F. Petersen, M. Thornquist, C. Buckner, G. Counts, N. Nelson, J. Meyers, R. Clift, E. Thomas

The Effects of Infection Prevention Regimens on Early Infectious Complications in Marrow Transplant Patients: A Four Arm Randomized Study

Summary: Three hundred and forty-two patients with hematological malignancies underwent allogeneic marrow transplantation from family donors and were allocated to receive 1) no specific infection prophylaxis in a conventional hospital room (control, 100 patients), 2) prophylactic systemic antibiotics (PSA) in a conventional hospital room (PSA group, 101 patients), 3) decontamination and isolation in a laminar air flow (LAF) room (LAF group, 65 patients) and 4) PSA in an LAF room (LAF+PSA group, 76 patients). Patients were studied for bacterial and fungal complications from the day of admission and until engraftment. LAF isolation was discontinued before engraftment in 27% (LAF+PSA group) to 32% (LAF group) of isolated patients. PSA was not given according to protocol in 26% (LAF+PSA group) to 27% (PSA group) of patients on prophylactic antibiotics. Septicemia occurred in 41%, 22%, 25% and 10% of patients in the control, PSA, LAF and LAF+PSA group, respectively. The incidence of septicemia was significantly less in the LAF+PSA group than in the control and LAF group with the incidence of septicemia significantly higher in the control group than in any of the other three groups. No other risk factors analyzed in proportional hazards regression tests were associated with septicemia acquisition. It is concluded that effective infection prevention modalities significantly reduce infection morbidity in transplant patients. Since most granulocytopenic transplant patients not receiving PSA will receive empiric or therapeutic broad spectrum antibiotics, the use of PSA in or out of LAF isolation is recommended as an effective modality to reduce septicemia acquisition.

Zusammenfassung: *Einfluß von Präventivmaßnahmen zur Infektionsprophylaxe auf frühe infektiöse Komplikationen bei Knochenmarkstransplantatempfängern. Vierarmige randomisierte Studie.* Bei 341 Patienten mit malignen hämatologischen Erkrankungen wurde eine allogene Knochenmarkstransplantation von Spendern aus der Familie durchgeführt. Die Patienten wurden den folgenden Studienarmen zugeordnet: 1) Keine spezifische Infektionsprophylaxe, Pflege in einem konventionellen Krankenzimmer (Kontrollen, 100 Patienten); 2) Systemische Antibiotikaprophylaxe (PSA) in konventionellem Krankenzimmer (101 Patienten); 3) Dekontamination und Isolation in einem Laminar Air Flow(LAF)-Raum (65 Patienten) und 4) PSA in einem LAF-Raum (76 Patienten). Vom Tag der Einweisung bis zur Transplantation wurden die Patienten auf Komplikationen durch bakterielle und Pilzinfektionen untersucht. Vor der Transplantation wurde die LAF-Isolation bei 27% der LAF plus PSA-Gruppe und bei 32% der LAF-Gruppe abgebrochen. Entsprechend Protokoll erhielten 26% der LAF plus PSA und 27% der PSA-Gruppe die Antibiotikaprophylaxe nicht. Septikämien traten bei 41% der Patienten der Kontrollgruppe, 22% der mit PSA in konventioneller Pflegeeinheit, bei 25% der in LAF-Räumen behandelten und bei 10% der in LAF-Räumen gepflegten und zusätzlich mit PSA behandelten Patienten auf. Die Septikämie-Inzidenz war unter LAF mit PSA signifikant geringer als in der Kontrollgruppe und der in LAF-Isolation gepflegten Patientengruppe; zugleich war die Septikämie-Inzidenz in der Kontrollgruppe signifikant höher als in einer der drei anderen Gruppen. Die proportionale Risiko-Regressionsanalyse ergab keine zusätzlichen Risikofaktoren für das Auftreten einer Septikämie. Wirksame Maßnahmen zur Infektionsprophylaxe können folglich die Infektionsmorbidität bei Transplantatempfängern signifikant vermindern. Da die meisten granulozytopenischen Transplantatempfänger eine empirische oder gezielte Therapie mit Breitspektrumantibiotika erhalten, wird die PSA unabhängig von LAF-Isolation als effektive Maßnahme zur Verminderung der Septikämien empfohlen.

