inoculated and incubated aerobically for isolation of aerobic and facultative organisms (aerobes). When inoculation on appropriate media was possible within an hour, anaerobic isolation using a BBL GasPak system was performed.

If contamination with bacteria from other sources such as drains, wound dressings, or fecal matter from fistula could be excluded, purulent wounds were cultivated at bedside both aerobically and anaerobically within an hour on the day of discovery.

Primary identification of isolated aerobic bacteria was performed according to routine procedures. As routine identification of anaerobic bacteria with gas-chromatography and biochemical methods was not available, identification of isolated strains was carried out by Gram-staining and colony morphology on freshly prepared prereduced media, blood agar supplemented with menadione and hemin, with and without neomycin or kanamycin/vancomycin. Susceptibility testing by the agar disc-diffusion method was used. The zones of inhibition of aerobic strains were measured after 16–20 hours of incubation at 37° . In all cases the anaerobes were grown in GasPak anaerobic jars at 37° for 48 hours and tested for susceptibility. Bacteria with MIC values $>4 \mu\text{g/ml}$ were classified as resistant.

Definitions of Septic Complications and Recording

All wounds were defined and graded before the code was broken. They were classified as infected when a clear collection of pus emptied itself spontaneously or after incision, or in the presence of a positive culture on debridement. For the clinical grading of abdominal wound sepsis the following system was used. Grade 0: No pus on debridement, but wound culture positive. Grade 1: Discharge of pus, but no separation of wound edges. Grade 2: Discharge of pus with separation of wound edges. Grade 3: Wound sepsis in continuity with an intra-abdominal process. Grade 4: A septic process in combination with a total wound rupture and/or a repeat laparotomy.

Anastomotic leakage was recorded by radiographic examination or at reoperation. Fistulas were defined as fecal discharge through the abdominal wall or as entero-enteric connections on radiograms or at re-

TABLE 1. Reasons for Exclusion From the Study

	Doxycycline	Placebo
Operation postponed	4	4
Inoperability	6	4
Preoperative infection	2	0
Intestinal lumen not opened	0	1
Other antimicrobial agents	1	2
Total	13	11
Included in study	58	60

operation, and septicemia according to the clinical picture mostly in the presence of a positive blood culture. The time of debut of the septic process has been set at the date of diagnostic confirmation, which in most cases coincided with the date for the first therapeutic measures taken. Wounds were inspected daily by one of the investigators, and all patients were followed for at least 30 days or to the complete resolution of septic complications.

Statistical Methods

The significance of differences were calculated by Fisher's exact test and Student's t test.

Results

Postoperative septic complications were defined and patients violating the protocol excluded before the code was broken. Thus 24 patients were withdrawn for various reasons (Table 1). This left 118 patients who were eligible for study; 58 in the treatment group and 60 patients in the placebo group.

The age and sex distributions of the patients were similar in each medication group with the exception of a small predominance of men in the control group. The

TABLE 2. Development of Abdominal and/or Intra-abdominal Sepsis Related to Diagnosis*

	Doxy- cycline	Placebo	Total
Malignant disease	7/42 ^{xx}	23/33 ^{xx}	30/ 75 ^{xxxx}
Cancer of the colon	5/29 ^x	15/20 ^{xx}	20/49 ^{xxx}
Cancer of the rectum	2/13 ^x	8/13	10/26 ^x
Benign disease	0/16	4/27	4/ 43
Ulcerative colitis	0/ 4	0/ 4	0/ 8
Crohn's disease	0/ 5	1/ 7	1/12
Polyp	0/ 2	2/ 8	2/10
Diverticulitis	0/ 4	1/ 4	1/ 8
Others	0/ 1	0/ 4	0/ 5
Total	7/58 ^{xx}	27/60 ^{xx}	34/118 ^{xxxx}

* Each x denotes one patient with an intra-abdominal abscess in the absence of abdominal wound sepsis.

