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Laminar Air Flow Versus Barrier Nursing in Marrow Transplant Recipients*

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Summary. Forty-eight patients with acute leukaemia in relapse ($n = 14$), acute leukaemia in complete remission ($n = 19$), chronic myeloid leukaemia ($n = 8$) or severe aplastic anaemia ($n = 7$) received a marrow transplant. The first 26 patients were nursed in laminar-air-flow plastic isolators while the next 22 patients were treated in barrier nursing rooms. Gnotobiotic parameters and morbidity in the 2 groups are compared. Good decontamination of the gastro-intestinal tract was obtained using either of the 2 isolation techniques. The incidence of bacterial and mycotic infections, as well as the supportive care required by the patients was almost equal in both groups. Our results also suggest that the incidence of graft versus host disease may decrease with efficient decontamination of the patients.

Key words: Bone marrow transplantation – Laminar air flow – Barrier nursing – Graft versus host disease

Previous analyses of bone marrow transplantation (BMT) results showed a high incidence of infectious complications, with significant morbidity, during the granulocytopenic period after marrow infusion [5]. Following engraftment the predominant problems are graft versus host disease (GVHD) and interstitial pneumonia (IP).

However, despite adequate granulocyte levels, bacterial and fungal problems continue to occur due to GVHD – related immunological deficiency [6].

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Table 1. Patient and donor characteristics

	LAF	BN
Number of patients	26	22
Male/Female	10/16	15/7
Age (median and range in years)	26 (16–41)	24 (10–41)
Aplastic anaemia	3	4
Acute leukaemia in relapse	13	3
Acute leukaemia in remission	10	7
Chronic myerloid leukaemia in chronic phase	0	8
HLA and mixed lymphocyte culture compatible donors:		
– siblings	22	19
– parents	1	1
– identical twin	1	1
– foreign	0	1
Autologous BMT	2	0

Infection of granulocytopenic patients with acute leukaemia has been effectively prevented by the use of laminar air flow isolation and gastro-intestinal decontamination with oral non-absorbable antibiotics [9, 22]. Previous publications have shown that GVHD in mice can be eliminated or ameliorated, depending on the degree of histocompatibility, by using germ-free transplant recipients [2, 4, 13, 14]. These results were explained by assuming the presence of cross-reacting antigens on intestinal bacteria and in the gut epithelial tissue [3].

Our study compares 2 techniques of isolation, laminar air flow (LAF) and barrier nursing (BN), with reference to gnotobiotic parameters, morbidity and supportive care required.

Special attention is paid to the incidence of GVHD in relation to gnotobiotic care.

Material and Methods

From December 1975 to March 1983, 48 bone marrow transplantations were performed at the West German Tumor Center.

From 1975 to 1981 all patients were admitted into laminar air flow (LAF) isolators ($n = 26$), while patients treated in the period from January 1982 to March 1983 ($n = 22$) were kept in single rooms under strict barrier nursing (BN) conditions. The patient and donor characteristics are given in Table 1.

Attendants to the barrier nursing rooms wore sterile gowns, gloves, masks and head-covers.

All material introduced into the LAF isolators or the BN rooms, including food, was sterilized.

In the LAF group all patients had subclavian or jugular central venous lines while patients in the BN group had Hickman right atrial catheters inserted. From patients with fever above 39 °C blood drawn from the central venous line was submitted for culture.

When a catheter-related septicaemia was suspected, a second sample, drawn at a peripheral site, was also cultured.

Total decontamination of LAF patients was attempted using the program shown in Table 2. On emergence of resistant bacterial strains either polymyxin E sulfate tablets (1,5 million units q. i. d.), or neomycin sulfate tablets (500 mg q. i. d.) were added.

Table 2. Decontamination procedure

Cephazolin solution	1000 mg b.d.
Gentamycin solution	80 mg q.i.d.
Amphotericin B tablets	200 mg q.i.d.
Amphotericin B suspension	300 mg q.i.d.
Nystatin tablets	1,0 million units q.i.d.
Nystatin suspension	0.3 million units q.i.d.
Neomycin sulfate ointment	30 mg b.d. into nose and vagina
Bacitracin ointment	1500 units b.d. nose and vagina
Hexitidine solution	20 mg q.i.d. mouth wash
Amphotericin B vaginal pessaries	50 mg b.d.