Introduction

Marrow transplantation is associated with a high risk of life-threatening bacterial and fungal infections (1, 2, 3, 4, 5). Several infection prevention modalities have been investigated in attempts to decrease the morbidity and mortality of infection in marrow transplant patients. Laminar air flow (LAF) isolation with decontamination procedures and prophylactic granulocyte (PG) transfusions were found to reduce infection acquisition significantly when compared to that of patients not receiving these

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F. Petersen, M. D., *M. Thornquist*, Ph. D., *C. Buckner*, M. D., *G. Counts*, M. D., *Nira Nelson*, M. T. (ASCP), *J. Meyers*, M. D., *R. Clift*, *E. Thomas*, M. D. from the Fred Hutchinson Cancer Research Center, and the University of Washington, Seattle, Washington 98104, U.S.A.

prophylactic modalities (6, 7, 8). Following the initial controlled studies, different infection prevention modalities were compared directly without use of a control group (9, 10, 11). The use of prophylactic broad spectrum systemic antibiotics was shown to be as effective as either the use of PG transfusions or decontamination and LAF isolation without PSA. When PSA was combined with LAF isolation, bacterial septicemia was virtually eliminated (11). However, despite a decrease in morbidity, mortality within the first 100 days from transplant was not significantly reduced by these preventive measures among patients transplanted for hematological malignancies (6, 7, 8, 9, 10, 11). Treatment of established infection has improved during the last decade and any type of infection prevention measure entails either some risk of side effects, high cost or both. Therefore, a randomized prospective study was performed to determine the impact of infection prevention measures on infection acquisition for patients receiving or not receiving any specific prophylaxis. This report presents an analysis of factors associated with bacterial and fungal infections during the pre-engraftment period in patients with hematological malignancies treated with allogeneic marrow transplantation and randomized to receive or not to receive LAF isolation and/or PSA as prophylaxis against bacterial and fungal infections.

Patients and Methods

All patients with hematologic malignancy admitted to the Fred Hutchinson Cancer Research Center or the Swedish Hospital Medical Center for allogeneic marrow transplantation were eligible for randomization or placement in a conventional hospital room or a LAF room. If both a conventional and a LAF room were available at admission, room assignment was randomized. If only one type of room was available, the patient was placed in that room. Once the room assignment was made, randomization to PSA or no PSA was performed. This randomization was performed even if patients were receiving antibiotics for therapeutic or empiric reasons at the time of admission. Thus, patients were allocated to one of four different regimens: 1) a conventional hospital room without any specific prophylactic measures (control group), 2) PSA in a conventional hospital room (PSA group), 3) decontamination and isolation in a laminar air flow room without PSA (LAF group) and 4) decontamination and LAF isolation with administration of PSA (LAF+PSA group). Three hundred and forty-two patients were entered in the study between March 1984 and June 1986. The protocol was approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center. The procedures were explained in detail and written consent was obtained from all patients or their legal guardians.

All patients were treated with cyclophosphamide (60 mg/kg body weight) on each of two successive days, followed by 10–15.75 Gy of total body irradiation (TBI) depending on the underlying disease or degree of histocompatibility (12, 13, 14, 15). Cyclosporine and methotrexate or *in vitro* T-lymphocyte depletion were used for GVHD prophylaxis (16, 17). Grading of acute GVHD and details of donor selection and supportive care are described elsewhere (18, 19, 20). All patients had a right atrial catheter (Davol Inc., RI) inserted before the transplant and maintained in place until departure from Seattle, death or removal for complications (21). Day 0 designates the day of marrow infusion. Granulocytopenia was defined as a peripheral absolute granulocyte count (AGC) below 500/mm^3. The day of engraftment was defined as the first day the absolute granulocyte count was self-sustaining above 500/mm^3. Patients were studied from the start of the preparatory regimen, usually ten days prior to marrow infusion, until death, day leaving Seattle, or day of engraftment, whichever occurred first.

Isolation and decontamination: LAF rooms (Medical SafeTEC, Indianapolis, Indiana) were used for this study (22). Decontamination procedures including skin cleansing and the administration of broad spectrum oral non-absorbable antibiotics (nystatin, vancomycin and neomycin) were begun upon admission to the hospital and are described elsewhere (6, 11). Patients received either sterile diets or cooked food items selected for a low bacterial content (23). Most patients were discharged to the outpatient department directly from the LAF room after engraftment but many were transferred to conventional rooms prior to discharge or death. Protocol adherence was defined as remaining in a LAF room until engraftment.

Cultures for aerobic bacteria and for fungi were obtained from the nose, throat, vagina, urine and stool (or rectal swabs if a stool specimen was not obtained) on admission and weekly thereafter until leaving the LAF room. Results of surveillance cultures from each site were categorized as *positive* (if there was any growth of bacteria or fungi present) or *negative.* Total decontamination was defined as concurrent negative surveillance cultures from the nose, throat and rectum.

Conventional hospital rooms: Patients were treated in single-bed rooms and all medical equipment was initially sterilized, kept in the room, and used for one patient only. Hospital personnel and visitors wore masks but did not use gowns or sterile gloves. Patients were not restricted to their rooms when ambulatory but wore masks when outside the room. Bacterial and fungal cultures were obtained only when clinically indicated.

