Europ. J. Cancer Vol. 16, pp. 859–869.

0014-2964/80/0601-0859 $02.00/0

Infection Prevention in Granulocytopenic Patients by Selective Decontamination of the Digestive Tract

DIRK TH. SLEIJFER,* NANNO H. MULDER,* HILLY G. de VRIES-HOSPERS,† VACLAV FIDLER,‡ HENDRIK O. NIEWEG,* DIRK van der WAAIJ† and HENDRIK K. F. van SAENE§||

**Division of Hematology, Department of Medicine, †Department of Medical Microbiology, ‡Department of Medical Statistics, §Department of Clinical Bacteriology and ||Laboratory for Public Health, University of Groningen, Oostersingel 59, Groningen, The Netherlands*

Abstract—*In a controlled prospective randomized trial we studied the effect of selective decontamination of the digestive tract (SDD) in granulocytopenic patients on the frequency of infections. By SDD it was aimed to suppress the pathogenic Gram-negative micro-organisms and yeasts without affecting the non-pathogenic anaerobic flora. This anaerobic flora was maintained intact because of its value for the colonization resistance of the gastrointestinal tract.*

SDD was accomplished by oral administration of nalidixic acid or co-trimoxazole or polymyxin E to suppress growth of aerobic Gram-negative bacteria, and amphotericin-B to inhibit growth of yeasts.

Gram-negative or yeast infections occurred in the control group 18 times in 12 patients; in the decontaminated group two times in two patients ($P<0.01$). Clinical infections occurred 15 times in 12 control patients and four times in three SDD treated patients ($0.01<P<0.05$). While nine patients in the control group died with an acquired infection none died in the SDD treated group ($P<0.01$).

It is concluded that SDD is a promising and widely applicable method of infection prevention. It decreases the need for treatment in a 'protected environment'.

INTRODUCTION

PROLONGED periods of neutropenia frequently occur in patients with aplastic anemia or with acute leukemia, either as a manifestation of the disease or of its treatment. Both the number of granulocytes and the duration of the neutropenia are related to the incidence and severity of infections [1–4]. The bacterial infections are predominantly due to Gram-negative rods [2, 4–10], which may in most cases find their port of entry in the patient's own gastrointestinal tract [7, 9, 11, 12]. However, yeasts and fungi may also cause severe infections in these patients [13]. Therefore, infection prevention has been attempted in neutropenic patients by "sterilization" of the gut either inside or outside a "protected environment" [3, 9, 11]. For sterilization of the digestive tract one or more of the following oral non-absorbable antibiotics have been used: gentamicin, vancomycin, cephaloridin and neomycin. The dosages of these oral antibiotics are such that not only the potentially pathogenic microorganisms but also the non-pathogenic anaerobic part of the flora is suppressed or eliminated [14–17]. In animal as well as human studies this anaerobic flora has been shown to limit colonization of the digestive tract by aerobic potentially pathogenic species and to prevent overgrowth by such microorganisms [18]. The potentially pathogenic Gram-negative flora of the digestive tract (*Pseudomonas aeruginosa*, Escherichiae, Citrobacter, Klebsiellae and Proteae) is not static in composition. Under normal conditions different species contaminate the digestive tract continuously by oral route [19–20]. However, most of these contaminating potentially pathogenic microorganisms colonize the g.i.-tract for short periods in low concentrations; very few can colonize, i.c. persist longer (several months). Certain species of the anaerobic flora constitute a natural barrier against newly ac-

Accepted 28 December 1979.

quired pathogenic bacteria in a manner as yet only partially understood. This barrier has been called colonization resistance [21–22].

The above mentioned antimicrobial drugs for "gut-sterilization" all lead to suppression of these "protective" anaerobic bacterial species and thereby of the colonization resistance.

A decrease of the colonization resistance considerably diminishes the threshold dose for colonization by aerobic potentially pathogenic species. This makes protective isolation necessary, particularly in a hospital environment in which resistant strains may exist.

Those drugs which suppress or eliminate potentially pathogenic microorganisms from the g.i.-tract lumen without affecting the CR-constituting anaerobic flora would leave the colonization resistance intact. We have used such drugs for SDD in neutropenic patients. Originally developed in experimental animals [23], this approach was followed in a prospectively randomized controlled study in which nalidixic acid, co-trimoxazole or polymyxin E were given either alone or in combination, but in all cases together with amphotericin-B. These antimicrobial agents in the dosages used do not affect anaerobic bacteria but can suppress growth of Enterobacteriaceae, Pseudomonodaceae and *Candida* species [24–33].

MATERIALS AND METHODS

Patients

In this prospective, randomized controlled trial, all consecutive adult patients with granulocytopenia due to bone marrow failure, acute myeloid leukemia, acute non-myeloid leukemia, or their treatment, and who were hospitalized between 01-01-1977 and 10-15-1978, were admitted to the study as soon as their peripheral granulocyte count had decreased below 1000 per mm^3. Patients were randomized to receive either oral antibiotics aimed at selective decontamination of the digestive tract (SDD) or to serve as a control group. The patients were stratified into the following three diagnostic groups in order to obtain an even distribution of these diagnoses over the SDD and the control group: aplastic anemia, acute myeloid leukemia and acute non-myeloid leukemia.