Table 3. Incidence and location of clinically or microbiologically documented infections

Site of infection	LAF	BN
Pulmonary (excluding I.P.)	3	1
Upper respiratory or mouth (excluding mucositis and Herpes simplex)	3	0
Oesophageal	2	1
Skin and soft tissues	3	0
Urinary tract	1	2
C.N.S.	1	0
Fever of unknown origin	9	7

Antimycotic therapy was initiated at least 3 days before antibiotics and both were maintained for 3 months.

Once daily patients bathed with 2% 1-dodecyl-1,4,7-triazo-octane-8-carbonic acid hydrochloride.

Patients of the BN group were subjected to the following decontamination program, beginning prior to admission into their rooms: 960 mg Co-trimoxazole tablets t.i.d. (day −14 to day +1), and 80 mg gentamycin solution q.i.d. (day −14 to day 50). Antimycotics were administered as to the LAF group. Patients bathed daily in filtered tap water.

The details of the conditioning regimen and the grafting procedure used were published in detail elsewhere [17, 18]. For prevention of GVHD patients were given methotrexate intravenously 15 mg/m^2 on day 1, an 10 mg/m^2 on day 3, 6, 11 and once weekly thereafter until day 100. Diagnoses of GVHD were made based on clinical and laboratory findings, as well as on results of skin and liver biopsies.

Oral washings, faecal and midstream urine samples from all patients were cultured twice weekly for anaerobes, aerobes and fungi. Samples were also taken from catheter insertion or exit sites and cultured for bacteria and fungi weekly. The bacteriological and mycological techniques of the cultures have been previously described [1, 7, 10, 11, 12, 16, 19].

Results

In the LAF group 73.7% of the faecal samples showed no bacterial growth (samples containing less than 10^3 organisms per gram of faeces were counted as germ-free), 87.7% showed no gram-negative rods and 75.2% were negative for fungi.

In the BN group 56% of the faecal samples showed no bacterial growth, 79.8% showed no gram-negative rods, and 95% were negative for fungi.

Table 4. Organisms responsible for septicaemias

Organism	Periods of septicaemia	
	LAF ($n = 21$)	BN ($n = 12$)
Staphylococcus epidermidis	15	7
Staphylococcus aureus	1	0
β-haemolytic streptococci	1	0
Enterococci	2	1
Pseudomonas aeruginosa	1	2
Corynebacteria	0	2
Torulopsis glabrata	1	0

Table 5. Comparison of the morbidity

	LAF group ($n = 26$)	BN group ($n = 22$)
Total fever days	632 days	316 days
Fever days per patient	24.5 days	15.8 days
Total periods of septicaemias	21	12
Septicaemic periods per patient	0.81	0.55

Table 6. Supportive care

	LAF ($n = 26$)	BN ($n = 22$)
No. of patients treated with systemic antibiotics	25	19
No. and % days on antibiotics	1010 (45.2%)	591 (48.6%)
No. and % patients treated with systemic Amphotericin B	5 (19.2%)	1 (5%)
No. of granulocyte transfusions per recipient	3	4.3
No. of platelet transfusions per recipient	12.9	10.7

Of the oral washings, 32% from the LAF group were germfree, 79% showed no gram-negative rods and 47% were negative for fungi. From the BN patients, 42% of the oral washings were germ-free, 90% showed no gram negative rods, and 55% were negative for fungi. The incidence and location of clinically or microbiologically documented infections are given in Table 3.

In the LAF group 21 septicaemic periods have been recorded. This compares with 12 septicaemic periods in the BN group. Table 4 shows the organisms responsible for septicaemic periods. It is of interest to observe the relation between the organisms colonizing the gastro-intestinal tract of a patient and the organisms isolated from the blood during a subsequent septicaemia.

In 67% of septicaemias which occurred in LAF group patients the same organism had been isolated from the faecal samples of the patient during the preceding week. In the BN group, the incidence of such a correlation was similar, 58%.