Prophylactic systemic antibiotics: Two PSA regimens were used in this study. From March 1984 until April 1985 a regimen consisting of parenteral vancomycin (2g/24h), ticarcillin (300mg/kg/24h) and tobramycin (5mg/kg/24h) was used. From May 1985 until June 1986 a regimen consisting of mezlocillin (18g/24h) and cefotaxime (12g/24h) was used. PSA was started the first day the absolute granulocyte count declined to less than 500/mm^3. If a patient had a history of penicillin allergy, a skin test was performed. In the rare instance of an allergic reaction, cefotaxime was substituted for ticarcillin or tobramycin for mezlocillin. Dosages of tobramycin and vancomycin were adjusted according to serum levels of those drugs. In case of renal impairment, the dose of ticarcillin, mezlocillin or cefotaxime was reduced according to renal function. The regimen was discontinued when the patient had a self-sustaining absolute granulocyte count above 500/mm^3 and was without symptoms or signs of infection. Protocol adherence was defined as 1) not receiving broad spectrum systemic antibiotics for any reason before the absolute granulocyte count declined to less than 500/mm^3 and 2) receiving PSA within 36 h of the first day the absolute granulocyte count declined to less than 500/mm^3 and continuing until engraftment.

Infection evaluation: Fever was defined as an oral temperature $\geq$ 38.3°C (101°F). An episode of septicemia was defined as a single positive blood culture associated with signs and symptoms

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of infection (documented local site of infection or fever) or two consecutive positive blood cultures with the same organism. A patient was considered recovered from septicemia when subsequent blood cultures became negative, the patient was free from signs and symptoms of infection and at least seven days had passed from the last positive blood culture.

The definition of an episode of major local infection required both documentation of the microbiological cause and the need for antibiotic and/or surgical intervention. A patient was considered recovered from a major local infection when all clinical and microbiological signs of the infection had resolved.

Infectious disease management: No restrictions were imposed on the attending physician's management of suspected or documented infections. Empiric treatment of febrile episodes usually consisted of the combination of broad-spectrum antibiotics used for prophylaxis. Systemic amphotericin B was frequently administered when the granulocytopenic patient had persistent fever while receiving broad-spectrum antibiotics, especially if the patient was colonized with fungi at any site. However, fungal colonization was not required. Antibiotics were altered according to the results of culture and sensitivity tests or if allergy or intolerance developed. Therapeutic granulocyte transfusions were rarely given and only to patients who were granulocytopenic and with clinical deterioration despite appropriate antibiotics or antifungals.

Statistics: The results were analyzed from the start of the preparatory regimen until the first day the absolute granulocyte count was self-sustaining above 500/mm^3 or death. Cumulative probabilities of septicemia, local major infections, any infectious episode, GVHD and survival were computed according to the methods of *Kaplan* and *Meier* (24). Significance testing was based on the log-rank test according to *Peto* and *Peto* (25). The simultaneous association between several different factors and the occurrence of septicemia was analyzed using a Cox proportional hazard regression test (26). The Chi-square test with Yates's correction was used to determine whether the frequency of events in two groups was different. Student's t-test was used to analyze the difference between two independent means.

Results

Patients Characteristics

Patients in the four groups were comparable with regard to age, phase of disease, degree of mismatch, number of days studied and GVHD prophylaxis (Table 1). Significantly more patients with acute nonlymphoblastic leukemia (ANL) were in the control group than in the LAF group ($p = 0.04$). Significantly more males were in the PSA group than in the control group and LAF group ($p = 0.04$). Significantly more patients in the PSA and LAF+PSA group received antibiotics at the time of admission when compared to patients in the control and

Table 1: Patient Characteristics.

Characteristics	Infection prophylaxis group Control*	PSA	LAF	LAF+PSA
Total no. of patients	100 (29%)	101 (30%)	65 (19%)	76 (22%)
Age				
Median and range (years)	26 (1–50)	25 (1–52)	25 (1–58)	28 (2–51)
Diagnoses				
Acute non-lymphoblastic leukemia	37 (37%)	31 (31%)	13 (20%)	26 (34%)
Acute lymphoblastic leukemia	20 (20%)	25 (25%)	17 (26%)	16 (21%)
Chronic myelogenous leukemia	35 (35%)	33 (32%)	29 (44%)	23 (30%)
Malignant lymphoma	4 (4%)	6 (6%)	3 (5%)	9 (12%)
Myelodysplastic syndrome	4 (4%)	6 (6%)	3 (5%)	2 (3%)
Disease phase				
Complete remission or chronic phase	60 (60%)	54 (53%)	33 (51%)	48 (63%)
Relapse, accelerated phase or blast crisis	36 (36%)	41 (41%)	25 (38%)	24 (32%)
Primary active disease not relapse or remission	4 (4%)	6 (6%)	7 (11%)	4 (5%)
Sex				
Female	45 (45%)	30 (30%)	29 (45%)	31 (41%)
Male	55 (55%)	71 (70%)	36 (55%)	45 (59%)
Observation period				
Median/mean days observed (range)	30/31.5 (17–166)	29/30.7 (13–59)	32/34.3 (20–122)	31/31.3 (18–53)
Graft-versus-host-disease-prophylaxis				
T-lymphocyte depleted marrow *(in vitro)*	12 (12%)	9 (9%)	3 (4%)	6 (8%)
Cyclosporine & methotrexate	88 (88%)	92 (91%)	62 (96%)	70 (92%)
HLA-match				
HLA identical	75 (75%)	69 (68%)	43 (66%)	57 (75%)
HLA non-identical	25 (25%)	32 (32%)	22 (34%)	19 (25%)
Patients receiving antibiotics at the time of admission	13 (13%)	28 (28%)	8 (12%)	16 (21%)

* No specific infection prophylaxis; PSA: prophylactic systemic antibiotics in a conventional room; LAF: decontamination and laminar air flow isolation; LAF+PSA: decontamination and laminar air flow isolation with prophylactic systemic antibiotics.

