

**Outcome of Diffuse Alveolar Hemorrhage in Hematopoietic Stem Cell Transplant  
Recipients**

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## **Abstract**

Previous studies have reported mortality rates of about 80% in hematopoietic stem cell transplant recipients with diffuse alveolar hemorrhage. This retrospective study describes the clinical course of 48 such patients: mean age 47.7 years, 52% autologous transplant and 67% peripheral stem cell source. The hemorrhage occurred within one month of transplant in 28 patients. Symptoms included dyspnea in 92%, fever in 67%, cough in 56%, and hemoptysis in 15%. Intensive care unit admission was required in 85% and mechanical ventilation in 77%. Most of the patients were treated with intravenous methylprednisolone 1 g daily for three days and then tapered off after a median of 22 days. The hospital mortality was 48%. The cause of death was respiratory failure in 15 of the 23 deaths. Mortality was 28% in autologous compared to 70% in allogeneic transplant recipients ( $P = 0.0040$ ). The mortality rate of patients whose hemorrhage occurred within the first 30 days of transplant was 32% compared to 70% of those with late hemorrhage ( $P = 0.0096$ ). This study shows that survival rate of hematopoietic stem cell transplant recipients with diffuse alveolar hemorrhage is better than previously reported and early onset and autologous transplant are favorable prognostic indicators.

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## **Introduction**

The International Bone Marrow Transplant and the Autologous Blood and Marrow Transplant Registries estimate that over 30,000 autologous and approximately 17,000 allogeneic hematopoietic stem cell transplants were performed in 1998. Pulmonary complications develop in 30% to 60% of hematopoietic stem cell transplant (HSCT) recipients (1, 2). Diffuse alveolar hemorrhage (DAH) occurs in about 5% of both allogeneic and autologous HSCT recipients (3). The presenting symptoms of DAH usually include dyspnea and dry cough (4). Hemoptysis is uncommon (4). Even with corticosteroid therapy, the reported mortality rate of DAH exceeds 70% (5). Although DAH develops in the early post-transplant period in most patients, it may also occur late (6). However, the difference in outcome between early and late DAH and the prognostic significance of the type and source of stem cell in HSCT recipients with DAH have not been well studied. This retrospective study describes the clinical course and prognostic factors of HSCT recipients with DAH

## **Methods**

Design:

In this retrospective, cohort study, we reviewed the medical records of HSCT recipients with DAH. DAH was defined by the presence of widespread alveolar injury manifested by multi-lobar pulmonary infiltrates, increased alveolar to arterial oxygen gradient, absence of infection compatible with the diagnosis, and bronchoalveolar lavage (BAL) showing progressively bloodier return or the presence of  $\geq 20\%$  hemosiderin laden

macrophages (3). Our protocol for the immunocompromised host with diffuse pulmonary infiltrates involved sending BAL fluid for cytologic and microbiologic examinations including Gram stain, bacterial culture, acid-fast bacilli stain, mycobacterial culture, fungal stain and culture, direct fluorescence antibody and culture for Legionella, special acid-fast stain for Nocardia, calcofluor white stain for *Pneumocystis carinii*, viral culture and shell vial assay for cytomegalovirus. Urine and blood cultures were also obtained routinely to rule out potential infections. The percent of hemosiderin-laden macrophages in BAL fluid was measured in most patients but was not part of the protocol.

#### Subjects and setting:

From our bone marrow transplant database, we identified 1215 patients who had HSCT from October 1994 through June 2002: 130 had bronchoscopy and 48 had DAH. The study was approved by the Mayo Foundation Institutional Review Board. Patients under age of 17 years and those who did not authorize their medical records to be reviewed for research were excluded from the study.

#### Measurements:

We collected baseline demographic and transplant related patient characteristics. Neutrophil engraftment was defined as absolute neutrophil count of  $0.5 \times 10^9/L$  on two or more consecutive days. The onset of DAH was divided into early, occurring within the first 30 days of transplant, and late after 30 days from transplant. Peri-engraftment period was defined as the period within 5 days of neutrophil engraftment.

The following data were obtained: the presence of fever, cough, hemoptysis, and dyspnea at the time of DAH; the ratio of the arterial oxygen tension to the fraction of inspired oxygen; the percent of hemosiderin-laden macrophages in BAL fluid, pathology findings of lung tissue; admission to the intensive care unit, mechanical ventilation, hospital mortality, and cause of death. The cause of death was obtained from the death certificates as determined by the pathologist. Treatment with and dose of corticosteroid, the number of days the initial daily corticosteroid dose was administered, and the total duration of corticosteroid therapy were also noted.

#### Analysis:

Means and standard deviations were used to summarize approximately normally distributed data, while medians and ranges were used for skewed data. For statistical comparisons between groups, we used Student's t, the rank sum, chi square and Fisher's exact tests. We created a multivariate logistic regression model by entering baseline characteristics that are associated with hospital mortality at a statistically significant level by univariate analyses. The odds ratios (OR) arising from logistic regression analysis and 95% confidence intervals (CI) were calculated. We considered P values < 0.05 as statistically significant. We used StatView software, Version 5.0.1, SAS Institute Inc., Cary, NC, 1992 – 1998, for statistical analyses.