Some patients were hospitalized more than once, and each hospitalization period was considered to be a separate case.

The study period of a case was terminated upon discharge from the hospital, when three times in succession the granulocyte count was above 1000 per mm^3, or at death. Cases studied for less than 7 days, or in whom the protocol was not correctly followed, were excluded from the study.

After randomization, the choice of the antibiotics used for selective decontamination was based on the results of the microbiological surveillance and on known or presumed hypersensitivity.

Microbiological surveillance

In both the selectively decontaminated and control group, cultures from the throat and the feces were performed three times per week. Cultures were made from stools or occasionally from an anal swab.

Solely an aerobic culture was made on the specimens, with special attention given to potential pathogens such as aerobic Gram-negative rods (MacConkey agar, Merck), yeasts and fungi (Sabouraud agar, Merck), Staphylococci and Streptococci (blood agar, Oxoid) and *Haemophilus influenzae* (Levinthal agar, Oxoid).

Gram-negative rods were identified and biotyped with A.P.I. 20 E-system (A.P.I. System S.A. La Balme Les Grottes, France) [12, 34, 35].

From all different biotypes the sensitivity pattern was determined by a standard series of antibiotics currently in use for the treatment of infections. In addition the sensitivity of nalidixic acid, co-trimoxazole and polymyxin E was determined.

Surveillance of the colonization resistance

Contamination experiments with antibiotic resistant Enterobacteriaceae showed that anaerobes are responsible for the difference in the "threshold contamination dose for colonization" between conventional and antibiotic-treated or germ-free mice [21, 22]. In other experiments it was shown that mice colonized with exclusively aerobic bacteria isolated from conventional mice had no resistance to colonization with resistant Enterobacteriaceae, while human anaerobes caused an increase in the C.R. of the gastrointestinal tract in animals as well as in man [18]. Also, it was found that nalidixic acid [23], co-trimoxazole and polymyxin did not influence the C.R.

The C.R. during antibiotic therapy can be directly expressed as the log concentration of

a specific resistant microorganism [22]. If the C.R. is decreased by a complete decontamination, only a few contaminating bacteria resistant to the antibiotics used become established in unusually high concentrations in the digestive tract [36], so that a decreased C.R. is reflected in an increased concentration of resistant microorganism.

During therapy with nalidixic acid, co-trimoxazole or polymyxin, the unaffected C.R. is expressed by a constant concentration of the naturally resistant enterococci in the stool [23]. This observation was confirmed by others [37, 38].

Because the success in recovering anaerobes from the stool is largely determined by the care used in transportation and by laboratory facilities, and because isolation and identification of anaerobes are time-consuming [39], we decided to routinely use the concentration of the enterococci in the stool of the SDD patients as a practicable measurement of the colonization resistance, instead of culturing anaerobes. Wade *et al.* [40], evaluating the use of co-trimoxazole—albeit in a slightly lower dose per day—as infection prophylaxis, however, found with extensive anaerobic cultures of the stool that the anaerobes were preserved, while the aerobes were suppressed.

Selective decontamination

As the goal of this trial was to suppress aerobic Gram-negative bacteria and yeasts to undetectable concentrations, the results of the microbiological surveillance determined the choice of the antimicrobial drugs used for SDD. Differences in the sensitivity pattern of the aerobic digestive tract flora and inevitably occurring side effects, such as allergy to an antimicrobial drug, required the availability of a number of different antibiotics. At the onset of the study nalidixic acid, co-trimoxazole, polymyxin E and amphotericin-B were available for this purpose. These antibiotics leave the colonization resistance intact, and the first three can be used interchangeably.

Selective decontamination of the digestive tract (SDD) for Gram-negative rods was consequently attained with nalidixic acid (8 g/day) or with co-trimoxazole (three times a day two tablets, each tablet containing 80 mg trimethoprim and 400 mg sulfamethoxazole) or with polymyxin E (800 mg/day). For selective elimination of yeasts, an amphotericin-B suspension (2 g/day) was used. With exception of co-trimoxazole, the daily doses of the antimicrobial drugs were divided into four portions. All drugs were given orally.

Hematological surveillance

White blood cells were counted by the Coulter counter (>3000 cells per mm^3) or in a counting chamber (<3000 cells per mm^3).

Absolute levels of granulocytes were measured in the hemocytometer or calculated from a differential count and the total white blood cell count. Differential counting was performed on 300 cells in a buffy coat smear. Counting of granulocytes was repeated three times a week.

