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Topical Ampicillin against Wound Infection after Colorectal Surgery

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TRANSECTION of the bowel during operation for cancer of the large intestine involves a risk of microbial contamination of the wound. The incidence of wound infection is accordingly high, varying from 10 to 50 per cent.[1,11,24,25] In 1967 Nash and Hugh [19] demonstrated that topical ampicillin reduced the incidence of infections. A similar investigation in 1970 [2] produced the same findings, but suspicion was aroused that ampicillin might increase the incidence of wound dehiscence. The trial was therefore replicated and this report presents our findings in both studies.

Clinical Material

The series comprises the 240 patients who had either colonic resections or abdomino-perineal excisions of the rectum for cancer from March 1st 1969 to September 20th 1970. Of the 240, 55.4 per cent were women, and the median age was 68 years with a range from 34 to 91 years. One hundred and twelve patients had cancer of the rectum, which was treated with low anterior resection in 46 and abdominoperineal excision in 66.

We employed a triple blind, fixed dose, random allocation scheme and closed sequential analysis according to Armitage.[3] All patients had mechanical preparations of the colon by means of purgation, enemas and low residue diet. With the exception of 55 low rectal carcinomas, the patients also had Nebacetin^{R} (neomycin sulfate and bacitracin) 1.5 Gm. every 6 hours and 100 mg. chlorchinaldole every 8 hours for 3 days before operation.

Patients were included in the investigation after the diagnosis of cancer had been established and the bowel was transected. They were then allocated to either the treatment or control groups by a list of random digits. All ancillary treatment with systemic antibiotic agents were decided before allocation. After closure of the peritoneum with continuous catgut, the fascia and skin were sutured with interrupted silk. If the code prescribed ampicillin, 1 Gm. of Pentrexyl^{R} powder was applied to the subfascial and subcutaneous spaces before the fascial sutures were tied.

Two patients died postoperatively before wound infection could be evaluated. They were withdrawn from the study and other patients were substituted blindly and at random. The only other escape clause, i.e. allergy to penicillin or ampicillin, was not evoked.

Wound infections were defined as accumulations of pus occurring within 30 days of operation and requiring surgical revision.

Results

The first part of the trial was terminated when closed sequential analysis of 11 wound infections in 80 patients had demonstrated the statistically significant superiority of ampicillin ($p < 0.05$). The second part of the trial was terminated when closed sequential analysis of 14 wound infections in an additional 160 patients again had demonstrated the statistically significant superiority of ampicillin ($p < 0.05$). The probability that two con-

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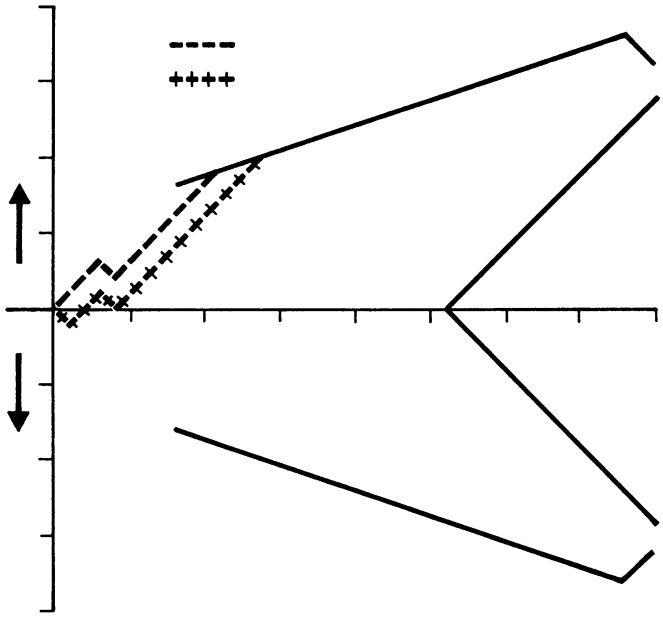

FIG. 1. Closed sequential design for comparison of the incidence of wound infections in colorectal surgery between 120 patients treated with topical ampicillin in the would and 120 controls. The first trial comprised 80 patients (————), the second trial 160 patients (++++). The boundaries are chosen with less than 5% risk of falsely finding a difference and with less than 5% risk of overlooking a true difference of magnitude, 10–30%.

secutive, identical trials could yield the same results due to chance is less than 0.0025 (Fig. 1).

Three infections occurred in the 120 wounds treated with ampicillin (2.5%), against 22 infections in 120 controls (18.3%). This difference is highly significant ($\chi^2 = 14.47$, $p < 0.0005$). The ampicillin prophylaxis has only failed in one patient (Table 3, Patient 2) who harbored autochthonous *E. coli* in his wound, originating from the bowel. The two other wound infections in the treatment group (Table 2, No. 1; Table 3, No. 1) were caused by staphylococci, resistant to methicillin (therefore also to ampicillin), that invaded the wound from the environment after operation.

Wound dehiscence occurred in nine patients in the ampicillin group and in nine patients in the control group. This difference is of course not statistically significant ($\chi^2 = 0$), but it does not prove that the frequencies are in fact identical. The power of the test is 0.58 ($\alpha = 0.05$, one tailed test, $\pi_1 = 0.075$, $\pi_2 = 0.150$, $N_1 = N_2 = 120$) which means that the risk of overlooking a doubling in the incidence of wound dehiscence from 7.5 to 15.0 per cent is 42 per cent.

