
Microbial Colonization of Tumors in Relation to the Upper Gastrointestinal Tract in Patients with Gastric Carcinoma

SVANTE SJÖSTEDT,* LARS KAGER,* ANDERS HEIMDAHL,† and CARL ERIK NORD‡

The microbial colonization of the oropharynx, the esophagus, the stomach, and the duodenum was studied in relation to the microbial flora found on tumor and gastric mucosal biopsies in 23 patients with gastric carcinoma. The tumor was colonized in all patients, and the stomach, the esophagus, the duodenum, and the gastric mucosa were colonized in 96%, 87%, 83%, and 78% of the patients, respectively. The most common microorganisms isolated were *streptococci*, *bifidobacteria*, *lactobacilli*, and *Bacteroides* species, belonging to the normal oropharyngeal flora. Microbial colonization with gram-negative rods, *Clostridium* species or yeasts, was present in at least one site in 91% of the patients. *Clostridium* species were isolated from 57% of the patients. The total numbers of microorganisms recovered from the tumor biopsies did not vary with the intraluminal gastric pH. A relation between the gastric pH and the total number of microorganisms in the gastric juice existed. Significant higher numbers of different strains of microorganisms ($p < 0.005$) colonized the tumor compared to the gastric mucosa. Anaerobic microorganisms colonized the tumor significantly more often than the mucosa ($p < 0.001$). Antibiotic agents used as prophylaxis in gastric cancer surgery should cover both aerobic and anaerobic microorganisms, including *B. fragilis*.

PATIENTS with gastric carcinoma undergoing surgery are at high risk of developing postoperative infectious complications. The risk of infection is related to the density of the microbial colonization of the stomach, and the microorganisms causing infections are usually present in the stomach at the time of operation.^{1,2}

The luminal floras of the oropharynx, the esophagus and the stomach, have previously been studied in patients with different diseases of the stomach by Sjöstedt et al. (Table 1).³ Patients with gastritis, a history of previous gastric resection, and gastric carcinoma were found to have the highest pH of the gastric fluid and also

From the Department of Surgery,* Oral Surgery,† Huddinge University Hospital, Huddinge, Sweden, and the National Bacteriological Laboratory,‡ Stockholm, Sweden

to harbor more microorganisms in the stomach. Patients with gastric carcinoma were found to harbor the largest numbers of different microbial species and also more species not belonging to the normal oropharyngeal microflora than patients with any other gastric diseases. Patients with gastric carcinoma are almost invariably colonized in the stomach with microorganisms derived from the normal oropharyngeal flora but also often with enteric gram-negatives and yeasts. These patients have also been found to harbor anaerobes such as *Clostridium* species and *Bacteroides* species, including *B. fragilis*, in the stomach.¹⁻⁴

In previous reports the microflora has been studied by means of aspiration of the intraluminal content. In this study not only the luminal flora of the oropharynx, the esophagus, the stomach, and the duodenum were studied, but also the microbial colonization of the tumor itself, which was compared with the normal gastric mucosa in patients with carcinoma of the stomach.

Materials and Methods

Twenty-three patients, 20 men and 3 females (mean age: 68.5 years) were studied. They all had histologically verified gastric carcinoma diagnosed at an earlier endoscopy. The samples for microbiologic analysis were obtained during an endoscopy performed as a part of the preoperative evaluation of the patient.

Before endoscopy, mixed saliva samples of 1 mL were collected by the patient spitting into a sterile glass tube.

Samples of 1 mL of fluid from the esophagus, the stomach, and the duodenum were collected during endoscopy by means of aspiration through a sterile polyethylene tube introduced into the biopsy channel of the

Reprint requests: Svante Sjöstedt, Department of Surgery, Karolinska Institute, Huddinge University Hospital, S-14186 Huddinge, Stockholm, Sweden.

Submitted for publication: July 15, 1987.