Tables 5 and 6 show that both systems of isolation give comparable results for the morbidity and supportive care parameters measured. The only exception being that patients of the BN group required significantly less systemic antimycotic therapy.

Patients at risk for GVHD were 22 in the LAF group and 20 in the BN group. Acute GVHD occurred in 1 patient of the LAF group, as compared to 2 patients of the BN group. All 3 cases were graded III to IV. Chronic GVHD with de novo onset was diagnosed in 3 patients of the LAF group and in 5 patients of the BN group. All cases of acute GVHD were lethal while 3 of the chronic GVHD patients are still living. The total incidence of GVHD in patients at risk ($n = 42$) was 26,1% while the incidence of acute GVHD was 7%.

The actualial incidence of GVHD on day 175 post BMT was 33%. On day 175 nineteen patients were still at risk and no GVHD was observed beyond that day. Nine patients of the LAF group are still living. The main causes of death in this group were infection ($n = 4$), interstitial pneumonia (I. P.) ($n = 1$), acute GVHD ($n = 1$), chronic GVHD ($n = 3$), leukaemic relapse ($n = 6$), cardiac ($n = 1$) and hepatic failure ($n = 1$).

In the BN group 10 patients are living. The main causes of death were infection ($n = 3$), I. P. ($n = 4$), acute GVHD ($n = 2$), chronic GVHD ($n = 2$) and cardiac failure ($n = 1$).

The median observation time of survivors in both groups is 707 days.

Discussion

LAF isolation is effective in preventing infections in granulocytopenic patients [9, 22], and positively influences survival of marrow transplant recipients [20]. Our study shows that results achieved with BN isolation are not worse than those of LAF isolation. The incidence of septicaemias and days with fever appear to be lower in the BN group. This may be due to differences between the two groups regarding the type and stage of leukaemia.

In the LAF group, half of the patients ($n = 13$) were transplanted during leukaemic relapse. This compares with only 3 relapse patients in the BN group. The susceptibility of relapse patients to develop fever and septicaemia is higher than that of patients in complete remission.

Most of the microorganisms isolated from blood samples were strains of coagulase negative Staphylococcus epidermidis, substantially more from the LAF group than from the BN group. This difference may be related to the change of the decontamination program for the BN group.

Another factor which might have played a role is the use of Hickman lines as compared to subclavian or jugular catheters in the LAF group.

The increased incidence of coagulase negative staphylococcal infections in both groups, despite decontamination therapy, may imply resistance and have been a consequence of the widespread use of broad-spectrum antibiotics. However, the possibility of contamination of blood cultures cannot be ruled out in every case. No period of septicaemia in either group was attributed to catheter infection.

Although a higher percentage of the faecal samples obtained from LAF patients were germ-free, the reverse was true for fungi. In agreement with other investigators [8,15] complete decontamination of the oropharynx of patients in either group was

difficult. Contrary to the opinion of other study groups [5] our results demonstrate the value of routine monitoring cultures in predicting or assisting in the diagnosis of subsequent infection. In more than half of the cases of septicaemia the pattern of faecal isolates, in retrospect, foreshadowed the subsequent infection. It remains a future task to prove with biotyping that the organisms isolated from the faecal and blood samples belong to the same strain.

The low incidence of acute GVHD in both groups is presumed to be related to the efficient decontamination. Similar observations were made by the Seattle-group in a study of 130 patients with aplastic anaemia [20]. Wether the mechanisms involved here are the same as suggested to occur in germ-free mice [2, 13, 14] remains uncertain.

Although the number of cases with I. P. is higher in the BN group, it is our opinion that this complication has nothing to do with the mode of isolation used. In our cases of I. P. an infectious agent could not be identified. The prior exposure of the lungs to radiation may have played a role in these "idiopathic" interstitial pneumonias. Other studies have shown that the incidence of I. P. in patients treated with total body irradiation is 40%–50% compared with only 16% in patients treated with Cyclophosphamide only [21]. In agreement with these findings, none of our aplastic anaemia patients developed I. P.

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