



Bacteraemia during the aplastic phase after allogeneic bone marrow transplantation is associated with early death from invasive fungal infection

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Summary:

Episodes of bacteraemia during the aplastic phase were studied in 500 allogeneic bone marrow (BMT) recipients, regarding incidence, microbial aetiology, risk factors, mortality and causes of death. One hundred and sixty-four patients (33%) had at least one positive blood culture. Gram-positive cocci (α -streptococci and coagulase-negative staphylococci) were found in 146/164 cases (89%). Gram-negative bacteria were present in only seven cases. Receiving marrow from an unrelated donor was the only significant risk factor for bacteraemia in univariate regression analysis. Within 60 days after BMT, 69/500 patients died. The mortality rate was significantly higher among those with positive blood cultures during the aplastic phase, 44/164 (27%) than in those without bacteraemia, 25/336 (7%). Death directly caused by sepsis was unusual in patients with α -streptococci or CNS-bacteraemia (8/146, 5%). In contrast, three of seven patients with gram-negative bacteraemia died of the infection. However, in patients with bacteraemia, 21 of 44 deaths were attributable to invasive fungal infections (18 candida, three aspergillus; autopsy findings). Among patients with negative blood cultures during the aplastic phase, 6/25 died of invasive fungal infection (three candida, one saccaromyces and two aspergillus). This indicates that early bacteraemia is associated with death from invasive fungal infection. Therefore, efforts to shorten the neutropenic period after BMT, prevention, early detection of invasive fungal infections and adjustments of immunosuppressive regimens when marrow from an unrelated donor is used, may improve the outcome after BMT.

Keywords: bone marrow transplantation; bacteraemia; fungal infection; mortality; risk factors

positive bacteraemia and invasive fungal infections, but a decrease of gram-negative infections has been reported since the introduction of ciprofloxacin used as an intestinal decontaminant during the aplastic period.¹ A prolonged period of severe neutropenia, disruption of mucosal barriers due to toxicity of the conditioning regimen and interrupted anatomical barriers by long-term indwelling central venous lines are the major risk factors for infections following BMT.^{2–4} The aim of this retrospective study was to investigate the incidence, aetiology and risk factors for bacteraemia during the aplastic period in 500 consecutive BMT recipients in a single centre. The study also focused on mortality during the first 60 days post-BMT, causes of death and possible relation to bacteraemia.

Material and methods

Demography

Five hundred consecutive patients who underwent allogeneic BMT between 1975 and June 1995 were studied retrospectively, following approval by the Ethics Committee.

There were 311 (62%) males and 189 (38%) females. The median age of recipients was 24 years (range 1–58) and the median age of donors was 30 years (range 1–67).

Pretransplant diagnoses were haematological malignancies in 418 (84%) patients, severe aplastic anaemia in 47 (9%) and non-haematological diseases in 35 (7%) (Table 1). Three hundred and sixty-four (73%) patients received bone marrow from HLA-A, -B, -DR identical siblings, seven from identical twins, seven from HLA-A, -B, -DR identical parents, 45 (9%) from 1–2 antigen mismatched related donors and 75 (15%) from HLA-A, -B, -DR identical and two from 1-antigen mismatched (A or DR) unrelated donors.

Conditioning and GVHD prophylaxis

The BMT procedure has been described previously.^{5–8}

Patients with haematological malignancies received cyclophosphamide (CY) 60 mg/kg for 2 days combined with total body irradiation (TBI) in a total dose of 10 Gy and a median lung dose of 9 Gy ($n = 334$, 67%), or busul-

Infection, especially septicaemia during the aplastic period is a serious complication after allogeneic bone marrow transplantation (BMT). An increased incidence of gram-

Table 1 Demography of 500 BMT patients grafted between 1975 and 1995 at Huddinge Hospital