Clinical surveillance and treatment

Complete physical examination and radiographic examination of the chest and sinuses as well as microbiological investigations were performed in each patient on the day of randomization and repeated when the patient had fever. In case of a suspected infection, other specimens i.e., blood, urine and sputum were cultured. When axillary temperature rose above 38.5°C blood cultures were performed.

All patients, the selectively decontaminated as well as the control group, were treated in conventional four-bed hospital rooms under standard conditions. Standard non-sterile hospital food was provided. The patients of both groups were treated by the same group of physicians. Patients with acute non-myeloid leukemia were treated with a regime consisting of vincristine, prednisone and l-asparaginase. Daunorubicin was added when indicated. Acute myeloid leukemia was treated with a regime consisting of arabinosyl cytosine, 6-thioguanine and daunorubicin [41] or with a less aggressive therapy consisting of lower dosages of the same drugs. When indicated, supportive treatment was given. This included R.B.C., granulocytes or platelet transfusions as well as i.v. supply of broad-spectrum bactericidal antibiotics (gentamicin + carbenicillin) and local or systemic antimycotic therapy. Local antimycotic therapy consisted of oral application of amphotericin-B in orabase (R) [42], or lozenges.

Registration of acquired infections

Fever day. Registered when axillary temperature was above 38.5°C.

Microbiologically documented infection. Defined as the presence of definite signs and symptoms of infection plus the isolation and identification of pathogenic microorganisms from blood, urine, sputum or local sites.

Clinically documented infection. Defined as the presence of definite signs and symptoms of infection with negative cultures.

Non-infectious, "allergic" fever. Fever associated with a non-infectious cause such as blood transfusion, administration of anti-leukemic therapy or with an allergic reaction to drugs.

Fever of unknown origin. Defined as a fever not associated with signs or symptoms of infection and without positive cultures or manifest allergic reactions.

Statistical analysis

The end-point of the trial was determined beforehand, so that the control group and the SDD-treated group would consist of at least 50 patients each. This number was chosen so that the comparison of the percentages of infected patients ($\alpha=0.05$) could reveal a 75% reduction in the number of infected patients in the SDD group with 95% chance. Of the control group patients, 30–50% were expected to develop an infection; this expectation was based on previously treated patients and on data published by others [4–10].

When comparing the percentages of patients, the Fisher's exact test was used with $\alpha=0.05$.

RESULTS

Patients

One hundred and thirteen cases were randomized and 105 were evaluable; 20 patients were hospitalized more than once. Eight patients were not evaluable because of death or discharge from the hospital within 7 days, or because the period of SDD was less than 7 days as a result of a short period of granulocytopenia.

Pertinent details concerning the evaluated patients are given in Table 1. No important difference in the number of patients nor in the average age was found between the SDD- and the control group. In both groups the total number of weeks on study was comparable. This was also the case with the distribution of periods with granulocyte counts less than 100 per mm^3 (35%, resp. 38%), between 100 and 500 per mm^3 (35%, resp. 32%) and above 500 per mm^3 (30%, resp. 30% of the weeks of study) among the subgroups.

Microbiological surveillance

Inventory. In all 105 cases Gram-negative rods were cultured from the feces on admission; in 26 cases these microorganisms were cultured from the throatswab (13 cases in the control group). In the 105 cases investigated on admission, the fecal flora was sensitive to nalidixic acid in 96.9%, to co-trimoxazole in 78.7% and to polymyxin E in 80.4%. No cases of microorganisms resistant to all three antibiotics could be found.

Control patients. The aerobic part of the fecal population (Enterobacteriaceae, Pseudomonodaceae and *Candida* species) of the control patients was constantly changing during their hospital stay; this had also been reported by others [19, 20].

In 37 control patients Gram-negative rods were isolated from throat cultures.

Table 1. *Patient characteristics*

	Acute non-myeloid leukemia		Aplastic anemia		Acute myeloid leukemia		All diagnoses	
	SDD	control	SDD	control	SDD	control	SDD	control
Number of entrances	17	16	19	20	22	19	58	55
Excluded	1	1	1	1	3	1	5	3
Number of cases studied	16	15	18	19	19	18	53	52
Males	10	11	10	11	10	11	30	33
Females	6	4	8	8	9	7	23	19
Average age (yr)	37.2	29.7	42.9	53.5	52.5	53.3	44.6	46.6
Number of weeks of study	73.0	46.5	58.0	66.0	78.5	79.5	209.5	192.0
Weeks with granulocytes per mm^3								
$\leqslant 100$	13.0	11.0	21.5	21.5	38.0	42.0	72.5	74.5
101–500	33.0	18.5	20.0	20.5	21.5	22.5	74.5	61.5
$>501<1000$	27.0	17.0	16.5	24.0	19.0	15.0	62.5	56.0
Number of cases with infection at admission	0	1	4	3	2	4	6	8

Selective decontamination. From the 53 SDD patients, 32 started with nalidixic acid; successful decontamination (suppression of aerobic Gram-negative bacteria and yeasts to undetectable concentrations) was achieved after an average period of 6.9 days (S.D. 3.9 days). Eighteen patients started with co-trimoxazole, resulting in decontamination after 8.9 days (S.D. 4.6 days). In three patients who started with nalidixic acid, treatment had to be changed to co-trimoxazole within a couple of days because of nausea; they were decontaminated in 9.0 days (S.D. 1.7 days). None of the patients were initially treated with polymyxin E.