Table 2: Protocol performance.

	Infection prophylaxis group			
	Control*	PSA	LAF	LAF+PSA
No. of patients	100	101	65	76
Protocol adherence				
Had LAF discontinued before engraftment:				
– Medical reasons	–	–	10 (15%)	17 (22%)
– Patient request	–	–	11 (17%)	4 (5%)
Started PSA > 36 hours**	–	6 (6%)	–	9 (12%)
Antibiotics started for empiric or therapeutic reasons***	100 (100%)	21 (21%)	64 (98%)	11 (14%)
Antimicrobial therapy				
Day post-transplant antibiotics started				
median/mean	2/1.2	– 3/3.8	4/2.6	– 1/2.4
(range)	(– 12 to 11)	(– 12 to 4)	(– 12 to 9)	(– 12 to 6)
Days antibiotics given				
median/mean	18/19.2	23/24.0	18/20.9	22/23.0
(range)	(2–94)	(11–55)	(0–98)	(4–46)
Proportion of study time (%) antibiotics were given				
median/mean	59/60.9	74/77.2	56/58.1	71/72.4
No. of patients receiving i. v. amphotericin B	61 (61%)	61 (61%)	36 (55%)	36 (47%)
Day post-transplant i. v. amphotericin started				
median/mean	8/6.8	7/6.3	8/6.6	8/7.3
(range)	(– 12 to 22)	(– 12 to 19)	(– 12 to 22)	(– 12 to 21)
Fever				
Day post-transplant fever started				
median/mean	2/1.0	2/2.1	4/3.1	4/3.8
(range)	(– 12 to 9)	(– 12 to 15)	(– 12 to 10)	(– 12 to 35)
Days of fever				
median/mean	10/10.7	9/10.1	8/10.8	6/8.13
(range)	(1–27)	(1–27)	(0–69)	(1–30)

* No specific infection prophylaxis; PSA: prophylactic systemic antibiotics in a conventional room; LAF: decontamination and laminar air flow isolation; LAF+PSA: decontamination and laminar air flow isolation with prophylactic systemic antibiotics; ** patients in either PSA group who did not receive PSA until > 36 hours after the AGC had declined to less than 500/mm^3; *** patients who received broad-spectrum systemic antibiotics for empiric of therapeutic indications regardless of the AGC.

PSA group (p = 0.04–0.02). None of these factors had an impact on septicemia acquisition as tested in a proportional hazard regression analysis (Table 4).

Protocol Compliance

Twenty-one patients in both the LAF group (32%) and the LAF+PSA group (27%) had LAF discontinued before engraftment. Twenty-seven patients in the PSA group (27%) and 20 patients in the LAF+PSA group (26%) started antibiotics either too early or too late. A total of 32 patients (42%) in the LAF+PSA group did not receive prophylaxis according to the protocol. The reasons for not adhering to the protocol are shown in Table 2.

Twelve patients (18%) in the LAF group and nine patients (12%) in the LAF+PSA group obtained concurrent complete aerobic decontamination of oropharynx, nose and stool (or anus if stool samples could not be obtained) on at least one set of surveillance cultures obtained after seven days in isolation. Ten patients (15%) in the LAF group and six patients (8%) in the LAF+PSA group continued to be totally decontaminated until engraftment.

All but one patient in the LAF group eventually received i. v. broad-spectrum antibiotics. Patients receiving PSA started antibiotics a median of three days before the transplant, compared to a median of four days after the transplant for patients not receiving PSA. Patients on PSA received antibiotics during 75% (mean) of the granulocytopenic period compared to 59% (mean) for patients not on PSA. These differences were significant ($p < 0.02$) (Table 2).

Forty-seven to 61% of patients received i. v. amphotericin B (Table 2). There were no significant differences between the four groups in the use of i. v. amphotericin B. All but one patient in the LAF group developed fever during the study period. The day fever started and days of fever while granulocytopenic are shown in Table 2.

Septicemia

Only five patients (1%) were granulocytopenic beyond day 45. The Kaplan-Meier probabilities of developing a first episode of septicemia for patients in the four groups are shown in Figure 1. Details of septicemias are shown in Table 3.

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Table 3: Septicemia.