Bacteriology

In 136 (74%) of 185 patients receiving preoperative oral antibiotics, stool cultures showed no aerobic or anaerobic growth. Five wound infections occurred in the group (Table 1), one due to *Staphylococcus aureus*, two to *E. coli* and one to *E. coli* and Proteus mixed; one was not swabbed for culture (Table 2).

TABLE 1. *Distribution of Patients in the Treatment and in the Control Group According to Efficacy of Anti-microbial Intestinal Preparation.*

	Ampicillin		Controls	
	No. Patients	Wound Infections	No. Patients	Wound Infections
Preparation Efficient (no growth in culture)	67	1	69	4
No or Inefficient Preparation	53	2	51	18
Total	120	3	120	22

In 104 patients with either no or inefficient intestinal preparation 20 wound infections occurred, most of them due to *E. coli* (Table 3). In 15 the peroperative intraluminal cultures contained bacteria later found in cultures from the wound.

The figures in Table 1 indicate that ampicillin substantially counteracts wound contamination in instances of no or inefficient intestinal antisepsis. No other focal or generalized infections with ampicillin-resistant microorganisms occurred in the patients, and no side effects due to ampicillin were noted.

No instances of staphylococcal enterocolitis were encountered among the patients in the trial. Particularly, coagulase-positive staphylococci were not isolated in significant number from any of the 240 intestinal cultures.

Discussion

The efficacy of preoperative antibiotic preparation of the large bowel in prevention of wound infections has been studied in a number of investigations. The views emerging are, however, controversial.[9] Recent controlled trials have demonstrated that antibiotics may reduce the

TABLE 2. *Microbial Flora of Infected Wounds in Five Patients in Whom Intestinal Antisepsis Was Efficient.*

No.	Topical Ampicillin	Microorganisms and Antibiotic Susceptibility	Origin
1	+	*Staph. aureus* (multiresistant)	Exogenous, nosocomial
2	–	*E. coli* (sens.)	Enterogenic
3	–	*E. coli* (sens.)	Probably enterogenic
4	–	*E. coli* + Proteus (both sens.)	Probably enterogenic
5	–	Suppurative wound, no culture	Unknown

The wound bacteria were all present in great number.

TABLE 3. *Microbial Flora of Infected Wounds in 20 Patients in Whom Intestinal Antisepsis was Inefficient or Was Not Carried Out.*

No.	Topical Ampicillin	Microorganisms and Antibiotic Susceptibility	Origin
1	+	*Staph. aureus* (methicillin-res.)	Uncertain, exogenous
2	+	*E. coli* (sens.)	Enterogenic, autochtonous
3–9	–	*E. coli* (sens.)	Enterogenic, autochtonous
10	–	*E. coli* (sens.)	Probably enterogenic
11	–	*E. coli* (multiresistant)	Enterogenic, nosocomial
12	–	*E. coli* (sens.) + anaer. strept.	Enterogenic
13	–	*E. coli* (sens.) + anaer. strept.	Unknown (no culture from bowel)
14	–	*E. coli* (sens.) + E. coli (partly sens.) (+) Klebsiella species	Enterogenic
15	–	*E. coli* (sens.) + Bacteroides + hemolytic streptococci gr. G	Enterogenic
16	–	*E. coli* (sens.) + anaer. strept. (+) Proteus (+) Staph. aureus	Uncertain, probably enterogenic
17	–	*E. coli* (sens.) + strept. faecal. + Staph. aureus (meticillin-res.)	Unknown (no culture from bowel)
18	–	*E. coli* (sens.) + Staph. aureus (methicillin resistant)	Mixed enterogenic and exogenous
19	–	Proteus species + Klebsiella species (both multiresistant)	Enterogenic, nosocomial
20	–	Proteus (sens.) and Candida	Enterogenic

The bacteria were present in great number except when indicated with (+) *Sens.* denotes normal broad sensitivity, including sensitivity to ampicillin.

frequency of infections,[24,25] but even in the best preparation it is still above 20 per cent.

The effectiveness of systemic antibiotics is equally controversial even in more or less controlled trials.[4,5,7,14,15,16,21,23]

The efficacy of topical antibiotics in the prevention of wound infections in abdominal surgery rests, however, on a sound experimental as well as clinical foundation.[6,8,10,12,13,17,18,19,22,26] The most important source of pathogenic bacteria in colonic surgery is the patient himself. A form of "Lister antisepsis" is, therefore, rational.[27] The particular advantages of ampicillin powder is broad spectrum bactericidal effect, ease of application, freedom of side effects and low cost.

It has been claimed, that large doses of penicillin G reduce the tensile strength of healing wounds, but Pohl and Hunt [20] were unable to prove this in an experiment on rabbits. Nor was it substantiated in this investigation.

We might have used a placebo in this trial, but fearing interference with the spontaneous frequency of infections we chose the more laborious triple-blind design, in which ampicillin was administered by one group, results evaluated and ancillary therapy prescribed by another.

Summary

Two consecutive, nearly identical controlled triple blind trials with sequential analysis demonstrated, that topical ampicillin offers a statistically significant reduction in the frequency of wound infections after operation for cancer of the colon and rectum. Side effects were not seen. An initially aroused suspicion that ampicillin increased the frequency of wound dehiscence could not be confirmed.

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