TABLE 3. Development of Abdominal Wound and/or Intra-abdominal Sepsis Related to Type of Operation Performed*

	Doxycycline	Placebo	Total
Ileocecal resection and right hemicolectomy	2/18	6/14 ^x	8/ 32 ^x
Resection of colon and left hemicolectomy	2/ 9	2/ 4	4/ 13
Anterior resection			
High	0/11	3/ 8	4/ 19
Low	1/ 3 ^x	5/ 7 ^x	6/ 10 ^{xx}
Abdomino perineal resection	2/12 ^x	8/12	10/ 24 ^x
Pancoloproctectomy	0/ 3	0/ 5	0/ 8
Colotomy	0/ 2	3/10	3/ 12
Total	7/58 ^{xx}	27/60 ^{xx}	34/118 ^{xxxx}

* Each x denotes one patient with an intra-abdominal abscess in the absence of abdominal wound sepsis.

mean age was 59.9 ± 15.6 years in the treatment and 59.5 ± 17.1 years in the control group. The diagnoses and the types of operations performed on the patients in each group are given in Tables 2 and 3. Malignant conditions were more frequent in the treatment group, and polyps and colotomies in the placebo. In the total series 64% of the patients had a malignancy and 24% an inflammatory bowel disease. In 27% of the operations excision of the rectum was performed. Abdominal drains were used when indicated and the rate was 38% in the treatment and 37% in the control group. No complications or adverse effects of major significance attributed to the medication were recorded.

Mortality

The total mortality within 30 days was low, 2.5%. In the treatment group one patient with an intra-abdominal abscess after a pull-through operation most likely succumbed to a septic shock. In the placebo group one patient died on the 4th day in a combined picture of sepsis and cardiac failure. A second patient died of septicemia after a second operation caused by a subcutaneous wound rupture and peritonitis.

Antimicrobial Distribution

At the time of incision the average serum level of doxycycline was $4.0 \mu\text{g/ml}$ (Table 4). The variation with sex was most likely due to differences in body weight. In many cases the level in bowel tissue was higher than in serum due to an accumulation in the mucosal layer. In a pilot study preceding this trial, levels in the abdominal wall muscle tissue were found to be equal with or above serum levels three hours after the administration of 200 mg parenterally, while the levels in the subcutaneous fat and the oment remained below serum levels at all instances and in some cases never exceeded $1 \mu\text{g/g}$ tissue. Despite postopera-

TABLE 4. Doxycycline Levels in Serum at Incision and in Bowel Tissue on Removal

	Serum µg/ml			Ileum µg/g			Colon µg/g			Tumor µg/g
	♂	♀	Total	Mucosa	Muscul.	Total	Mucosa	Muscul.	Total	
n	24	30	54	12	12	18	33	33	33	19
X̄	3.3	4.6	4.0	10.0	3.9	7.9	5.1	2.7	4.1	6.6
SD	1.2	1.8	1.7	7.2	1.9	6.4	2.6	1.0	1.7	2.8
Range	0.2*-5.9	2.1-9.6	0.2-9.6	3.4-29.0	1.5-8.1	3.9-28.4	1.7-14.6	1.2-5.3	1.4-7.6	2.1-12.6

* Indicates patient with only 1.5 h between administration and sampling.

tive intestinal paralysis and parenteral nutrition, oral administration resulted in adequate serum levels.⁶

Sensitivity of Bacterial Contaminants

All strains isolated in the operative field were tested for susceptibility to doxycycline and the incidence and the resistance of the strains in the two groups were compared. The only significant difference was an increase in resistance to doxycycline from 22% (n = 45) in the placebo to 50% (n = 32) in the treatment group among the aerobic strains isolated from the site of the completed anastomosis (p < 0.02). In the total series 28% (n = 109) of the aerobes and 17% (n = 78) of the anaerobes isolated at operation were classified as resistant (MIC > 4 µg/ml).

Incidence of Postoperative Septic Complications

The incidence of postoperative septic complications in each group are listed in Table 5. Abdominal septic complications have been related to diagnosis and type of operation in Tables 2 and 3. Abdominal wound sepsis occurred in 5/58 patients (8.6%) in the treatment and in 25/60 patients (41.6%) in the control group (p < 0.001). Other septic complications from the intestinal field were apparently more numerous in the control group and mainly presented in combination with an abdominal wound infection, 9/11 compared with 1/3 in the treatment group. The total number of patients with one or more infective sequelae in the

abdominal field was significantly reduced with doxycycline (p < 0.001) (Tables 5 and 8).

Severity of Surgical Septic Complications

Abdominal septic complications classified as grade 3 and 4 were more frequent in the control group, 10/60 vs 1/58 (p < 0.01) (Table 6). The date of confirmation of a septic complication differed significantly and abdominal wound sepsis appeared five days later in the treatment group without any observable drawbacks (p < 0.01).

