Tokai J Exp Clin Med., Vol. 10, No. 2, 3, pp. 197–204, 1985

Problems and Results of Selective Decontamination in Leukemia Patients

Ingo GÜNTHER, Rita BRIJMOHAN-GÜNTHER, Günter KUNDT*, Ursula KABEN** and Renate-Maria TESELER***

*Clinic of Internal Medicine, *Center for Medical Statistics, **Clinic of Dermatology, ***Center for Stomatology, Wilhelm-Pieck-University Rostock, G.D.R.*

Infectious complications play a major part during the cytostatic treatment of patients suffering from acute leukemia, as well as in bone marrow transplantations. For infection prevention, the method of selective decontamination (SD) of the digestive tract was used. This procedure eliminates the potentially pathogenic aerobic bacteria and yeasts while leaving the anaerobic intestinal microflora unaffected. The protocol of the Gnotobiotic Project Group was used in treating 33 patients with SD and the results were compared with those from a comparable control group consisting of cases selected from files who had been treated without SD in the past.

A statistical difference was obtained in favor of the SD patients regarding frequency and severity of infection, time between admission and the first signs of infection, days febrile, and in the additional necessity of antibiotics ($p < 0.01$). SD involves in addition to a scheduled intake of tablets, microbiological surveillance, personal hygiene and an intact hemostasis, and optimal results can be obtained given the help of the patients' compliance. SD has won a secured place in treatment tailored upon the pathophysiological concept of infection prevention, even though there are problems remaining, e.g., gram-positive cocci, yeasts and infection of the oropharynx.

INTRODUCTION

The association of life-threatening infections with prolonged decreased granulocytopenia due either to bone marrow failure, acute leukemia or its treatment is well known. The risk of infection increases with the duration and degree of granulocytopenia. Also important is the disposition of the damaged orogastrointestinal mucosa due to cytostatics. Both encourage the easy entry of colonizing bacteria and therefore allow the rapid spread of infection with frequent bacteremia (1). The majority of the infecting organisms are gram-negative bacilli, gram-positive cocci and yeasts (5). The alimentary canal is the obvious source of colonizing microorganisms and this site has been the focus of most recent preventive approaches. Different regimens were designed to suppress the intestinal flora as much as possible before onset of infection (13). This can be obtained by total decontamination. It eradicates the potentially pathogenic microorganisms as well as the much less pathogenic anaerobes. With the concept of colonization resistance (CR), van der Waaij was able to make clear that the presence of the normal anaerobic flora undertakes a protective function and plays the key role in controlling and limiting the potential for overgrowth of pathogenic species which might colonize the gut (11). The method of SD is based on the concept of CR and its validity has been proven in animal experiments (10).

Acute leukemia could be a clinical model to study the problems of infection prevention. In a retrospective report of 295 patients suffering from acute leukemia who were treated in our hospital between 1962 and 1977, the death rate due to infectious complications was 71%.

MATERIALS AND METHODS

We treated 33 patients during remission in-

Ingo GÜNTHER, Clinic of Internal Medicine, Wilhelm-Pieck-University Rostock, 2500 Rostock 1, Ernst-Heydemann-Street No. 6, G.D.R.

duction therapy with SD for infection prevention in the conventional ward without isolation. SD can be accomplished with both absorbable (cotrimoxazole, nalidixic acid) and nonabsorbable (polymyxin, neomycin, nystatin) antimicrobial agents. The drugs we used for SD were polymyxin M (Medexport Moscow, USSR) 2 mill. U = 0.25 g/day and fungicidin (Spofa, Czechoslovakia) 4–6 mill. U/day in a combination with berlocombin (VEB Berlin Chemie, GDR) 6 tablets/day (trimethoprim 480 mg, sulfameracin 720 mg) or nalidixic acid 6–8 g/day (nevigramon, Chinoin A.G. Budapest, Hungary) or neomycin 1 g/day (mycerine, Medexport Moscow, USSR). The number of tablets ranged from 17–40 daily in the different schemes. In comparison to the protocol outlined by the Gnotobiotic Project Group of the E.O.R.T.C., we administered berlocombin instead of cotrimoxazole (2400 mg sulfamethoxazole, 480 mg trimethoprim) and polymyxin M in a lower dosage (0.25 g instead of 0.6 g) in place of polymyxin B.