TABLE 1. Numbers of Microorganisms Isolated from the Upper Gastrointestinal Tract in Patients Without Gastric Disease³

Microorganisms	Log Numbers of Microorganisms/mL		
	Oropharynx	Esophagus	Stomach
Aerobic species			
Micrococci, staphylococci	9×10^7	0	$<10^2$
Hemophilus neisseria	9.7×10^6	0	$<10^2$
Streptococci	7.4×10^7	$<10^3$	$<10^2$
Anaerobic species			
Bifidobacteria lactobacilli	3.1×10^6	$<10^2$	$<10^3$
Veillonella	3.3×10^7	$<10^2$	$<10^3$
Fusobacteria	6.5×10^5	0	0
Bacteroides	2.2×10^7	$<10^3$	$<10^3$

endoscope. To prevent contamination a new sterile tube was placed in the biopsy channel each time the endoscope was moved to a new site. In the esophagus and the duodenum 1 mL of sterile saline (0.9%) was first injected into the lumen and then aspirated, and by this technique a luminal washing was obtained. In the stomach it was always possible to collect 1 mL of gastric fluid without a luminal washing.

After all luminal samples had been obtained the tumor was located. Three biopsies from the visually unaffected mucosa as far away as possible from the tumor were obtained and placed in three glass tubes with sterile saline. With a new pair of biopsy-forceps three biopsies from the tumor were then taken and placed in three glass tubes with sterile saline. All samples were immediately transported to the laboratory and processed.

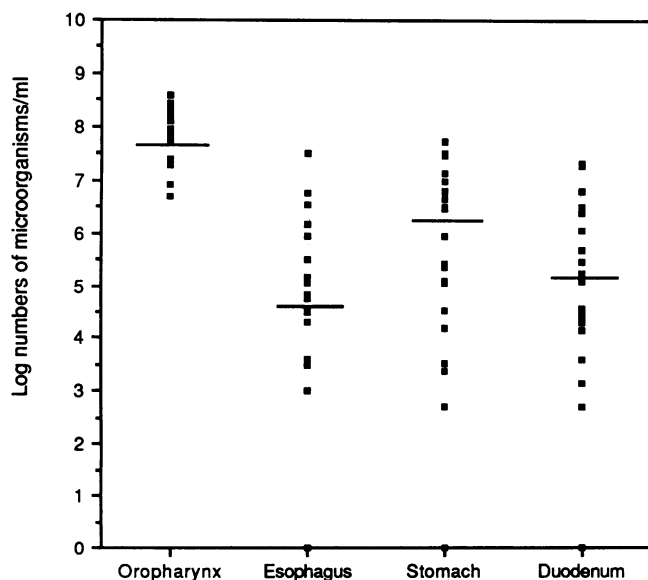


FIG. 1. Total numbers of microorganisms isolated from the oropharynx, esophagus, stomach, and duodenum in 23 patients with gastric carcinoma.

The samples of saliva, esophageal washings, gastric fluid, and duodenal washings were suspended in prereduced peptone yeast extract medium. They were diluted, inoculated on nonselective and selective media and manipulated as described by Heimdahl and Nord.⁵

The biopsies from the first 11 consecutive patients were cut into small pieces, homogenized, and then suspended in 4.5 mL prereduced peptone-yeast extract medium. Aliquots of 0.1 mL were then inoculated on selective and nonselective media.

In the other 12 consecutive patients a quantitation of the microflora isolated from the biopsies was also made. These biopsies were first weighed and then cut into small pieces, homogenized, and suspended in prereduced peptone-yeast extract medium. Tenfold serial dilutions were prepared to 10^{-4} . Each dilution was inoculated on nonselective and selective media.

The aerobic agar plates were incubated for 24 hours (luminal samples) or 48 hours (tissue samples) at 37 C, and the anaerobic agar plates for 2 days (luminal samples) or four days (tissue samples) at 37 C in an anaerobic chamber (Forma Scientific®, Marietta, OH).