Relaparotomies were performed in 12 patients (Table 7). In the treatment group they were all caused by nonseptic complications, and furthermore septic complications from the second procedure did not appear, whereas postoperative sepsis or anastomotic breakdowns caused all of the relaparotomies in the control group.

Macroscopical Contamination

Gross macroscopical peritoneal contamination during surgery *i.e.* extraluminal fecal deposition or loss of intraluminal fluid drops, as well as accidental intestinal perforations, were registered (Table 8). The incidence did not differ between the groups. In both groups contamination in comparison with noncontamination increased the rate of abdominal wound and/or intra-abdominal sepsis (p < 0.03 doxyc.; p < 0.001 control). When contamination occurred this rate was reduced

TABLE 5. Postoperative Surgical Septical Complications

	Doxycycline		Placebo	
	n	%	n	%
Abd. wound sepsis	5/58	8.6%	25/60	41.6%
Intra-abd. abscess	1*		4(2)	
Anastomotic leakage	2(1)†		5(4)	
Fistula	1(1)†		5(5)	
Peritonitis	0		2(2)	
Septicemia	1*		5(5)	
Total	7/58	12.1%	27/60	45.0%

Figures within brackets denote the number of cases with simultaneous wound sepsis. The differences in wound sepsis and totally between the two groups are highly significant (p < 0.001).

* Same patient.

† Same patient.

TABLE 6. Severity of Abdominal Wound Infections and Day of Diagnostic Confirmation

	Doxycycline (n 58)		Placebo (n 60)		
	n	Day	n	Day	
Grade 0	0		0		
Grade 1	2	12*, 19	3	10*	3,9
Grade 2	2	10*, 15*	12	3*, 4*, 5*, 6*, 7*, 7*, 7*, 10*, 14*	7, 7, 8
Grade 3	1	8*	5	7*, 10*	7, 8, 30
Grade 4	0		5	3*, 7*, 10*	4, 5
	5	X̄ = 12.8 ± 4.3	25	X̄ = 7.9 ± 5.3	

* Macroscopical peritoneal contamination during operation.

TABLE 7. Indications for Repeat Laparotomy

	Doxycycline	Placebo
Postoperative bleeding within 24 hours	2	0
Necrosis of sigmoidostomy	1	0
Ileus	1	0
Wound separation (infected)	0	5
Anastomotic leakage	0	2
Drainage of intraabdominal abscess	0	1
Total	4	8

from 79% in the control to 33% in the doxycycline group. Also, in the absence of contamination, prophylaxis significantly reduced this rate.

Abdominal Wound Cultures

The rate of positive wound cultures upon closure did not differ between the groups and within them the incidence of abdominal wound sepsis did not differ significantly with the wound culture finding (Table 9). Between the groups the abdominal wound sepsis rate differed only when the wound culture was negative ($p < 0.002$).

Satisfactory cultures from infected sites without possible interference from intestinal leakage or surface contamination from the skin, drains, or wound dressings were secured in 14/25 patients with abdominal wound sepsis in the control group, and in 86% of these one or more anaerobic strains were isolated. In the treatment group cultures were considered optimal in two patients and both were negative. In the remaining three patients only aerobes were isolated.

Influence of the Type and Location of the Lesion

In the control group abdominal sepsis was more frequent in malignant than in benign disease ($p < 0.001$), whereas the difference was not significant in the treatment group. In malignant disease the rate of abdominal sepsis was reduced from 70% in the control group to 17% with prophylaxis ($p < 0.001$). The sepsis rate in benign cases in the control group was too low to demon-

strate a significance of difference with prophylaxis (Table 2).

Elective proctectomies in inflammatory disease were in no case associated with abdominal sepsis, whereas proctectomies for cancer became infected in 42%. Resection of the bowel without anastomosis, *i.e.* abdomino-perineal resection or pancoproctectomy, was accompanied by a difference in the rate of abdominal sepsis in the two groups ($p < 0.05$). It was not possible to discern a difference in the incidence of abdominal sepsis in the control group between strictly intra- and mainly extraperitoneal procedures. Prophylaxis significantly reduced the abdominal sepsis rate in both types of procedures ($p < 0.01$; $p < 0.01$).