We raised objections to a randomized prospective clinical trial because of ethical reasons. Our control group was therefore a historical one. These were patients who were treated in our department in the last 8 years. Patient registrations were searched systematically in order to find patients for the control group comparable to group SD (I). These patients did not differ in sex, age, diagnosis, cell type, stage of disease and the presence of infection upon admission. We found 20 SD patients in conformity to 16 control patients. The other 13 SD patients comprise SD group (II). Their data are represented in Table 1. The decontamination phase started as soon as possible after admission and before instituting polychemotherapy. The criteria for termination of the decontamination was a neutrophil count above 1.5 Gpt/l and when no further remission induction therapy was considered.

For the remission induction therapy, we gave an aggressive regimen of polychemotherapy. For acute myeloid leukemia (age up to 60 years), the TAD regimen (daunorubicin, cytosine-arabinoside and thioguanin) or for the older patients, the COAP regimen (cyclophosphamide, oncovin, cytosine-arabinoside and prednisolone) was utilized. For other forms of leukemia, a combination of oncovin, daunorubicin, l-asparaginase and prednisolone was administered.

Bacteriological and mycological surveillance was done once a week. In most cases we also determined the level of beta-aspartylglycine in fecal supernatant on a weekly basis.

RESULTS

Microbiological Monitoring

Enterobacteriaceae, Pseudomonas spp. and *Staphylococcus aureus* were eliminated from the fecal samples after one week of SD. During this time we found that in the feces, enterococci were present in high concentrations (10^6 – 10^8 CFU/g) as well as *Staphylococcus epidermidis* and aerobic spore forms. Eight patients had negative cultures during the prophylaxis period. During SD after the first negative culture was obtained, we isolated 88 rods. Table 2 lists the bacteria found and Fig. 1 relates their frequency, concentration and susceptibility. 77.3% of the bacteria were gram negatives, of which 22.7% were *Staphylococcus aureus.* In 78.4% of the rods, the concentration was lower than 10^5 CFU/g. With the use of gentamicin, ampicillin and oxacillin, the resistance rate was reduced from 14 to 4 samples with gram-negative rods (*Pseudomonas* sp., 10^4 CFU/g in 2 patients) and from 4 to 1 sample with *Staphylococcus aureus* (10^3 CFU/g). High fecal bacteria concentration and first, second and third evidence are important for differentiating the contamination and colonization rates. The connection between the isolated rods, their frequency and concentration before or at the onset of infection is shown in Table 3.

The SD combination was monitored in cases of drug-resistant strains in concentrations higher than 10^5 CFU/g feces. The drug regimen was modified as indicated by the results from bacteriological surveillance, clinical course, intolerance of medication or allergic reactions. Sixteen out of 33 patients received the initial SD scheme during the entire granulocytopenic period and the initial SD drugs were replaced once in 13 cases, twice in 4 cases.

We analyzed 350 oral washings bacteriologically. The total CFU/ml were $< 10^5$ in 27, 10^5 in 32 and $> 10^5$ in 291 samples. The following strains were most commonly encountered: α-haemolytic *Streptococcus,* β-

haemolytic *Streptococcus, Staphylococcus epidermidis, Candida albicans, Neisseria* species, enterococci and aerobic spore forms. Gram negatives were seldom found. There were no quantitative estimations of the different strains. During infection in the oropharynx, we found α-and β-haemolytic streptococci.