Organisms cultured	Infection prophylaxis group Control*	PSA	LAF	LAF+PSA
No. of patients at risk	100	101	65	76
Coagulase-negative staphylococcus	19	10	8	4
Streptococcus spp.	14	0	2	0
Staphylococcus aureus	4	1	2	0
Enterococcus	0	1	2	0
Diphtheroid spp.	2	1	0	0
Bacillus	1	0	0	0
Eubacterium	1	0	0	0
Streptomyces	1	0	0	0
Gram-positive isolates total	42	13	14	4
Total no. episodes (while receiving antibiotics < 24 h)	38 (16)	12 (11)	14 (6)	4 (3)
Total no. of patients	36 (36%)	11 (11%)	13 (20%)	3 (4%)
Pseudomonas spp.	4	2	1	1
Escherichia coli	3	1	0	0
Bacteroides spp.	1	2	0	0
Klebsiella spp.	0	3	1	0
Enterobacter spp.	1	1	0	0
CDC enteric 17	1	0	0	0
Veillonella sp.	0	1	0	0
Neisseria sp.	0	1	0	0
Haemophilus sp.	0	1	0	0
Capnocytophaga	0	1	0	0
Agrobacterium	0	0	0	1
Moraxella sp.	0	0	0	1
Gram-negative isolates total	10	13	2	3
Total no. of episodes (while receiving antibiotics < 24 h)	10 (8)	12 (11)	2 (2)	3 (2)
No. of patients	10 (10%)	11 (11%)	2 (3%)	3 (4%)
Candida albicans	3	3	3	2
Candida tropicalis	1	4	0	1
Candida lusitania	1	0	0	0
Torulopsis glabrata	0	1	0	0
Fungal isolates total	5	8	3	3
Total no. of episodes (while receiving i. v. amphotericin < 24 h)	5 (1)	8 (1)	3 (1)	3 (3)
Total no. of patients	5 (5%)	8 (8%)	3 (5%)	3 (4%)
All isolates total	57	34	19	10
All episodes total	49	25	17	10
All patients total	41 (41%)	22 (22%)	16 (25%)	8 (10%)

* No specific infection prophylaxis; PSA: prophylactic systemic antibiotics in a conventional room; LAF: decontamination and laminar air flow isolation; LAF+PSA: decontamination and laminar air flow isolation with prophylactic systemic antibiotics.

Control Group

Forty-one patients (41%) developed 49 episodes of septicemia from which 57 separate organisms were isolated. Nineteen of 44 bacterial episodes (43%) occurred after the patients had been receiving i. v. broad-spectrum antibiotics for more than 24 hours. Forty-two (74%) of the 57 isolates were gram-positive, ten (18%) were gram-negative and five (8%) were fungi. The probability of developing septicemia among patients in the control group was 41% (Figure 1) which was significantly higher than in any of the other three groups (log-rank $p = 0.03$, 0.007 and 0.001 for the PSA, LAF and LAF+PSA group, respectively, in two-way comparisons).

PSA Group

Twenty-two patients (22%) developed 25 episodes of septicemia from which 34 separate organisms were isolated. Seventeen of the 26 bacterial episodes (65%) occurred after the patients had been receiving i. v. broad-spectrum antibiotics for more than 24 hours. Thirteen (38%) of the 34 isolates were gram-positive, thirteen (38%) were gram-negative and eight (24%) were fungi. The probability of developing septicemia was 21% (Figure 1), which was not significantly different from the probability for patients in the LAF+PSA group (log-rank $p = 0.06$) or patients in the LAF group (log-rank $p = 0.4$).

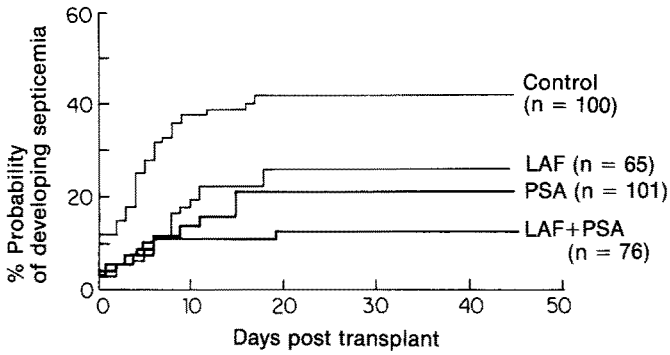

Figure 1: Kaplan-Meier probability of developing a first episode of septicemia for granulocytopenic patients in the control, LAF, PSA and LAF+PSA groups. Patients were censored the first day they reached a self-sustaining absolute granulocyte count above 500/mm^3, death or day 45, whichever occurred first.

LAF Group

Sixteen patients (25%) developed 17 episodes of septicemia from which 19 separate organisms were isolated. Four of the 14 bacterial episodes (29%) occurred after the patients had been receiving i. v. broad-spectrum antibiotics for more than 24 h. Seven (41%) of the 17 episodes occurred while the patient was isolated in LAF. Fourteen (74%) of the 19 isolates were gram-positive, two (10%) were gram-negative and three (16%) were fungi. Patients in the LAF group had a 24% probability of developing septicemia within 45 days post transplant (Figure 1) which was not significantly different from the probability for patients in the LAF+PSA group (log-rank p = 0.4). A single patient in the LAF group had a very protracted granulocytopenic period and developed septicemia on day 87.