Fecal Gram-negative rods in SDD patients. Following successful decontamination, 16 patients remained completely free of potentially pathogenic Gram-negative rods (Enterobacteriaceae and Pseudomonodaceae) in their stool cultures. In 26 patients Gram-negative bacteria were occasionally found in low concentrations ($\leqslant 10^3$ bacteria per gram feces). These microorganisms were often different in species and biotype from those cultured during the inventory period. Usually, these isolated Gram-negative bacteria were still sensitive to the drugs used for decontamination (this had been reported separately [43], and they disappeared within 2–3 days.

In 40% of the cases in which resistant microorganisms were isolated, they also disappeared without changing the antimicrobial therapy; in 60% the antimicrobial therapy was changed, promptly resulting in negative fecal cultures.

Oropharyngeal Gram-negative rods in SDD patients. Thirteen of the 53 decontaminated patients were found to have sporadically Gram-negative rods in their throat cultures.

Of the microorganisms isolated from the throat swabs in the SDD group, 70% was sensitive to the antibiotic used for SDD. Usually the contaminating agent disappeared without change of treatment.

Evaluation of the colonization resistance in SDD patients. Since we decided to use the concentration of the enterococci in the stool of the SDD patients as a measurement of the colonization resistance, the concentration of these microorganisms naturally resistant to the antimicrobial agents used was determined in each fecal culture.

During the selective decontamination, the concentration of the enterococci in the feces remained constant and did not differ from the concentration during the inventory period.

Infection prevention

As statistical analysis on the effect of SDD on the occurrence of infections is most appropriately done by comparing the number of infected patients, these data are therefore presented separately (Tables 2 and 3) from the data on occurrence of infections in both

Table 2. The number of patients who experienced one or more infections during SDD in comparison with the control group of patients

Type of infection	Number of patients SDD	Control	*P*-value
All kinds of infections (F.U.O. included)	10	24	<0.01
Infections due to Gram-negative bacteria or yeasts	2	12	<0.01
Clinically documented infections	3	12	0.01–0.025

Table 3. Number and percentage of infected patients during various stages of granulocytopenia in the selectively decontaminated and control group

Granulocyte count	Number and percentage of infected patients SDD	Control	*P*-value
⩽100	6 (26%)	14 (56%)	0.025–0.05
101–500	2 (6%)	11 (35%)	<0.01
>500	3 (10%)	5 (17%)	>0.10
Total	10 (19%)	24 (46%)	<0.01

groups (sometimes more than one during the hospitalization of a patient) (Tables 4 and 5).

Because selective decontamination was exclusively directed against Gram-negative rods and yeasts, it was only expected to be effective in preventing infections due to these microorganisms. However, patients treated with co-trimoxazole may have been protected against Gram-positive cocci, although they were not necessarily suppressed in the g.i.-tract by the drug. Nevertheless, an overall decrease in infection frequency of more than 75% was achieved by selective decontamination of the digestive tract (Table 4). Only one Gram-negative and one yeast infection occurred in the SDD patients. One of these patients developed cellulitis due to extravasation of infusion solution and this area became infected by *Acinetobacter calcoaceticus*. This microorganism was not cultured from the stool or the throat swab at the time of infection. The other patient who could not continue the antifungal part of the SDD medication because of nausea, developed a *Candida krusei* sepsis shortly after developing overgrowth in the gut with the same organism. The incidence of Gram-positive infections was similar in both the SDD and the control group (resp. 3 and 5 infections). Also, the number of clinically documented infections was reduced in the decontaminated patients.

Table 4. The number of infections in SDD treated and in control patients

	SDD	Control
Total number of infections	9	38
Infections due to Gram-negative bacteria or yeasts	2	18
Infections due to Gram-positive bacteria	3	5
Clinically documented infections	4	15
Episodes with F.U.O.	7	7

Table 5. Occurrence of episodes with infections and fever of unknown origin during various stages of granulocytopenia in selectively decontaminated and control patients

Leucocyte count	Microbiologically proven infections		Infectious episodes caused by Gram-neg. bacteria or yeasts		Clinical Infectious episodes		Fever of unknown origin	
	SDD	control	SDD	control	SDD	control	SDD	control
Aplastic anemia								
⩽100	1	5	0	4	1	0	0	0
101–500	0	2	0	1	0	2	0	0
>500	0	1	0	1	0	0	0	0
Acute myeloid leukemia								
⩽100	2	8	1	6	2	6	1	3
101–500	0	1	0	1	1	2	3	2
>500	0	1	0	1	0	2	1	0
Acute non-myeloid leukemia								
⩽100	1	4	1	3	0	1	1	0
101–500	0	0	0	0	0	1	0	2
>500	1	1	0	1	0	1	1	0
All diagnoses								
⩽100	4	17	2	13	3	7	2	3
101–500	0	3	0	2	1	5	3	4
>500	1	3	0	3	0	3	2	0
Total	5	23	2	18	4	15	7	7

Twelve patients in the control group and five in the SDD group developed Candida lesions ($P=0.051$). Nearly all occurred in the mouth and were successfully treated with local amphotericin-B.