Aerobic bacteria were identified as described by Heimdahl and Nord,⁵ and anaerobic bacteria were identified using biochemical tests and gas-liquid chromatography.⁶

The pH of 4 mL of aspirated gastric juice was estimated using a pH-Meter 29 (Radiometer®, Copenhagen).

Statistical methods used were paired *t*-test and Fisher's exact test.

Results

Oropharynx

All patients harbored normal numbers (Table 1) of aerobic bacteria such as *streptococci*, *micrococci/staphylococci*, and *hemophilus/neisseria* and anaerobic bacteria such as *bifidobacteria/lactobacilli*, *veillonella*, *fusobacteria*, and *bacteroides*. The median total counts of microorganisms were 7.0×10^7 /mL (Fig. 1). Microorganisms not belonging to the indigenous oropharyngeal flora were colonizing 17/23 (73.9%) of the patients. *Clostridium* species were found in 39.1%, gram-negative aerobic rods in 30.4%, and yeasts in 21.7% of the patients (Tables 2 and 3).

Esophagus

The total counts of microorganisms were lower than in the oropharynx (median: 6.0×10^4 microorganisms/mL) (Fig. 1). Colonization of the esophagus was found in 20/23 (87%) of the patients. *Streptococci* were found in 87%, *micrococci/staphylococci* in 60.9%, and *bifido-*

TABLE 2. Colonization with Microorganisms not Belonging to the Indigenous Oropharyngeal Microflora in 23 Patients with Gastric Cancer

Organisms	No. of Patients Colonized					
	Oral Cavity	Esophagus	Stomach	Duodenum	Mucosa	Tumor
<i>Streptococcus fecalis</i>	1	1	1	1	1	1
<i>Escherischia coli</i>	1	—	2	3	—	—
<i>Klebsiella pneumoniae</i>	1	—	3	2	1	1
<i>Klebsiella ozaenae</i>	1	—	—	—	—	—
<i>Enterobacter cloace</i>	2	—	1	—	—	—
<i>Proteus morgani</i>	—	—	1	1	1	1
<i>Pseudomonas maltophila</i>	1	—	1	—	—	—
<i>Serratia species</i>	1	—	—	—	—	—
<i>Hafnia alvei</i>	—	—	—	1	—	—
Nonidentified*	—	—	—	—	—	—
Gram-negative rods	—	—	—	—	—	1
<i>Clostridium perfringens</i>	—	—	2	2	—	2
<i>Clostridium species</i>	9	3	3	5	—	4
<i>Candida albicans</i>	2	2	3	3	1	1
<i>Torulopsis glabrata</i>	2	—	—	—	—	1
<i>Torulopsis candida</i>	1	—	—	—	—	—

* Nonidentified gram-negative rods colonized the tumor in one patient.

bacteria/lactobacilli in 52.2% of the patients. Aerobic gram-negative rods did not colonize the esophagus, but *Clostridium* species were found in 13%, yeasts in 8.7%, and *enterococci* in 4.3% of the patients (Tables 2 and 3).

Stomach

The luminal gastric flora had a higher concentration of microorganisms (median total counts of microorganisms: 3.0×10^6 /mL) than the esophageal flora but not as high as the oropharyngeal flora (Fig. 1). Twenty-two (95.7%) of the patients harbored microorganisms in the gastric juice. There was a clear correlation between the total numbers of microorganisms and the pH of the gastric juice (Fig. 2). *Streptococci* were found in 87%, *bifidobacteria/lactobacilli* in 78.3%, and *micrococci/staphylococci* in 60.9% of the patients. Microorganisms not belonging to the normal oropharyngeal microflora

were found in 11/23 (47.8%) of the patients. *Clostridium* species were found in 21.7%, aerobic gram-negatives rods in 21.7%, yeasts in 13.0%, and *enterococci* in 4.3% of the patients (Tables 2 and 3). In only two patients did these microorganisms also colonize the oropharynx.