As we did not have the possibility of examining the indicator strains of anaerobes, the beta aspartylglycine in fecal supernatant was assessed instead. This was done in collaboration with Dr. J. Welling, University Hospital Groningen, The Netherlands. The results are shown in Table 4.

The mycological surveillance during SD is summarized in Table 5. Four of 7 patients, who had a positive precipitation reaction, died from mycosis.

Clinical Results

Fifty percent of the SD patients were without infections. Major infections occurred in 30%, and minor infections in 20%. Among the 16 patients in our comparative control group, 15 had infections (11 patients with major, 4 patients with minor infections).

The index of infections/patient was 2.1 for the control and 0.75 for the SD groups. We did not observe septicemias with gram negatives. In summarizing the acquired infections we came to the conclusion that infections by yeasts and gram positives and infection of the oropharynx are the most frequently encountered complications (Table 6).

The time interval between admission and the first sign of acquired infection was statistically significant by the logrank test in favor of SD (I, II) ($x^2 = 19.62$, d.f. = 1, $P < 0.001$) (Fig. 2).

We also obtained a statistical significance ($P < 0.01$) in favor of the SD groups for days febrile, for days requiring the additional use of systemic antibiotics, for acquired infections, for the rate of remission and for survival.

Ten SD patients died between day 55 and day 180 of treatment: 3 due to cerebral hemorrhage, 2 to pneumonia, 1 due to pneumonia and exacerbation of tuberculosis, 3 to candidiasis and 1 due to a mucor-plus candida mycosis.

DISCUSSION

For the last 80 years, it has been well known that the gastrointestinal microflora could prevent or provoke endogenous infections (6).

Since 1970, several approaches have been designed to reduce the risk of infection by suppressing the gastrointestinal flora using oral nonabsorbable antibiotics (13). This method is effective in reducing infection, but is dangerous for the patient in a normal conventional ward (13). There are few disadvantages to this method, and important steps were taken to clarify and prevent the few dangers that existed. Van der Waaij's concept showed clearly the value of a stabilized CR (10, 11). It was also established that reverse isolation was not necessary. In comparing total with selective decontamination during induction therapy for acute leukemia, Bhaduri and coworkers drew results which indicated no difference (2). And it has been reported that during SD, granulocyte transfusions were seldom required (3). All evidence indicate that the best results can be achieved with the patients' compliance, regular intake of tablets, personal hygiene and microbiological monitoring. Microbiological surveillance during SD yields information regarding the contamination rate, the colonization rate and that crucial to antibiotic selection in cases of fever or infection. The rules for antibiotic therapy in granulocytopenic infections as recalled by Schimpff, Klastersky, Pizzo and others are valid during SD. Most of the antibiotics were seen to destroy the CR indicating that SD must be continued in the interest of thwarting the potentially pathogenic rods which try to colonize. Our own experience show that a reliable elimination of *Enterobacteriaceae* is not possible using the lower dosage of polymyxin in our scheme because of its inactivation (11). Yeast cell reduction was ineffective using the 4–6 mill. U fungicidin we employed, and therefore it is necessary to apply more effective fungistatics.

The beta-aspartylglycine determination has been proven as an indicator of disturbed anaerobic flora (12). Even though no such reason was present, beta-aspartylglycine was sometimes assessed as positive after administration of antibiotics or cytostatics.

No toxic side effects on liver or kidney function or pathological serum levels of folic acid were observed.

Our results of SD are similar to those from previously reported studies (2, 4, 5, 7).

Schmeiser published results indicating that total and selective decontamination were very effective in preventing severe infections in patients receiving allogeneic bone marrow transplantations (9). In their study, total decontamination was found to be more effective in infection prevention and in reduction of the incidence and severity of GvH disease in bone marrow transplantation. This differs from the experience in remission induction therapy.

SD has won a place in the therapeutic concept for infection prevention, even though there are still problems to be conquered, e.g., gram positives, yeasts and infection of the oropharynx. And while working to directly resolve these problems, we are also aiming to find new drugs to breach these gaps.