Perineal and Other Infections

Cases where a significant collection or discharge of pus occurred in the perineal field requiring surgical debridement or drainage, were recorded as infected. Infection occurred in 3/15 (20%) in the treatment group and in 8/17 (47%) in the control group. In the former group it was the sole, 0/3, septic complication, whereas 6/8 were combined with some type of abdominal sepsis in the latter group.

The influence of doxycycline prophylaxis on the incidence of remote infections *i.e.* urinary and pulmonary infections was also studied (Table 10). A significant reduction of urinary tract infections was found ($p < 0.02$), while the reduction of pulmonary complications was less pronounced ($p < 0.04$).

Discussion

In the last decade a number of prospective and controlled studies have demonstrated that prophylactic use of antimicrobials, provided basic requirements are met, significantly reduces the high rate and morbidity of septic complications in colorectal surgery.^{2,8} Concomitantly the importance of intestinal nonsporing anaerobes for the development of surgical sepsis was established. Consequently, a characteristic feature of recent intestinal antisepsis programs has been the in-

TABLE 8. Incidence of Surgical Sepsis Related to Operative Peritoneal Macroscopical Contamination

	Contaminated			Noncontaminated			Total		
	Doxyc.	Placebo	p	Doxyc.	Placebo	p	Doxyc.	Placebo	p
	18	19		40	41		58	60	
Abd. wound sepsis	4	15	0.001	1	10	0.01	5	25	0.001
Abd. wound and/or intraabd. sepsis	6	15	0.01	1	12	0.001	7	27	0.001
Abd. wound and/or intra-abd. sepsis perineal sepsis	7	16	0.01	3	13	0.01	10	29	0.001

TABLE 9. Abdominal Wound Sepsis Related to Outcome of Wound Culture Upon Closure

Wound sepsis/positive culture			Wound sepsis/negative culture			Wound sepsis/culture missing		
Doxycycline	Placebo	p	Doxycycline	Placebo	p	Doxycycline	Placebo	p
3/18 (17%)	12/29 (41%)	0.08	1/31 (3%)	10/17 (37%)	0.001	1/9 (11%)	3/4 (75%)	NS

clusion of antimicrobials specifically directed against the anaerobes, *i.e.* erythromycin, tetracycline, and metronidazole in combination with nonabsorbable aminoglycosides in order to reduce the aerobic part of the intestinal flora.^{2,8} It has not been elucidated, however, if the observed effects on the incidence of wound sepsis after intestinal antisepsis, according to this principle, are a result of the mainly quantitative reduction of the intestinal flora, a systemic effect caused by the absorption and resulting serum and tissue levels of the agent directed against the anaerobes, or a combined effect.

Short term systemic prophylaxis with penicillin G, cephaloridine, and lincomycin have been highly effective in elective colorectal surgery,⁸ and aminoglycosides in combination with clindamycin in cases with intestinal perforations.¹⁴ To be effective, adequate serum and tissue levels must be present at the time of primary lodgement of bacteria in the operative field.¹³ The question of duration is more controversial as the prolonged use of antimicrobials might lead to the selection and emergence of resistant strains, and it has been advocated by some that the usage should be confined to the immediate pre- and postoperative period. Others claim that prophylactic antimicrobials exert their primary effect on the healing of anastomoses. In dogs a five day continuation was found to be advantageous to induce healing per primam,⁹ while this prolongation resulted in a high rate of pseudomembraneous colitis with a combination of lincomycin-gentamicin in man.¹

Though intrainsisional instillation of antimicrobials is effective in the prevention of wound sepsis, resulting serum and tissue levels are unpredictable and its effects on intra-abdominal sepsis dubious.

Tetracyclines constitute an important but disputed group of antibiotics used for prophylaxis in colorectal surgery.⁵ In a controlled study by Washington et al.,¹⁵ preoperative preparation of the colon with tetracycline-neomycin significantly reduced the rate of wound sepsis and apparently also the number of intra-abdominal septic complications. In another study, where tetracycline alone was administered pre- and postoperatively for five days, the effects were less pronounced.⁷

Doxycycline is a highly lipophilic tetracycline derivative which is rapidly and almost completely absorbed from the upper part of the small intestine, even in the presence of postoperative enteric paralysis.⁶ Thus, in

this series, oral administration did in no way impede on the main principle of high tissue concentrations and a minimum of interference with the intraluminal flora. Its favourable antibacterial spectrum and its absence of antimetabolic properties and accumulation in renal failure make doxycycline an interesting alternative as an agent in systemic prophylaxis in colorectal surgery.