Duodenum

The median total counts of microorganisms were 1.0×10^5 /mL (Fig. 1). Microbial colonization was found in 19/23 (82.6%) of the patients. *Bifidobacteria/lactobacilli* were found in 65.2%, *streptococci* in 60.9%, and *veillonella* in 43.5% of the patients. Microorganisms not belonging to the normal oropharyngeal flora were found in 11/23 (47.8%) of the patients. *Clostridium* species colonized 30.4%, aerobic gram-negative rods 17.4%, yeasts 13.0%, and *enterococci* 4.3% of the patients (Tables 2 and 3).

TABLE 3. Microbial Colonization of the Upper Gastrointestinal Tract, Gastric Mucosa, and Tumor in 23 Patients with Gastric Carcinoma

	Oropharynx	Esophagus	Stomach	Duodenum	Mucosa	Tumor	At Least 1 Site Colonized
Micrococci/staphylococci	*	60.9	60.9	34.8	43.5	73.9	82.6
Streptococci/other gram-positive cocci	*	87	87	60.9	60.9	91.3	100
<i>Hemophilus/Neisseria</i>	*	39.1	30.4	30.4	13	13	60.9
Enterococci	4.3	4.3	4.3	4.3	—	4.3	8.7
Enteric gram-negative microorganisms	12.7	—	17.4	17.4	4.3	8.7	34.8
<i>Bifidobacteria/Lactobacilli</i>	*	52.2	78.3	65.2	13	47.8	95.7
<i>Veionella</i>	*	34.8	43.5	43.5	13	17.4	78.3
<i>Fusobacteria/leptotrichia</i>	*	21.7	47.8	26.1	—	—	60.9
<i>Bacteroides</i>	*	39.1	43.5	34.8	—	26.1	73.9
<i>Clostridium species</i>	39.1	13.0	21.7	30.4	—	26.1	56.5
Yeasts	21.7	8.7	13.0	13.0	4.3	4.3	30.4
Total % of patients colonized	73.9	87	95.7	82.6	78.3	100	—

* Normal oropharyngeal flora.

Values are given as % of patients colonized.

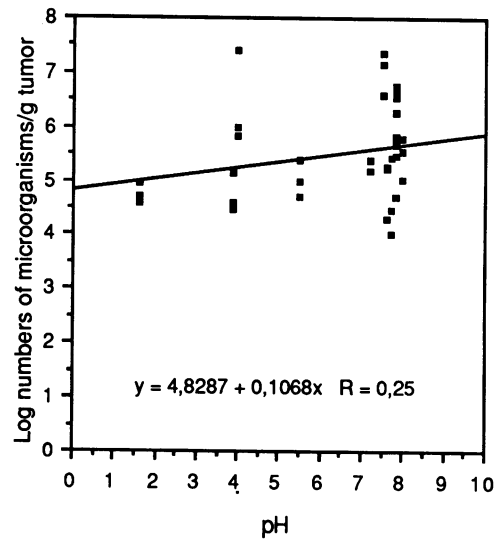
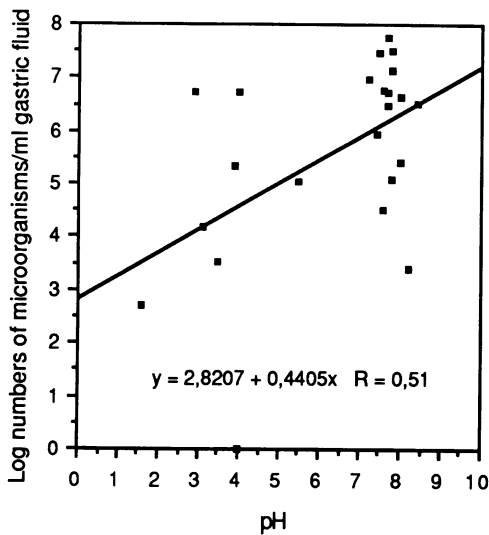


FIG. 2. (left) Relationship between total viable counts of microorganisms/mL gastric juice and gastric pH in 23 patients with gastric carcinoma. A significant correlation ($r = 0.51$) was found between increase in pH and numbers of microorganisms. The equation of the regression line is shown in the figure. (right) Relationship between total viable counts of microorganisms/g tumor tissue and gastric juice pH in 36 tumor biopsies from 12 patients with gastric carcinoma. No significant correlation was found ($r = 0.25$). The equation of the regression line is shown in the figure.