LAF+PSA Group

Eight patients (10%) developed ten episodes of septicemia from which ten separate organisms were isolated. Five of the seven bacterial episodes (71%) occurred after the patients had been receiving i. v. broad-spectrum antibiotics for more than 24 hours. Four (40%) of the ten isolates were gram-positive isolates, three (30%) were gram-negative and three (30%) were fungi. Patients in the LAF+PSA group had a 10% probability of developing septicemia (Figure 1). Two patients had four of seven bacterial episodes while isolated in LAF and having received i. v. broad-spectrum antibiotics for more than 24 h (two with gram-positive and two with gram-negative organisms isolated).

When patients in the PSA and LAF+PSA group, who started PSA 36 h after the decline of the granulocyte count to less than 500/mm^3, were excluded from analysis and patients in the LAF and LAF+PSA group were censored at the time they had LAF discontinued, patients in the LAF+PSA group hat a significantly lesser probability of developing septicemia compared to patients in any of the other three groups. Patients in the control group had a significantly higher probability of developing septicemia than patients in any of the other three groups and patients in the LAF group had a probability of septicemia that was not significantly different from patients in the PSA group. Episodes of septicemia caused by gram-positive organisms other than coagulase-negative staphylococcus occurred earlier (mean = 3.8 days post transplant) com-

Table 4: Proportional (Cox) hazards regression test of the simultaneous association between risk factors and the development of septicemia in the pre-engraftment period.

Risk factors	No. of patients at risk	Relative risk	P-value
Infection prophylaxis			
No specific prophylaxis (control group)	100	1.00	
PSA only	101	0.66	
LAF only	65	0.66	
LAF+PSA	76	0.25	0.018
All LAF	141	0.56	0.021
All PSA	177	0.54	0.032
Sex			
Males	207	1.00	
Females	135	1.05	0.86
*Age**	342	1.17	0.13
Treatment with broad spectrum antibiotics at admission			
Yes	65	1.04	0.92
No	277	1.00	
Diagnosis			
Acute lymphoblastic leukemia	78	0.73	
Acute non-lymphoblastic leukemia	107	1.86	0.09
Chronic myelogenous leukemia	120	1.06	
Other	37	1.00	
Disease phase			
First complete remission/ Chronic phase	135	122	
Remission beyond first relapse/ accelerated phase	91	1.20	
Relapse/blast crisis	95	1.08	
Other	21	1.00	0.97
Mismatch			
None	252	1.00	
One HLA antigen mismatched	39	1.29	
Two HLA antigens mismatched	41	1.06	
Three HLA antigens mismatched	6	1.05	
HLA matched, unrelated	4	1.37	0.99

PSA: prophylactic systemic antibiotics; LAF: decontamination and laminar air flow isolation; LAF+PSA: decontamination and laminar air flow isolation with prophylactic systemic antibiotics; *analyzed for the additional risk of each additional decade.

pared to those caused by gram-negative organisms (mean = 7.7 days post transplant, $p = 0.4$), those caused by coagulase-negative staphylococcus (mean = 8.2 days post transplant, $p > 0.05$) and those caused by fungi (mean = 10.1 days post transplant, $p < 0.001$).

Proportional hazard regression analyses were performed for the further evaluation of risk factors associated with development of septicemia. Infection prophylaxis regimen, sex, active infection at admission, underlying disease, disease phase, and degree of HLA matching were tested and the result is shown in Table 4. Of these factors, only infection prevention was a significant predictive factor for development of septicemia (Table 4).

Impact of Antibiotic Regimen

Two hundred and eighty-six of the 341 patients (84%) receiving i. v. antibiotics received either tobramycin, ticarcillin and vancomycin (187 patients) or cefotaxime and mezlocillin (99 patients). There was no significant difference between patients receiving the two regimens in regard to development of septicemia while on or off antibiotics, renal impairment, days of fever and number of patients dying without engraftment (Table 5). However, 38 patients (38%) receiving cefotaxime and mezlocillin had subsequent alteration of the antibiotic regimen compared to 15 (8%) patients receiving tobramycin, ticarcillin and vancomycin ($p < 0.001$). Twenty-eight of the alterations in the cefotaxime and mezlocillin group were the addition of i. v. vancomycin, and five were the addition of an aminoglycoside. Five of alterations in the tobramycin, ticarcillin and vancomycin group were the addition of a cephalosporin. The remaining 15 alterations in both groups were to a variety of other antibiotics.

Table 5: Impact of types of antibiotics administered empirically of prophylactic.