Diagnosis	Number of patients	
SAA	47	
AML	127	
CR1		85
CR2-4		13
PR		11
Early relapse		7
Relapse		11
ALL	118	
CR1		40
CR2-4		70
PR		2
Early relapse		3
Relapse		3
Lymphoma	12	
CML	115	
CP1		94
CP2		9
Accelerated phase		12
Myelofibrosis	4	
Myeloproliferative syndrome	1	
MDS	14	
JCML	3	
CP1		1
CP2		1
Accelerated phase		1
CLL	1	
Myeloma	23	
Metabolic disorders	33	
Other	2	

SAA = severe aplastic anaemia; AML = acute myelogenous leukaemia; ALL = acute lymphoid leukaemia; CR = complete remission; PR = partial remission; CML = chronic myelogenous leukaemia; CP = chronic phase; MDS = myelodysplastic syndrome; JCML = juvenile chronic myelogenous leukaemia; CLL = chronic lymphoid leukaemia.

phan (BU) 4 mg/kg on each of 4 consecutive days ($n = 54$, 11%), in combination with CY (120 mg/kg) (BUCY).⁵ In 30 patients receiving T cell depletion, total lymph node irradiation (TLI, 6 Gy) in combination with CY (120 mg/kg) was given prior to TBI 7.5 Gy.⁶ Patients with aplastic anaemia and HLA-identical sibling donors ($n = 35$, 7%) received CY 50 mg/kg for 4 consecutive days; six of these patients received additional irradiation and another two BU. Among patients with SAA and unrelated donors, five were given CY + TBI, six CY + TLI and one BUCY. Patients with metabolic diseases were given BU (80 mg/m²) and CY (2g/m²) ($n = 29$, 6%).⁷ All patients who received marrow from unrelated donors and since 1988, those with SAA, regardless of donor, were also given ATG (3–5 mg/kg) or OKT3 (5 mg) for 5 days.

Methotrexate ($n = 85$, 17%), cyclosporin ($n = 57$, 11%), methotrexate + cyclosporin A ($n = 320$, 64%) or T cell depletion ($n = 30$, 6%) were used as GVHD prophylaxis.^{7,8} One patient received cyclosporin and prednisolone. No prophylaxis was given to seven patients who received bone marrow from identical twins.

Engraftment

Engraftment was defined as a stable level of WBC $\geq 0.2 \times 10^9/l$ after the post-transplantation nadir.

Isolation, prophylaxis and antimicrobial therapy

All patients were isolated in rooms with positive airflow pressure.^{9,10} One relative was allowed to stay in the patient's room during the whole transplantation procedure.

Initially, all personnel used protective gowns, gloves and masks when nursing patients or being in their rooms. Since 1988, this was limited to protective gowns and hand disinfection. Patients received polymyxin-B/nalidixic acid and oral amphotericin-B as prophylactic gut-decontamination until May 1986 ($n = 154$, 31%). Thereafter, 346 patients (69%) received ciprofloxacin, 500 mg twice daily, or equivalent doses for children > 1 year of age, in combination with oral amphotericin B.¹¹ Since 1985, all patients with HSV-IgG titres $\geq 10\,000/l$ or a previously recurrent HSV infection have received acyclovir prophylaxis.¹² In addition, two studies with acyclovir or valacyclovir as CMV prophylaxis were performed during this period.¹³

Blood cultures were obtained as soon as the temperature rose above 38.4°C or was $> 38.0^\circ\text{C}$ at least twice within 24 h. Empirical therapy with antibiotics was instituted immediately after samples for cultures had been obtained. The primary antibiotic regimen used was trimethoprim/sulfamethoxazole in combination with an aminoglycoside (amikacin), except in patients with known hypersensitivity to sulphonamides.¹⁴ When necessary, treatment was adjusted according to bacterial susceptibility, if the aetiology of the infection had been established.^{15,16} Amphotericin B, 0.3–0.8 mg/kg or liposomal amphotericin B (AmBisome; NeXstar, Boulder, CO, USA) 1–3 mg/kg, given as empirical antifungal therapy, was usually initiated after 4–5 days of antibiotic resistant fever. In addition, between January 1990 and August 1991, 69 BMT patients were included in a study on prophylactic use of liposomal amphotericin B or placebo against invasive fungal infections; 30 of these patients received an active drug.¹⁷