Most infections occurred in the control patients in the period during which they had less than 100 granulocytes, especially in patients with acute leukemia. The decrease in the infection incidence in these patients by selective decontamination is remarkable (Table 5). However, not only the number of infections was reduced, but also the number of patients

who acquired one or more infections during leukopenia was substantially reduced ($P < 0.01$). This is evident for microbiologically as well as clinically documented infections (Table 2), especially in patients with less than 500 granulocytes (Table 3).

The reduction of the number of infections by selective decontamination of the digestive tract was especially remarkable in the respiratory and urinary tract (Table 6).

Table 6. Site and number of infections in the SDD treated and control group patients

Site	Microbiologically and clinically documented infections SDD	Control
Urinary tract	0	8
Respiratory tract	3	15
Pharynx	0	1
Blood	3	8
Skin/soft tissue	3	3
Anorectal	0	1
Others	0	2

Infection prevention seems to be possible both upon first admission as well as during subsequent hospitalizations. There were 22 first hospitalizations in leukemic SDD patients, three patients developed five infections (one Gram-negative and one Gram-positive infection), while in the 20 leukemic patients without SDD 10 patients developed 22 infections (eight Gram-negative and two Gram-positive infections). During 13 subsequent hospitalizations in the SDD leukemic group two patients had two infections, while during 13 study periods in the control leukemic group three patients developed six infections (four Gram-negative and one Gram-positive infection).

The percentage of days (4%) with an axillary temperature above 38.5°C was significantly reduced in the group of SDD patients as compared to the percentage (15%) in the control group.

Death due to acquired infection. Nine of the 52 control patients but none of the 53 SDD patients died of infection ($P < 0.01$).

Side effects. Nausea occurred frequently but in no case necessitated discontinuation of SDD. One patient treated with nalidixic acid developed phototoxicity and three patients developed skin rashes. No patients developed skin rashes during treatment with co-trimoxazole alone; in one such patient with a skin rash, more than one drug could have been responsible.

DISCUSSION

In this report an effective method for infection prevention without the use of a protected environment in granulocytopenic patients is presented. The method is based on the concept of the colonization resistance [21–22]. The colonization resistance is a natural barrier maintained by certain species of the anaerobic flora which prevents colonization and overgrowth by acquired contaminating potentially pathogenic microorganisms. Thus, for selective suppression or elimination of aerobic Gram-negative bacteria as well as of yeasts and fungi, we used only those antimicrobial drugs (nalidixic acid, co-trimoxazole, polymyxin E and amphotericin B) which leave the anaerobic flora unaffected, even when applied in doses which are sufficiently high to eliminate the sensitive aerobic species.We have called this method selective decontamination of the digestive tract (SDD).

"Total bowel sterilization" was considered to be hazardous without protective environment, particularly because only CR-decreasing antibiotics such as neomycin and cephaloridin were available for this purpose. Following successful "total bowel sterilization" with these antibiotics, a substantial number of patients may acquire resistant strains of Gram-negative rods, and yeasts or fungi [44]. Even when these strains are still sensitive to the antibiotics used for total decontamination, they often persist in the bowel [45]. When the contaminant is resistant it may cause a rapid and massive overgrowth in the g.i. tract, which in turn may result in invasion and possibly a life-threatening infection [46]. As a consequence of the increased risk of acquisition of resistant strains—decreased threshold dose for colonization—total bowel sterilization must be combined with a protected environment in order to reduce the chance of an unfortunate contamination.

During selective decontamination, i.e., oral administration of drugs for which the aerobic flora was sensitive, overgrowth with orally acquired sensitive or resistant contaminants from the hospital food or other environmental sources did not occur in our study. As our patients (the control group as well as the SDD group) were treated on an open ward and received the normal, non-sterile hospital food, contamination by new exogenous Gram-

negative rods will have occurred daily. This was confirmed by our routine three weekly culturing which showed continuously appearing and disappearing Gram-negative microorganisms in the throats of the control patients as well as a changing potentially pathogenic flora in the stool of these patients during their hospital stay.