Gastric Mucosal Biopsies

Eighteen (78.3%) of the patients were colonized on the mucosal biopsies, and 17/23 (73.9%) had growth of aerobic microorganisms, and 7/23 (30.4%) had growth of anaerobic microorganisms. *Streptococci* (in 60.9% of the patients) and *micrococci/staphylococci* (in 43.3% of the patients) were the most common findings. Aerobic gram-negative rods were found in one patient (4.3%) and yeasts were found in another patient (4.3%). None of the patients was colonized with *Clostridium* species on the normal mucosa (Tables 2 and 3). The mean number of different strains was 2.9 on the mucosal biopsies (Table 4, Fig. 3).

Tumor Biopsies

All patients were colonized on the tumor and 22/23 (95.7%) had growth of aerobes and 20/23 (87%) had growth of anaerobes. Anaerobic bacteria colonized the tumor significantly ($p < 0.001$) more often than they did the normal mucosa (Table 4). *Clostridium* species were found on the tumor in 26.9% of the patients, signifi-

cantly ($p < 0.05$) more often than on the normal mucosa. *Streptococci* (in 60.9% of the patients) and *micrococci/staphylococci* (in 43.3% of the patients) were the most common findings (Tables 2 and 3). Ten (43.5%) of the patients were colonized with microorganisms not belonging to the normal oropharyngeal microflora. Aerobic gram-negative rods were found in 8.7% and yeasts in 4.3% of the patients. The mean number of different strains was 6.5 on the tumor biopsies, which was significantly ($p < 0.0005$) more than on the mucosal biopsies (Table 4, Fig. 3). The total counts of microorganisms on the tumor biopsies from patients with a pH of 4 or less did not differ from the patients with a higher pH (Fig. 2). The total numbers of microorganisms were 2–30 times higher on the tumor samples than on the mucosa samples in all but one patient.

Discussion

In this study, the microbial colonization of the oropharynx, the esophagus, the stomach, and the duodenum was compared with the colonization of the tumor and the gastric mucosa in patients with gastric carcinoma.

We have previously reported on the intraluminal flora of the upper gastrointestinal tract in patients with different gastric diseases including carcinoma.³ The oropharynx of patients with carcinoma are colonized with gram-negative rods, *Clostridium* species, and yeasts. This is probably not due to their gastric disease because the same microbial colonization in patients with other gastric diseases and even in normal subjects was found.³ *Clostridium* species, however, were only found in patients with carcinoma.

In the esophagus, the concentration of microorganisms was much lower than in the oropharynx. This can only in part be explained by the sampling procedure because the dilution of the esophageal fluid with 1 mL of

TABLE 4. Comparison Between Microbiologic Findings from Mucosal and Tumor Biopsies in 23 Patients with Gastric Carcinoma

	Mucosa	Tumor	P Value
No. of patients colonized	18	23	$p < 0.05^*$
Aerobes	17	22	NS
Anaerobes	7	20	$p < 0.001^*$
Gram-negative rods	1	2	NS
Clostridium species	0	6	$p < 0.05^*$
Bacteroides	0	6	$p < 0.05^*$
Yeasts	1	1	NS
Mean No. of strains	2.9	6.5	$p < 0.0005^\dagger$
Aerobic strains	2.4	4.2	$p < 0.0005^\dagger$
Anaerobic strains	0.7	2.4	$p < 0.0005^\dagger$

* Fischer's exact test.