Bacteraemia and invasive fungal infection (IFI)

Bacteraemia was defined as the first positive blood culture related to a febrile episode during the aplastic period (WBC $< 0.2 \times 10^9/l$). Routinely, two bottle cultures were obtained each time, except in small children where only one aerobic bottle was obtained each time. At least one positive bottle was required for the definition of bacteraemia. Between 1975 and 1989, the bacteriological laboratory made their own blood culture bottles, 1990 to 1991 bottles from KEBO (Oxoid, Basingstoke, UK) were used and from 1992 the Bactec system (Becton Dickinson, Franklin Lakes, NJ, USA) was used as the blood culture method. Invasive candida infection was defined as either candidaemia, and/or positive cultures from at least two organs, except the gastrointestinal tract when obtained at autopsy, in patients who died within 60 days after BMT. Aspergillus pneumonia was defined as pulmonary infiltrates and positive cultures or direct microscopy of BAL, sputum or autopsy specimens.

Statistical methods

The logistic regression model was used in univariate analysis.¹⁸ Bacteraemia during the aplastic phase after BMT was

regarded as the event. All patients with or without bacteraemia during the aplastic phase after allogeneic BMT were included in the study. Risk factors that might have influenced the development of bacteraemia were studied. In comparing absolute numbers, χ^2 analysis was used.

Risk factors for bacteraemia during aplastic phase

Risk factors analysed were recipient age and gender, donor age and gender, pretransplant diagnosis, disease stage (low risk for transplantation-related mortality (TRM): acute leukaemia in 1st complete remission, CML 1st chronic phase, aplastic anaemia, metabolic disorders; high risk for TRM: others), pretransplant serology for cytomegalovirus (CMV) and herpes simplex virus (HSV) in the recipient, HLA-match, related and unrelated donors, conditioning regimen (TBI or not), splenectomy, type of GVHD prophylaxis and bone marrow cell dose.

Mortality rate

Mortality rate was studied in all patients up to 60 days after BMT. Autopsy was performed in all patients during the study period. Bacterial and fungal cultures, as well as specific microbiological stains, were performed from parenchymal organs in all fatal cases. Causes of death were based on the results of the autopsy and clinical observations before death. Causes of death were analysed in detail regarding a possible relation to the bacteraemic episode, defined as: death within 14 days after the latest positive blood culture with development of acute respiratory distress syndrome (ARDS), shock or multiorgan failure (MOF). Mortality from IFI was defined as MOF/ARDS and positive autopsy cultures from at least two organs, excepting the gastrointestinal tract in cases of candidaemia, or from pulmonary cultures in the aspergillus cases, without evidence of other pathogens or other conditions that could be fatal.

Results

Engraftment

Median time to engraftment was 14 days (range 6–35), 29 of 500 patients (6%) died without having engrafted.

Bacteraemia, incidence and aetiology

At least one positive blood culture, obtained during a febrile period, was found in 164 of the 500 patients (33%). When the data were divided into 5-year periods, no significant difference in the incidence of bacteraemia was noticed during the whole 20-year observation period. Bacteraemia among patients who received bone marrow from unrelated donors occurred in 37/77 (48%) and was significantly higher than in recipients of related bone marrow transplants, 127/423 (30%) ($P < 0.01$). The median time from BMT to bacteraemia was 8 days (range 0–30). One hundred and twenty-three of 164 (75%) patients with bacteraemia engrafted after day 14 compared to 149/336 (43%) of patients without bacteraemia; $P < 0.0001$. The micro-

organisms found were α -streptococci in 80 cases (49%) and coagulase-negative staphylococci (CNS) in 67 cases (41%). Ten (6%) cases of bacteraemia were caused by other gram-positive bacteria. In contrast, only seven (4%) episodes were caused by gram-negative rods. Gram-negative bacteraemia occurred in six patients before, and in one case after the introduction of ciprofloxacin as prophylactic gut decontamination.