In our SDD treated patients the contamination by exogenous Gram-negative microorganisms has only occasionally resulted in positive cultures of oropharynx swabs and feces. Furthermore, positive cultures regarding Gram-negative bacteria of throat swabs and feces in no case persisted for a week or longer (colonization), not even in those cases in which the contaminating microorganisms were resistant to the antimicrobial drugs used. This observation together with a constant concentration of the enterococci in the stool strongly suggests that the colonization resistance in our SDD patients remained intact, preventing persistence after the acquisition of new microorganisms. These results also indicate that an intact C.R. is equally effective for both resistant and sensitive contaminating microorganisms. In a separate paper comprehensive data are published on the bacteriological data [43].

Two of the antimicrobial drugs used in our study, co-trimoxazole and nalidixic acid, are well absorbed and may, in addition to their SDD effect, have had an additional systemic effect. The reduced number of positive cultures in patients with clinical infections could be due to the systemic effect of co-trimoxazole and nalidixic acid. However, this potential bias on the evaluation of SDD *per se* does not change our results. Furthermore, it is noteworthy that the number of clinical (not bacteriologically documented) infections was also reduced by SDD.

A possible disadvantage of the use of these prophylactic antimicrobial drugs could be the development of resistance among Gram-negative bacteria. However, in these patients this was not found to occur significantly [43], although incidental acquisition of resistant strains did occur. In no case did these invariably short "colonizations" lead to an infection or to an increase of episodes with "fever of unknown origin".

An obvious side effect of nalidixic acid and to some extent of amphotericin-B was the occurrence of nausea. This was of particular importance in the patients who were given chemotherapy with cytostatic drugs, which in themselves usually cause nausea and vomiting.

The anti-fungal part of the SDD medication consisted of oral amphotericin-B suspension. This was given in order to prevent yeast colonization in the gastrointestinal tract, which might lead to yeast infections. The crux of yeast infections during infection prophylaxis with co-trimoxazole has been reported by Hughes [47]. However, Hughes used considerably higher doses of 12 tablets per day, aimed at prevention of *Pneumocystis carinii* infection. High doses of co-trimoxazole may affect the CR and therefore enhance Candida colonization. As judged from the occurrence of yeast infections (mainly Candida lesions in the oropharynx), a reduction of these lesions was seen in the SDD positive patients ($P = 0.051$). This means that as a result of both the maintenance of a good colonization resistance as well as of oral amphotericin-B treatment. Candida infections did not constitute a major problem.

The beneficial effects of selective decontamination of the digestive tract with nalidixic acid or co-trimoxazole or polymyxin were recently confirmed by others. In the Pneumocystis prophylaxis studies of co-trimoxazole by Hughes *et al.* [47] it was found that in children with acute lymphocytic leukemia, the use of co-trimoxazole prevented Gram-negative bacterial infections as well as Pneumocystis. Recently, the results of prophylactic co-trimoxazole in hospitalized granulocytopenic patients were published by Gurwith *et al.* [48]. However, only Guiot and Van Furth [49] used antimicrobial agents based on the concepts of selective decontamination in infection prevention.

Since we have shown that SDD can be effective in infection prevention and can decrease the number of deaths related to infection, we feel that this method may be preferable to total decontamination plus protective isolation. This view is primarily based on differences in the patient's comfort in treatment, convenience for the staff and in the cost. In our opinion SDD appears to be a very promising and possibly more widely applicable method for infection prevention in granulocytopenic patients.

Acknowledgement—We thank B. Houwen, M.D. for his critical advice. we gratefully acknowledge the technical assistance of Miss Tine Polling and Mrs. W. J. A. Bruins-van der Weij.