† Paired t-test.

saline cannot explain the fall in concentration from 10^7 microorganisms/mL in the oropharynx to 10^4 microorganisms/mL in the esophagus. Other factors influencing the density of the esophageal flora can be the peristalsis of the esophagus causing a rapid washout of the microbes, secretion from the mucosa resulting in a dilution with less ability for microbial attachment or local immunologic factors. It is noteworthy that gram-negative rods in no case were isolated from the esophagus whereas *Clostridium* species and yeasts were, which is in accordance with our previous findings.³

Reports of the findings of microorganisms in preoperative and peroperative gastric aspirates have been published. In an earlier study it was found that patients with gastric carcinoma have higher bacterial counts and are colonized with higher numbers of different species than patients with other gastric diseases.³ Gatehouse et al.¹ found growth of microorganisms in preoperative gastric aspirates in all of 35 patients investigated, and 54% of these patients had a total viable count greater than 5×10^6 organisms/mL, which is in an accordance with our findings. Muscraft et al.⁴ investigated 31 patients with gastric carcinoma and compared them with patients with intact stomach receiving cimetidine and patients with resected stomachs. They found that *E. coli* (in 51% of the patients) and *Clostridium* species (in 25.8% of the patients) were more common in the carcinoma group. They also reported high frequencies of *Streptococcus fecalis* (70.9%) and *B. fragilis* (38.7%). In the present investigation these frequencies of *E. coli*, *S. fecalis*, or *B. fragilis* were not found, but a comparable frequency of *Clostridium* species of 21.7% and a frequency of *Bacteroides* species of 43.5% in the gastric aspirates were found.

The duodenal flora has not previously been studied in patients with gastric carcinoma. Normally, there is no permanent flora in the duodenum, but subjects with achlorhydria may be colonized with low numbers of microorganisms (median 10^3 microorganisms/mL). *Enterococci*, aerobic gram-negatives, oral aerobes and anaerobes and yeasts but not *Clostridium* species have been recovered.⁷ We found a colonization in 82.6% of the patients and a median count of 1.0×10^5 microorganisms/mL; *Clostridium* species were found in 30.4% of the patients with gastric carcinoma.

No correlation between the colonization of the different sites of the gastrointestinal tract was found. For example, of the 11 patients colonized in the gastric aspirates with aerobic gram-negative rods, *Clostridium* species or yeasts, only two were colonized with the same microorganisms in the oropharynx.

It is generally agreed that there exists a relationship between the pH of the gastric fluid and the numbers of microorganisms in the gastric fluid.^{3,4,8,9} Gastric aspirates with a pH of 4 or less are usually sterile. In this

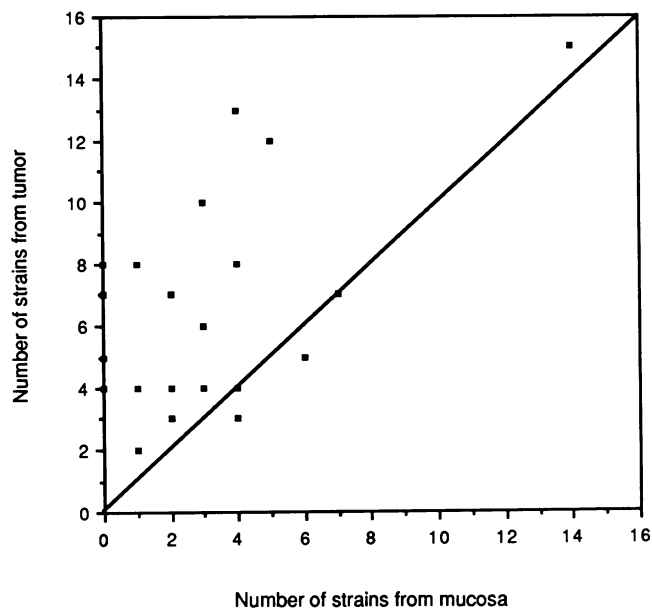


FIG. 3. The number of different predominant strains of microorganisms isolated from gastric mucosal biopsies in relation to the number of different strains isolated from tumor biopsies in 23 patients with gastric carcinoma. Points situated above the diagonal line indicate patients with a larger number of predominant strains on the tumor than on the mucosa. Points below the diagonal line indicate patients with a larger number of strains on the mucosa than on the tumor.