Fungal infections

Invasive fungal infection (IFI) was diagnosed in 27/69 (39%) patients who died within 60 days of BMT, 21 cases in 44/164 patients with early bacteraemia and six in 25/336 patients without bacteraemia during the aplastic phase ($P < 0.0001$). One patient with candidaemia survived. Among the 21 patients with early bacteraemia and invasive fungal infections, 18 had candida infection (4/18 non-albicans) and three pulmonary aspergillosis. In this group, candidaemia was diagnosed before death in 12 patients, seven during the aplastic phase. Six patients died of IFI, without any early bacteraemic episodes, three had invasive candida infection (one candidaemia, two disseminated candidiasis diagnosed at autopsy, all *C. albicans*), one had evidence of disseminated saccaromyces infection, as well as positive blood cultures, which was also detected at autopsy; two were clinically diagnosed as pulmonary aspergillosis, which was confirmed by cultures taken at autopsy.

Risk factors

The univariate regression analysis showed that patients who received bone marrow from unrelated donors had a significantly increased risk of bacteraemia; 37/164 (23%) compared to 40/336 (12%); $P < 0.01$. However, HLA-mismatched BMT was not associated with an increased risk of bacteraemia among patients who received marrow from related donors.

Mortality rate

Sixty-nine of 500 patients died within 60 days after BMT. Twenty-nine of 69 died without engraftment. Twenty-six of those 29 patients had previously had at least one episode of bacteraemia/candidaemia.

Patients with early positive blood cultures: Forty-four of 164 (27%) patients died within 60 days after BMT. Total mortality within 60 days, in patients with α -streptococci or CNS bacteraemia was 37/147 (25%), compared to 7/17 (41%) in those with other aetiologies. In 12/44 patients (27%), death was considered to be directly attributable to the bacteraemic episode (ARDS, MOF). Twenty-one of 44 deaths (48%) among patients with early bacteraemia were attributable to IFI (autopsy diagnosis). In 11/44 cases (25%), death was caused by VOD, CMV-associated interstitial pneumonia (CMV-IP) or unexpected bleeding.

Patients with early negative blood cultures: Twenty-five of 336 (7%) patients died within 60 days after BMT. Six of 25 deaths (24%) were caused by IFI, two pulmonary

aspergillosis, three candida and one saccaromyces species. In the remaining 17 cases (78%), death was caused by VOD, CMV-IP, acute GVHD, relapse or unexpected bleeding. Two patients died of septic syndrome without having had positive blood cultures (Figure 1).

Discussion

The incidence of septic syndrome combined with positive blood cultures in our material did not differ from that of other BMT units.^{19–21} The frequency of bacteraemia has not changed between different periods, in spite of less strict isolation, ie allowing relatives to stay in the room, no use of gloves and masks, but only hand disinfection and no sterile food. As reported before, the predominant micro-organisms found were gram-positive bacteria, especially α -streptococci and CNS.^{19,20} Gram-negative rods were uncommon, especially after the introduction of prophylaxis with ciprofloxacin. Invasive fungal infections were often diagnosed at autopsy.

Early death, especially during the aplastic period after BMT, is often related to infection,²² which was also found in our study. Positive blood cultures were seen in 26 of 29 patients who died without engrafting.