	Ticarcillin Tobramycin Vancomycin	Cefotaxime Mezlocillin	P-value
No. of patients	187	99	
Had alteration of antibiotics after start	15 (8%)	38 (38%)	< 0.001
Had i. v. amphotericin B added	118 (63%)	52 (53%)	0.12
No. of patients with serum-creatinine > 1.5 mg%	70 (37%)	45 (45%)	0.25
No. of patients requiring renal dialysis	30 (16%)	23 (23%)	0.17
Total days of fever median/mean (range)	10/10.8 (1–68)	8/8.6 (1–36)	0.07
No. of patients developing septicemia	48 (26%)	30 (30%)	0.50
Total no. of septic episodes	56	33	
No. of septic episodes with fungal isolates	11 (20%)	6 (18%)	
No. of septic episodes with bacterial isolates	49 (88%) 47 (80%)	29 (88%) 23 (79%)	
No. of septic episodes while receiving antibiotics > 24 h Total bacterial isolates	30 (61%)	13 (45%)	
Organisms isolated (while receiving antibiotics)			
Coagulase-negative staphylococci	16 (0%)	9 (56%)	
Other gram-positive isolates	1 (3%)	2 (13%)	
Gram-negative isolates	15 (47%)	5 (31%)	
Bacterial isolates total	32	16	
No. of patients dying before engraftment	14 (7%)	10 (10%)	

Major Local Infection

Fifty-four patients developed 69 episodes of major local infections. The probability of developing a major local infection was 27%, 28%, 10%, and 8% for patients in the control, PSA, LAF and LAF+PSA groups, respectively. The differences in probabilities between the control and PSA groups and between the LAF and LAF+PSA groups were not statistically significant (log-rank $p = 0.9$ and 0.6 respectively). Patients in the LAF group had a significantly lower probability of developing major local infection than patients in the control group (log-rank $p = 0.015$) and patients in the PSA group (log-rank $p = 0.009$). Patients in the LAF+PSA group also had a significantly lower probability of developing major local infection when compared to patients in the control group ($p = 0.002$) and patients in the PSA group ($p = 0.001$). In 11 of the 69 episodes (16%), the same organism was isolated from blood cultures.

Seventy-eight separate organisms were isolated from the 69 episodes. Of these, 13 (17%) were coagulase-negative staphylococci, 13 (17%) other gram-positive organisms, 25 (32%) gram-negative organisms, 25 (32%) fungi and two (3%) protozoa. Details of the sites infected and types of organisms isolated for patients in the four groups are shown in Table 6.

Survival and Causes of Death

The number of patients dying and the causes of death in patients not achieving engraftment are shown in Table 7. A total of 28 patients (8%) died without obtaining engraftment. Of these, 17 (61%) died with fungal or bacterial infection as the only or a major contributory factor. Five patients had septicemia, five local major infection and six combined local infection and septicemia. There was no significant difference in deaths from bacterial or fungal infection between the patients in the four study groups.

Two patients did not achieve engraftment and left Seattle on days 76 and 154, respectively. One died on day 87 from a gram-positive septicemia and leukemic relapse (not in-

Table 6: Major local infections.

	Infection prophylaxis group			
	Control*	PSA	LAF	LAF+PSA
No. of patients at risk	100	101	65	76
Sites				
Enteritis	6	7	0	0
Lung	6	2	1	3
Oro-pharynx/oral cavity	4	6	3	2
i. v. catheter site	4	3	1	0
Skin	2	3	1	0
Urine	3	1	1	0
Anus/anal area	2	4	0	1
Esophagus	2	0	0	0
Other single separate sites	1	2	0	1
Total no. of sites	30	28	7	7
Total no. of episodes	29	27	7	6
Total no. of patients	21 (21%)	21 (21%)	6 (9%)	6 (8%)
No. of episodes combined with septicemia	6 (21%)	2 (7%)	1 (14%)	2 (33%)
Type of organism				
Coagulase-negative staphylococci	4	8	1	0
Other gram-positive organisms	7	4	1	1
Gram-negative organisms	13	10	2	0
Fungi	8	9	3	5
Protozoa	1	1	0	0
Total no. of organisms	33	32	7	6

* No specific infection prophylaxis; PSA: prophylactic systemic antibiotics in a conventional room; LAF: decontamination and laminar air flow isolation; LAF+PSA: decontamination and laminar air flow isolation with prophylactic systemic antibiotics.

Table 7: Causes of death before achieving engraftment.

	Infection prophylaxis group			
	Control*	PSA	LAF	LAF+PSA
No. of patients at risk	100	101	65	76
Causes of death				
Infection caused by				
Gram-negative organisms	1	2	2**	1
Gram-positive organisms	0	0	1	0
Fungal organisms	2	4	2**	2
Infectious deaths total	3 (3%)	6 (6%)	4 (6%)	3 (4%)
Regimen related toxicity	2	0	2	1
CMV pneumonitis	0	1	1	1
Cerebral hemorrhage	1	1	0	0
Acute graft-versus-host disease	0	1	0	0
Relapsed leukemia	0	0	0	1
Total no. of patients dying without engraftment	6 (6%)	9 (9%)	7 (11%)	6 (8%)

* No specific infection prophylaxis; PSA: prophylactic systemic antibiotics in a conventional room; LAF: decontamination and laminar air flow isolation; LAF+PSA: decontamination and laminar air flow isolation with prophylactic systemic antibiotics; ** one patient had fungal and gram-negative organisms recovered from the blood at death.

cluded in this analysis) and the other subsequently engrafted and has survived.