study, the colonization of the tumors, however, did not seem to be dependent of the pH of the gastric fluid. All patients with a pH of 4 or less were colonized on the tumor surface, and the total numbers of microorganisms did not differ significantly from the total numbers found on the tumors from patients with a higher pH. Consequently, the tumor may act as a reservoir on which the microorganisms may be protected from the acidity of the gastric juice and thus give rise to a continuous release of microorganisms into the gastric lumen. There were no significant differences between the species found in the intraluminal flora and the species found on the tumors.

Some significant differences were found between the colonization of the mucosa and the tumors. Microorganisms were found in higher numbers on the tumors in all but one patient. Growth of microorganisms were found on tumor biopsies from all patients whereas the mucosa showed no growth at all in five patients. The numbers of different strains isolated from the tumor biopsies were significantly higher than the numbers of strains found on biopsies from the mucosa. Anaerobes seemed to have a strong tendency to grow on the tumors; *Bacteroides* species and *Clostridium* species could only be isolated from the tumors. The fact that the biopsies from the normal mucosa showed some colonization in most patients is surprising, but one explanation is that elderly patients often have various degrees of

gastritis and that a damaged mucosa is more likely to be colonized.^{10,11}

Clostridium species, including *C. perfringens*, seems to be the microorganisms, not belonging to the normal oropharyngeal flora, that are most likely to colonize the upper gastrointestinal tract of patients with gastric carcinoma. *Clostridium* species have in other studies been found to colonize patients with carcinoma of the colon¹² and patients undergoing bone marrow transplantation.¹³ Overgrowth or colonization with *Clostridium* species may therefore in some way be associated with malignant disease.

Patients with gastric carcinoma are heavily colonized in the upper gastrointestinal tract, and microorganisms not belonging to the normal oropharyngeal flora can be found in most of the patients. These patients are at high risk of developing postoperative infectious complications, and previous reports have shown frequencies of between 13% and 56%.^{1,15,16}

Cephalosporins have been recommended as antibiotic prophylaxis in gastric surgery since the study of Polk and Lopez-Mayor in 1969¹⁷ and others.¹⁸⁻²³ In well-controlled studies, cephalosporins have been shown to significantly reduce the number of postoperative infections after gastric surgery. Stone et al.¹⁹ used cefazolin and reduced the rate of postoperative infections from 22% to 4%. However, there is no study dealing specifically with prophylaxis in patients with gastric carcinoma. All studies include patients with various gastric diseases, and the number of patients with gastric carcinoma are often not stated. Keighley et al.²⁴ have reported on selective antibiotic prophylaxis in gastric surgery, including patients with gastric carcinoma. Only patients with total viable counts of $>10^6$ microorganisms/mL were given antibiotics. The choice of antibiotics was guided by the preoperative culture. The patients received ampicillin, gentamicin, clindamycin, or combinations of these agents. Full anaerobic coverage was judged to be appropriate in 10.5% of the patients receiving prophylaxis. Although this model of selective use of antibiotic prophylaxis was successful with an infection rate of 8%, it appears to be impractical. In the choice of antimicrobial agents for prophylaxis, simpler guidelines are needed.

Streptococci, *staphylococci*, *enterococci*, *enterobacteria*, *Bacteroides* species, including *B. fragilis*, and *Clostridium* species have been isolated from gastric aspirates in patients with gastric carcinoma. These microorganisms have also been isolated from postoperative infections after gastric surgery.^{1-4,14-16,19,21} The present study has shown that in patients with gastric carcinoma the tumor itself is always colonized, often with anaerobic microorganisms, including *Bacteroides* species and *Clostridium* species.

From the present study and also from other studies it may be concluded that antimicrobial agents covering both aerobic and anaerobic bacteria, including *B. fra-*

gilis, should be used as antibiotic prophylaxis in patients with gastric carcinoma undergoing surgery.

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