Death due to bacteraemia caused by α -streptococci or CNS occurred in only 5%, although such micro-organisms were not always entirely sensitive to the primary empirical antibiotic therapy used (aminoglycoside and trimethoprim-sulphamethoxazole). In contrast, death associated with bacteraemia caused by other bacteria, in particular gram-nega-

tive bacteria, occurred in 4/17 (3/7 gram-negative bacteraemia). Thus, in general, prophylactic therapies and those initiated early are sufficient protection against such bacteraemias. It is therefore still important to continue using broad-spectrum antibiotics as first-line therapy in febrile episodes during the aplastic phase, since these types of bacteria are more virulent, although death from fulminant ARDS/MOF with α -streptococci bacteraemia has been described.²³ In the latter cases, treatment with adequate antimicrobial agents has not modified the outcome. However, the few cases of fatal α -streptococci or CNS infections do not indicate the use of vancomycin or teicoplanin as empirical therapy. A change of first-line antibiotics to agents more efficient against these two types of bacteria may be associated with several problems, mainly the risk for emergence of resistance against glycopeptides among the enterococcus and staphylococcus species.^{24–26} This calls for restriction in the use of such antibiotics. Another potential problem is that presently available antibiotics covering gram-positive bacteria are also effective against the anaerobic flora and therefore may increase the risk of invasive fungal diseases. In this series, invasive fungal infections were infrequent, but the associated mortality was high. IFI were also the principal cause of early death among our patients despite early empirical therapy with amphotericin B or liposomal amphotericin B.^{27,28} To improve the prognosis for patients with IFI and to reduce the incidence, some issues require attention. In our setting, only 13 of 27 patients with IFI were diagnosed by blood culture, seven of these during the aplastic phase. Better early diagnostic procedures are needed. Candida-DNA detection by poly-