Discussion

Early bacterial and fungal infections in granulocytopenic transplant patients have historically been associated with a significant mortality (27). We have previously shown that infection prevention measures for patients undergoing marrow transplantation for hematological malignancies significantly decreases infection morbidity (6, 7, 10, 11). However, none of these studies showed any impact on short or long-term survival. To investigate whether this apparent discrepancy was due to more effective in-

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fection surveillance and infection management, we continued an infection prevention study using PSA and LAF as single modalities or combined, and added a control group as the fourth arm to the study where no specific infection prevention was given. The results confirm earlier studies: that the lack of specific infection prophylaxis is associated with a significant increase in septicemia, especially that caused by gram-positive organisms, when compared to either PSA, LAF or LAF+PSA (6, 8, 11). Only patients transplanted in LAF with or without PSA had significantly fewer major local infections when compared to patients in either the PSA or the control group. PSA by itself did not increase protection against local infections when compared to the control group.

All but one patient developed fever in the granulocytopenic period regardless of infection experience. Thus, fever may not be a good measurement for the effectiveness of infection prevention modalitites in marrow transplant patients (28).

Most patients received one of two different antibiotic regimens in this study. Because of concern about nephrotoxicity from aminoglycosides in combination with cyclosporine, the antibiotic regimen was changed from tobramycin, ticarcillin and vancomycin to cefotaxime and mezlocillin. The change of antibiotic regimen had no influence on the early septicemia acquisition or on nephrotoxicity. However, significantly more patients had alteration of the cefotaxime and mezlocillin regimen, most by the addition of vancomycin. This was usually done for suspected as well as documented staphylococcus infections in patients remaining febrile after beginning cefotaxime and mezlocillin. Thus, in this study, cefotaxime and mezlocillin neither altered infection acquisition when compared to the tobramycin, ticarcillin and vancomycin regimen nor decreased renal toxicity, leaving the efficacy of the change uncertain.

In contrast to our previous studies, HLA partially matched patients and patients being treated for an infection at admission were included in this study. According to the regression analyses, neither partially matched transplants nor being treated for infection at the time of admission was a significant predictive factor for developing septicemia in the pre-engraftment period.

Twenty-eight (8%) patients died in the pre-engraftment period with no significant difference between the four groups. However, 17 of 28 deaths (61%) were related to infections. Thus a major proportion of early post-transplant deaths were related to bacterial and/or fungal infections. There may be several explanations for the apparent paradox of infection prophylaxis decreasing septicemia but not mortality. As this study primarily focused on the consequence of being assigned or not assigned to an infection prevention modality, all infectious complications were included in the analysis although many patients were not receiving the assigned prophylaxis at the time the infection developed. All post-transplant patients, regardless of infection prevention regimen, are at risk of development of serious noninfectious complications (i. e. mucositis, idiopathic pneumonitis, veno-occlusive disease of the liver, renal impairment etc.). These noninfectious complications may also predispose to invasion of pathogens or result in an inability to deliver the infection prevention modality and subsequently result in an increase in acquisition of infection. As patients in the present as well as earlier studies developed fewer infections when actually receiving a given prophylaxis compared to the overall group assigned to the prophylaxis, more attention to protocol adherence may be necessary to further reduce infection acquisition.

Even though this study seems to suggest that not using specific infection prevention modalities had no influence on early infectious deaths despite a significant difference in the rate of septicemias, one must interpret these result with caution. Because of the overall low mortality pre-engraftment, a potential beneficial impact on survival by infection prevention measures will require a greater number of patients than one center currently can accrue before becoming apparent. Patients transplanted for severe aplastic anemia have no risk of relapse, a low risk of fatal regimen toxicity and an overall higher probability of long-term survival than patients transplanted for hematologic malignancies (29, 20). The mortality for patients transplanted for aplastic anemia in LAF isolation is significantly lower than for patients transplanted for the same disease in conventional hospital rooms (30, 29). Regimen related toxicity, acute and chronic GVHD, non-bacterial interstitial pneumonia and relapse are the most frequent cause of death in patients transplanted for hematologic malignancies (18, 20). Thus, it may be necessary to reduce mortality from these causes before a potential impact of infection prophylaxis modalities on long-term survival can be evaluated in patients transplanted for hematologic malignancies. The type of infection surveillance and the interpretation of this surveillance may influence the consequences of not having patients on an infection prophylaxis regimen. Thus, all patients in the control group in this study were started on broad-spectrum antibiotics for the first episode of fever.

The use of PSA in our hands did not significantly increase the incidence of fungal infections or the development of resistant bacterial strains. Since the vast majority of transplant patients eventually will receive broad-spectrum antibiotics for empiric or therapeutic reasons and as PSA significantly decreased septicemia acquisition, PSA, in or out of LAF isolation, is recommended as infection prophylaxis for granulocytopenic marrow transplant patients.

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