To be valid, an investigation of this character should not deviate from normal clinical routine and hence the operations were performed by all competent members of the staff, and not confined to one surgeon only. The study was also strictly consecutive and operations were not scheduled in favor of it. With a few exceptions the patients with malignancies represented an unselected series of primary operations, whereas patients with ulcerative colitis and Crohn's disease constituted a more selected series of both primary and secondary operations.

The groups were comparable in all respects except for a small predominance of men and malignancy in the doxycycline group, and polyps and colotomies in the control. Despite a great number of elderly patients with advanced malignant disease the total immediate mortality was low.

Septic complications were fewer, mostly superficial, and occurred at a later stage in the doxycycline group. The total complication rate of 12.1% in the abdominal field is a most promising result. The corresponding frequency of 45% among the controls is of the same magnitude as in most other studies. Washington et al.¹⁵ reported more than 40% despite the fact that all operations were performed by one surgeon. We believe that even a small anastomotic break-down is of far greater importance than an isolated and superficial wound infection and maintain that all intra-abdominal, perineal, and remote infections should be taken into consideration when different methods and agents are compared.

Sepsis in the perineal wound has seldom been considered in earlier studies, but Rosenberg et al.¹² reported an infection rate of 28%. In our series the rates

TABLE 10. Incidence of Urinary and Pulmonary Infections

	Doxycycline	Placebo
Urinary tract infection	2	10
Bronchopneumonia	5	13

did not differ significantly, but the perineal abscesses were the single complication in the doxycycline group (20%), whereas in the control (47%) they were combined with complications in the abdominal field in 6/8 cases. These facts suggest that the resistance of the tissues is increased to such an extent that these infections will be more circumscribed.

Due to the pathological conditions associated with this type of surgery, operative contamination will always remain a problem and the magnitude of the inoculum will be the most decisive factor for the development of infection or not. Macroscopical contamination occurred in approximately 30% of the operations and carried significantly higher sepsis rates in both groups. In the doxycycline group, however, it was significantly reduced from 79% in the control to 33%, and, with one exception, occurred only in patients with lesions of questionable radical resectability or technical difficulties at operation.

Even in the absence of noticeable soiling the rate of infection remains high without prophylaxis. In a comparable study with 19 patients in the control group, 10/11 infections developed in the absence of contamination and anaerobes were isolated in all of them.¹⁶ Thus, contaminants are always present and a retrieval rate of 80% at the site of the anastomosis among the controls must be considered as representative under these conditions. A statistically insignificant reduction in the number of positive cultures was seen in the doxycycline group. The risk of contamination with resistant strains ought to be less when systemic prophylaxis is instituted shortly before the operation, compared to after one to two days of preoperative intestinal antisepsis. However, the observed difference in the number of resistant aerobes isolated at the anastomosis ($p < 0.05$) indicates a possible selection already at this early stage. Despite the fact that only 76% of the strains isolated in the operative field had MIC values below levels achieved in serum and tissues, with the exception of the subcutaneous fat, doxycycline was highly effective in this study.

The prognostic importance of a positive wound culture upon closure was not confirmed. However, the low incidence of wound sepsis in patients with a negative finding in the doxycycline group emphasizes the importance of surgical technique.

Relaparotomies are frequent in colorectal surgery and carry high morbidity and mortality rates. In the control group they were twice as common and necessitated by septic complications. They were also undertaken at a more crucial stage of the anastomotic healing process, and were often followed by protracted periods of surgical sepsis. In the doxycycline group they were caused by nonseptic conditions, and in all four cases the postoperative course was uneventful.

The incidence of remote infections may be taken as an indication of the general postoperative condition of the patient. Both urinary and respiratory tract infections were less frequent in the doxycycline group. This was probably due to a combined effect of the five day treatment with high tissue and urinary levels and the absence of surgical sepsis necessitating the use of ventilators, catheters, and drains.

This randomized double-blind study has demonstrated that the principle of high tissue concentrations of doxycycline intra and postoperatively, with a minimum of interference with the intestinal flora at the time of surgery, is valid. This, in combination with its few adverse effects, and the need to save the more potent agents for severe infections, makes this type of prophylaxis an attractive alternative to other methods and agents in colorectal surgery.

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