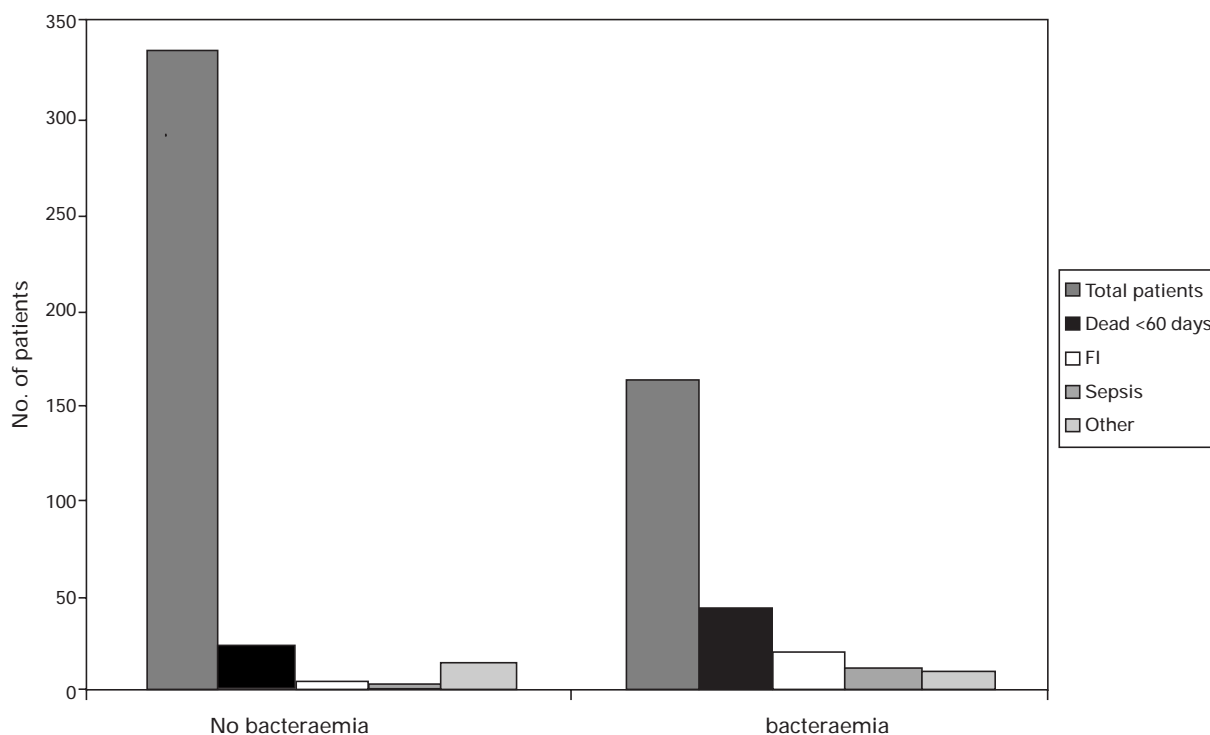


Figure 1 Mortality and causes of death within 60 days after BMT in patients with or without early bacteraemia. Total = number of patients with ($n = 164$) or without ($n = 336$) bacteraemia. Dead < 60 days = number of patients who died within 60 days post-BMT. FI = death within 60 days from invasive fungal infection. Sepsis = death within 60 days from septic syndrome. Other = death within 60 days from VOD, GVHD, CMV-IP or other causes.

merase chain reaction (PCR) is being developed to diagnose invasive candida in blood.²⁹ There are also reports indicating that blood cultures using large volumes of blood (≥ 20 ml blood) yield a higher positive rate.³⁰ However, even if better procedures are developed for more accurate diagnosis the outcome may still be poor in patients with verified invasive fungal disorders despite currently available treatment. Thus, antifungal prophylaxis may be a better way to handle this problem. A few centres have reported a reduced incidence of invasive fungal diseases when using fluconazole, 400 mg/day, as prophylaxis during the aplastic period.^{31,32} However, this may lead to selection of resistant candida strains such as *Candida krusei* and *Candida glabratae*. Moreover, fluconazole has no effect on aspergillus strains.³³ Use of amphotericin B for prophylaxis has not been accepted, because of the high incidence of nephrotoxicity using this drug.³³ The combination of amphotericin B with lipid-based delivery systems has significantly reduced the frequency of side-effects; however the high costs limit their use.^{27,28} In our study, most invasive candida infections (11 of 27) were associated with α -streptococci bacteraemia. This indicates that such fungal infections may have been associated with invasion from a disrupted gastrointestinal mucosal barrier. Thus, reducing mucosal damage may also reduce the risk for invasive fungal infections. Recently, it has been found that IL-11 is an important cytokine in the upregulation of mucosal barriers.^{34,35} Use of IL-11 may offer a prophylactic biological approach to improving mucosal ability in preventing invasion by these microbes. It has been reported that neutrophils, monocytes and eosinophils kill candida blastospores by phagocytosis. In addition, neutrophils and monocytes can also kill fungal hyphae. *In vitro* data suggest that myeloperoxidase-dehydroperoxide and the superoxide systems are the major mechanisms responsible for intracellular killing of candida. These systems may be upregulated several fold by the granulocyte-macrophage colony-stimulating factor GM-CSF, TNF α and in particular IFN γ , whereas a number of other cytokines are ineffective.³⁶

Univariate regression analysis clearly showed a significant difference in bacteraemia frequency between patients receiving grafts from unrelated compared to related donors (48 vs 31%), but no difference in mortality within 60 days between patient categories in the bacteraemia group and non-bacteraemia group. Furthermore, late infections are more common among patients receiving marrow from unrelated donors.³⁷ Our recipients of unrelated marrow receive more intensive immunosuppressive treatment (additional ATG/OKT-3 during conditioning, higher CsA dose and in some cases T cell depletion).³⁸ These data may indicate a need for adjustment of immunosuppressive therapy in such patients, although the increased incidence of GVHD in this group might be a limiting factor.³⁹ Furthermore, additional immunoprotective strategies should be considered in this patient category to reduce the risk of, in particular, mucosa-associated invasive fungal disorders and septicaemias, and the use of haematopoietic growth factors to reduce the duration of neutropenia should be considered.⁴⁰⁻⁴² The results of this study indicate that bacteraemia during the aplastic phase after BMT is associated with early death post-BMT, especially from invasive fungal infection and may be an

indicator for those at high risk of early transplant-related mortality.

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