REFERENCES

1. G. P. Bodey, M. Buckley, Y. S. Sathe and E. J. Freireich, Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Ann. intern. Med.* **64,** 328 (1977).
2. H. Y. Chang, V. Rodriguez, G. Narboni, G. P. Bodey, M.A. Luna and E. J. Freireich, Causes of death in adults with acute leukemia. *Medicine* **55,** 259 (1976).
3. V. Rodriguez, G. P. Bodey, E. J. Freireich, K. B. McCredie, J. U. Gutterman, M. J. Keating, T. L. Smith and E. A. Gehan, Randomized trial of protected environment-prophylactic antibiotics in 145 adults with acute leukemia. *Medicine* **57,** 253 (1978).
4. G. P. Bodey, V. Rodriguez, H. Y. Chang and G. Narboni, Fever and infection in leukemic patients. A study of 494 consecutive patients. *Cancer (Philad.)* **41,** 1610 (1978).
5. P. C. Vincent and G. C. de Gruchy, Complications and treatment of acquired aplastic anaemia. *Brit. J. Haematol.* **13,** 977 (1967).
6. S. Davis and A. D. Rubin, Treatment and prognosis in aplastic anaemia. *Lancet* **i,** 871 (1972).
7. S. C. Schimpff, V. M. Young, W. H. Greene, G. D. Vermeulen, M. R. Moody and P. H. Wiernik, Origin of infection in acute nonlymphocytic leukemia. Significance of hospital acquisition of potential pathogens. *Ann. intern. Med.* **77,** 707 (1972).
8. D. M. Williams, R. E. Lynch and G. E. Cartwright, Drug-induced aplastic anaemia. *Semin. Haematol.* **10,** 195 (1973).
9. G. P. Bodey and V. Rodriguez, Infections in cancer patients on a protected environment-prophylactic antibiotic program. *Amer. J. Med.* **59,** 497 (1975).
10. M. Valdivieso, Bacterial infection in haematological diseases. *Clin. Haematol.* **5,** 299 (1976).
11. A. S. Levine, S. E. Siegel, A. D. Schreiber, J. Hauser, H. Preisler, I. M. Goldstein, F. Seidler, R. Simon, S. Perry, J. E. Bennett and E. S. Henderson, Protected environments and prophylatic antibiotics. A protective controlled study of their utility in the therapy of acute leukemia. *New Engl. J. Med.* **288,** 477 (1973).
12. D. van der Waaij, T. M. Tielemans-Speltie and A. J. Roeck-Houben, Infection by and distribution of biotypes of Enterobacteriaceae species in leukaemic patients treated under ward conditions and in units for protective isolation in seven hospitals in Europe. *Infection* **3,** 188 (1977).
13. J. A. Krick and J. S. Remington, Opportunistic invasive fungal infections in patients with leukaemia and lymphoma. *Clin. Haematol.* **5,** 249 (1976).
14. A. M. Walter and L. Heilmeyer, *Antibiotika-Fibel*, p. 280. Georg Thieme Verlag, Stuttgart. (1975).
15. A. M. Walter and L. Heilmeyer, *Antibiotika-Fibel*, p. 370. Georg Thieme Verlag, Stuttgart. (1975).
16. A. M. Walter and L. Heilmeyer, *Antibiotika-Fibel*, p. 421. Georg Thieme Verlag, Stuttgart. (1975).
17. A. M. Walter and L. Heilmeyer, *Antibiotika-Fibel*, p. 520. Georg Thieme Verlag, Stuttgart. (1975).
18. D. van der Waaij, J. M. Vossen, C. Korthals Altes and C. Hartgrink, Reconventionalization following antibiotic decontamination in man and animals. *Amer. J. clin. Nutr.* **30,** 1887 (1977).
19. R. A. Shooter, E. M. Cooke, H. Gaya, P. Kumar, N. Patel, M. T. Parker, B. T. Thom and D. R. France, Food and medicaments as possible sources of hospital strains of *Pseudomonas aeruginosa*. *Lancet* **i,** 1227 (1969).
20. E. M. Cooke, R. A. Shooter, P. J. Kumar, S. A. Rousseau and A. L. Foulkes, Hospital food as a possible source of *Escherichia coli* in patients. *Lancet* **i,** 436 (1970).
21. D. van der Waaij, J. M. Berghuis-de Vries and J. E. C. Lekkerkerk-van der Wees, Colonization resistance of the digestive tract in conventional and antibiotic-treated mice. *J. Hyg.* **69,** 405 (1971).
22. D. van der Waaij and J. M. Berghuis-de Vries, Determination of the colonization resistance of the digestive tract of individual mice. *J. Hyg.* **72,** 379 (1974).