It is believed that studies from the standpoint of "correlative microbiology" can determinate the complicated physiological phenomena concerned in the interrelationship between the microflora and the host in order to shed light on these problems (8).

CONCLUSION

SD is a practicable, effective method for infection prevention and has won a place in the therapeutic program for acute leukemia. An optimal result can be obtained given the patients' compliance, personal hygiene and microbiological monitoring.

ACKNOWLEDGEMENT

We thank Mrs. Dr. C.M. Bohnenstengel and Mrs. C. Petzold from the District Hygiene Institute of Rostock/GDR (director: OMR Dr. U. Thielebeule) for the bacteriological investigations.

REFERENCES

1) Berg R: Factors influencing the translocation of bacteria from the gastrointestinal tract. In: Recent Advances in Germfree Research (eds., S. Sasaki *et al.*). Tokai University Press, Tokyo, pp. 411–418, 1981
2) Bhaduri S *et al*: Infection prophylaxis in acute leukemia patients. Comparison of selective and total antimicrobial decontamination of the gastrointestinal tract. Folia haematol 109: 377–389, 1982
3) Daenen S: Granulocyte transfusions and the impact of selective decontamination of the digestive tract. In: Applied Gnotobiology for Infection Prevention in the Immunocompromised Host (eds., I. Günther *et al.*) Wilhelm-Pieck-University Rostock, pp. 138–142, 1984
4) Dekker A *et al*: Selective decontamination of the digestive tract for the prevention of infection in acute leukemia, VIII. International Symposium on Germfree Research, Notre Dame, 1984
5) de Vries-Hospers H: Microbiological approach of selective decontamination of the digestive tract: a method of infection prevention in granulocytopenic patients. In: Applied Gnotobiology for Infection Prevention in the Immunocompromised Host (eds., I. Günther *et al.*) Wilhelm-Pieck-University Rostock, pp. 48—61, 1984
6) Küster E: Die bedeutung der normalen darmbakterien für den gesunden menschen. In: Handbuch der pathogenen Mikroorganismen (eds., W. Kolle *et al.*) Gustav Fischer Jena, Vol. 6, pp. 468–482, 1913
7) Kurrle E *et al*: Antimicrobial prophylaxis in acute leukemia: prospective randomized study comparing two methods of selective decontamination. Klin Wochenschr 61: 691–698, 1983
8) Ozawa A: Infection and indigenous bacterial flora. Asian med J 26: 105–119, 1983
9) Schmeiser Th *et al*: Application of antimicrobial prophylactic treatment to the prevention of infection and graft versus-host disease in allogeneic bone marrow transplantation. Exp hematol 12 (suppl. 15): 105—106, 1984
10) van der Waaij D: The colonization resistance of the digestive tract in man and animals. Zbl Bakt Suppl 7: 155–161, 1979
11) van der Waaij D: "Antibiotic Choice: The Importance of Colonization Resistance". Research Studies Press, Chichester-Singapore, pp 1–123, 1983
12) Welling GW: Beta-aspartylglycine, an indicator of decreased colonization resistance? In: New Criteria for Antimicrobial Therapy (eds., D. van der Waaij *et al.*) Excerpta Medica, Amsterdam-Oxford, pp. 65–73, 1979
13) Zinner St H: Prophylaxis of bacterial infections with oral antibiotics in neutropenic patients. Schweiz med Wschr 113 (Suppl. 14): 7–14, 1983