23. D. VAN DER WAAIJ and J. M. BERGHUIS-DE VRIES, Selective elimination of Enterobacteriaceae species from the digestive tract in mice and monkeys. *J. Hyg.* **72,** 205 (1974).
24. A. M. WALTER and L. HEILMEYER, *Antibiotika-Fibel*, p. 140. Georg Thieme Verlag, Stuttgart. (1975).
25. A. M. WALTER and L. HEILMEYER, *Antibiotika-Fibel*, p. 149. Georg Thieme Verlag, Stuttgart. (1975).
26. J. W. KISLAK, The susceptibility of *Bacteroides fragilis* to 24 antibiotics. *J. infect. Dis.* **125,** 295 (1972).
27. J. E. ROSENBLATT and P. R. STEWART, Lack of activity of sulfamethoxazole and trimethoprim against anaerobic bacteria. *Antimicrob. Ag. Chemother.* **6,** 93 (1974).
28. J. E. GARCIA SANCHEZ, A. C. GOMEZ GARCIA, J. PRIETO PRIETO and M. C. SAENZ GONZALEZ' Susceptibility of *Bacteroides fragilis* to 62 antimicrobial agents. In *Current Chemotherapy. Proceedings of the 10th International Congress of Chemotherapy.* (Edited by W. Siegenthaler and R. Lüthy) p. 289. American Society for Microbiology, Washington D.C. (1978).
29. J. E. ROSENBLATT and P. R. STEWART, Combined activity of sulfamethoxazole, trimethoprim, and polymyxin B against Gram-negative bacilli. *Antimicrob. Ag. Chemother.* **6,** 84 (1974).
30. T. A. STAMEY, M. CANDY and G. MIHARA, Prophylactic efficacy on nitrofurantoin macrocrystals and trimethoprim-sulfamethoxazole in urinary infections. Biologic effects on the vaginal and rectal flora. *New Engl. J. Med.* **296,** 780 (1977).
31. R. N. GRÜNEBERG, J. M. SMELLIE, A. LEAKEY and W. S. ATKIN, Long-term low-dose co-trimoxazole in prophylaxis of childhood urinary tract infection: bacteriological aspects. *Brit. med. J.* **2,** 206 (1976).
32. T. A. STAMEY and J. BRAGONJE, Resistance to nalidixic acid. A misconception due to underdosage. *J. Amer. med. Ass.* **236,** 1857 (1976).
33. A. KUCERS and N. MCK. BENNETT, *The Use of Antibiotics.* p. 561. William Heinemann, London (1977).
34. J. A. WASHINGTON, P. K. W. YU and W. J. MARTIN, Evaluation of accuracy of multitest micromethod system for the identification of Enterobacteriaceae. *Appl. Microbiol.* **22,** 267 (1971).
35. P. B. SMITH, K. M. TOMFOHRDE, D. L. RHODEN and A. BALOWS, API-system: a multitube method for identification of Enterobacteriaceae. *Appl. Microbiol.* **24,** 449 (1972).
36. D. VAN DER WAAIJ, J. M. BERGHUIS-DE Vries and J. E. C. LEKKERKERK-VAN DER WEES, Colonization resistance of the digestive tract and the spread of bacteria to the lymphatic organs in mice. *J. Hyg.* **70,** 335 (1972).
37. T. A. STAMEY and G. MIHARA, The effect of nalidixic acid on faecal and vaginal carriage of Enterobacteriaeceae in 54 women. In *New Criteria for Antimicrobial Therapy.* (Edited by D. van der Waaij and J. Verhoef) p. 234. Excerpta Medica, Amsterdam (1979).
38. G. MIHARA and T. A. STAMEY, The effect of low-dose co-trimoxazole on rectal and vaginal flora. In *New Criteria for Antimicrobial Therapy.* (Edited by D. van der Waaij and J. Verhoef) p. 243. Excerpta Medica, Amsterdam (1979).
39. S. L. GORBACH and J. G. BARTLETT, Anaerobic infections. *New Engl. J. Med.* **290,** 1289 (1974).
40. J. WADE, S. SCHIMPFF, M. HARGADON, J. BENDER, J. AISNER, V. YOUNG and P. WIERNIK, Trimethoprim-sulfamethoxazole: infection prophylaxis during granulocytopenia. Proceedings 15th annual meeting *Amer. Soc. clin. Oncol.* **20,** 350 (1979).
41. R. P. GALE and M. J. CLINE, High remission-induction rate in acute myeloid leukaemia. Lancet **i,** 497 (1977).
42. H. G. DE VRIES-HOSPERS and D. VAN DER WAAIJ, Amphotericin B concentrations in saliva after application of 2% amphotericin B in Orabase. *Infection* **6,** 16 (1978).
43. H. G. DE VRIES-HOSPERS, D. VAN DER WAAIJ, D. Th. SLEIJFER, N. H. MULDER, H. O. NIEWEG and H. K. F. VAN SAENE, Selective decontamination of the digestive tract in granulocytopenic patients; occurrence of resistance. In *New Criteria for Antimicrobial Therapy.* (Edited by D. van der Waaij and J. Verhoef) p. 117. Excerpta Medica, Amsterdam (1979).

44. J. Dankert, D. van der Waaij, W. Gaus, H. Gaya, D. Krieger and G. Linzenmeier, Protective isolation and antimicrobial decontamination in patients with high susceptibility to infection. *Infection* **6,** 175 (1978).
45. G. P. Bodey and V. Rodriguez, Protected environment-prophylactic antibiotic programmes; microbiological studies. *Clin. Haematol.* **5,** 395 (1976).
46. S. C. Schimpff, W. H. Greene, V. M. Young, C. L. Fortner, L. Jepsen, N. Cusack, J. B. Block and P. H. Wiernik, Infection prevention in acute non lymphocytic leukemia. *Ann. intern. Med.* **82,** 351 (1975).
47. T. W. Hughes, S. Kuhn, S. Chaudhary, S. Peldman, M. Verzosa, R. J. A. Aur, L. Pratt and S. C. George, Successful chemoprophylaxis for *Pneumocystis carinii pneumonitis*. *New Engl. J. Med.* **297,** 1419 (1977).
48. M. J. Gurwith, J. L. Brunton, B. A. Lank, G. K. M. Harding and A. R. Ronald, A prospective controlled investigation of prophylactic trimethoprim-sulfamethoxazole in hospitalized granulocytopenic patients. *Amer. J. Med.* **66,** 248 (1979).
49. H. F. L. Guiot and R. van Furth, Partial antibiotic decontamination. *Brit. med. J.* **1,** 800 (1977).