Table 1 Characteristics of patients

	Comparative Control Group	SD(I)	SD(II)
Number of cases	16	20	13
female	11	14	10
male	5	6	3
Age (years)			
range	16-75	17-79	19-74
median	42.4	44.1	52.9
Myeloid leukemia	12	15	12
Non-myeloid leukemia	4	5	1
first induction therapy	12	16	12
first relapse therapy	2	2	1
first blast crisis (CML)	1	1	-
second blast crisis (CML)	1	1	-
Infection upon admission	7	8	5
major	3	3	4
minor	4	5	1
FUO	2	3	0
Treatment period (days)			
total	1067	1724	1154
$\bar{x}$	66.7	86.2	88.8
minimum	23	46	52
maximum	122	210	173
% of granulocytopenia over the total period (Gpt/1 = 10^9/1)			
<0.1	10.5	23.7	28.4
0.101-0.5	22.63	23.3	23.2
0.501-1.0	12.3	16.3	14.9
1.001-1.5	10.4	12.4	7.7
>1.501	44.53	24.3	25.8

Table 2 Results of bacteriological surveillance of the feces during SD

Number of patients monitored	33
Patients with negative cultures during SD	8

Number of Fecal Samples with Proven Rods during SD after the First Negative Culture

Rods	No. of cultures	No. of patients
Staphylococcus aureus	20	12
Pseudomonas spp.	7	2
Pseudomonas aeruginosa	13	4
Pseudomonas fluorescens	3	1
Proteus morgagni	9	4
Proteus rettgeri	7	3
Proteus mirabilis	13	3
Proteus vulgaris	2	2
Escherichia coli	9	5
Enterobacter cloaceae	1	1
Klebsiella pneumoniae	4	3

Table 3 Occurrence, frequency and concentration of rods in the feces during SD

	Evidence was Obtained			
	successively ≥ 3 times		individually not more than two times	
	log conc.		log conc.	
Rods	≤ 5	> 5	≤ 5	> 5
S. aureus	2	-	12 (2)	1 (1)
Pseudomonas sp.	4	-	7	-
Proteus sp.	1	3 (2)	7	4
E. coli	-	1	3	2
K. pneumoniae	-	-	2	-

( ) Proven before or at the beginning of infection (angina, pneumonia) without proven connection

Table 4 Determination of beta-aspartylglycine during SD

Samples examined	268	Patient number	29
Total negative samples	204	pat. with neg. samples	15
Total positive samples	64	pat. with 2 pos. samples	5
samples weak	14	pat. with 3 ~ 4 pos. samples	4
samples positive	48	pat. with 5 pos. samples	5
		pat. with only pos. samples	2

Positive after antibiotics in 7 patients
Positive with and without antibiotics in 3 patients
Positive without antibiotics in 4 patients

Table 5 Mycological surveillance during SD

Patient Number	32
Positive cultures	
mouth	44.5%
sputum	45.3%
urine	13.6%
feces	7.4%
Serological results	
Movement of cell agglutination (titer)	
"anergic"*	2
constant	24
increased	2
decreased	4
increased as well as decreased	1
Precipitation reaction positive	7
Patients with systemic mycosis (autopsy findings)	4

* No specific antibody reaction (titer always below 1 : 40)

Table 6 Acquired infections during hospitalization

	Comparative Control Group	SD (I)	SD (II)
Stomatitis (local)	8	3	-
Periodontitis	2	1	-
Sinusitis	-	1	-
Angina	-	2	3
Bronchitis	1	-	1
Skin infiltration (ulcus, abscess, furuncle)	7	2	1 -
Cystitis	3	1	-
Enterocolitis	2	-	-
Gall bladder hydrops	1	-	-
Septicemia (blood culture*):	7	1	2
Escherichia coli	1	-	-
Pseudomonas aeruginosa	1	-	-
Staphylococcus aureus	2	-	-
Staphylococcus epidermidis	-	1	-
Candida albicans	2	-	1
negative	1	-	-
Pneumonia	3	1	5
Exacerbation of tuberculosis	-	-	1
Lung abscess	1	-	-

* Blood cultures were examined by the institute for Medical Microbiology and Epidemiology (Director: OMR Prof. Dr. sc. med. G. Naumann) of the Wilhelm-Pieck-University Rostock/GDR)

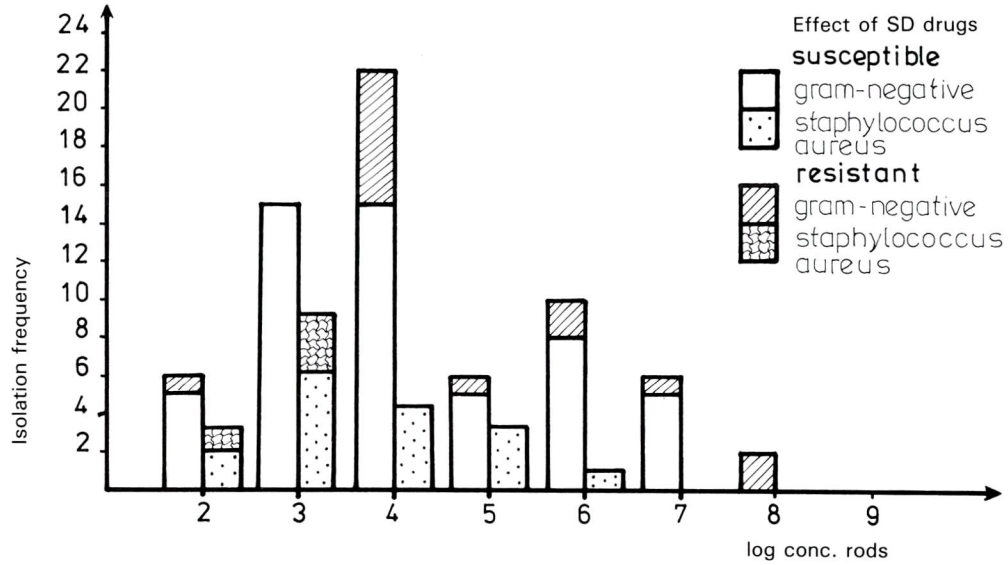

Fig. 1 Frequency, concentration and susceptibility of gram-negative rods (n = 67) and *Staphylococcus aureus* (n = 20) in the feces after the first negative fecal sample

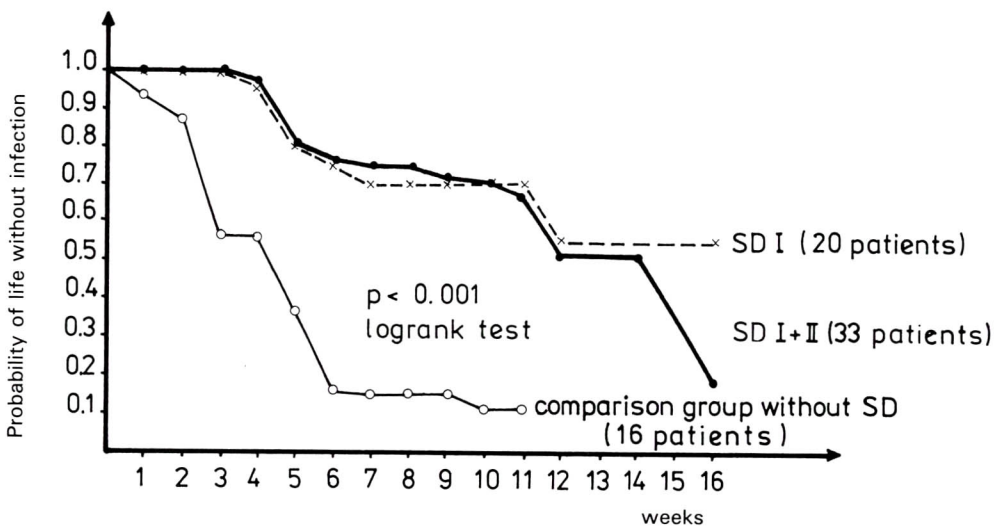

Fig. 2 Time interval between admission and the first signs of acquired infection