## Results

Most of the patients were white, and the most common indication for HSCT was hematologic malignancy (Table 1). The type of transplant was autologous in about half, and stem cell source was peripheral blood in two-thirds (Table 1). Among the 23 allogeneic transplant recipients, the stem cell source was peripheral blood in 11 and bone marrow in 12. Among the 25 autologous transplant recipients, the stem cell source was peripheral blood in 21 and bone marrow in 4. The DAH occurred at a median of 23.5 days (range from 4 to 1330) after transplant and 6 days (range from 17 days before to 1322 days after) after neutrophil engraftment. The onset of DAH was early in 28 (58%) patients. Excluding one patient who died before neutrophil engraftment, the DAH occurred during the peri-engraftment period in 17 (36%) of the 47 patients. Eight patients were receiving corticosteroids, for reasons other than DAH, at the time DAH developed. Symptoms included dyspnea in 44 (92%), fever in 32 (67%), cough in 27 (56%), and hemoptysis in 7 (15%). The ratio of the arterial oxygen tension to the inspired oxygen fraction was  $142 \pm 69$ .

The indication for bronchoscopy was the development of diffuse pulmonary infiltrates on chest radiographs. Bronchoscopy was performed at a median of 1 (range from 0 to 16) day after diffuse infiltrates were detected on chest radiographs. The BAL fluid return was described as being progressively bloodier in 42 (88%) patients. The median hemosiderin-laden macrophage, measured in 30 patients, was 8% (range from 0 to 93%). The hemosiderin-laden macrophages were 20% or higher in 12 (40%) of the 30 patients. In

one patient with no hemosiderin-laden macrophages in the BAL fluid despite progressively bloodier return during the first bronchoscopy, repeat bronchoscopy 17 days later showed 67% hemosiderin-laden macrophages. Six patients had 20% or higher hemosiderin-laden macrophages in the BAL fluid despite the absence of progressively bloodier return. The microbiology and cytology results of the BAL were negative in all patients.

Transbronchial lung biopsies were non-specific in two, and suggestive of acute and organizing pneumonia in one and alveolar hemorrhage in another one. Thoracoscopic lung biopsies showed diffuse alveolar damage in two patients. Autopsy was performed on nine patients at a median of 15 (range from 5 to 24) days after the onset of DAH. Diffuse alveolar damage was found in 8, DAH in 2, and bronchopneumonia in 2 of the nine autopsies.

Four patients never received any treatment for DAH for the following reasons: DAH was not considered the main medical problem in two, the alveolar hemorrhage was considered to be due to low platelets in one and clinical improvement was noted before the diagnosis was entertained in another one. Corticosteroid therapy was initiated in 36 patients at a median of 0 (range from -3 to 4) days following bronchoscopy. Eight patients were receiving corticosteroid treatment when they developed DAH: for graft-versus-hosts disease in four, hematologic malignancy in three, and cerebral edema in one. Among the eight patients who had been receiving corticosteroid before the development of DAH, the dose was increased in four and not changed in other four patients. The initial

corticosteroid used was intravenous methylprednisolone 1 g daily in 27, 2 g daily in five, and other doses in 12 patients. The initial daily corticosteroid doses ranged from 60 mg to 2 g of methylprednisolone. The initial daily corticosteroid dose was continued for a median of 3 days (range from 1 to 14). Eleven (31%) of the 36 patients in whom corticosteroid therapy was initiated for DAH died before completing corticosteroid treatment; among the 25 patients who completed corticosteroid treatment, the median length of corticosteroid treatment was 22 days (range from 2 to 117).

Forty-one (85%) of the patients were admitted to the intensive care unit. Thirty-seven (77%) patients received mechanical ventilator support: three non-invasive only, 25 invasive only, and 9 invasive and non-invasive ventilation. The median intensive care unit length of stay was 10 days (range from 1 to 63). The median length of hospital stay after the diagnosis of DAH was 14 days (range from 1 to 64). Twenty-three patients (48%) died in the hospital. The causes of death listed on the death certificates were respiratory failure in 15 (65%), sepsis in four (17%), and multiple organ failure, intracranial bleeding, multifocal leukoencephalopathy, and underlying multiple myeloma one in each.

We did not find statistically significant differences in age, gender, race and source of stem cell between survivors and non-survivors (Table 2). Fourteen of the 26 HSCT recipients (54%) who received total body irradiation died compared to 9 of the 22 HSCT recipients (41%) who did not receive total body irradiation ( $P = 0.3713$ ). The 28% mortality rate of autologous HSCT recipients was lower than the 70% mortality rate of

allogeneic HSCT recipients ( $P = 0.0040$ ) (Table 2). Among allogeneic transplant recipients, graft versus host disease was present in one of the 7 (14%) survivors compared to seven of the 16 (44%) non-survivors ( $P = 0.1722$ ). The 32% hospital mortality rate of early DAH was lower than the 70% mortality rate of late DAH ( $P = 0.0096$ ) (Table 2). Three of the 17 patients who developed DAH during the peri-engraftment period (18%) died in the hospital compared to 19 of 30 patients who developed DAH during the non peri-engraftment period (63%) ( $P = 0.0054$ ).

Seven (88%) of the eight patients who were receiving corticosteroids when they developed DAH died compared to 16 (40%) of the other 40 patients who were not receiving corticosteroids ( $P = 0.0204$ ). Two of the four patients who were not treated with corticosteroid died. Among the 36 patients in whom corticosteroid treatment was initiated after the diagnosis of DAH, 14 (39%) died. Among the 27 patients who completed corticosteroid treatment, the median length of corticosteroid treatment was 21 days (range from 2 to 117) for survivors compared to 22 (range from 3 to 70) days for non-survivors ( $P = 0.9254$ ). Twelve (44%) of the 27 patients who were treated with an initial daily dose of one gram methylprednisolone died compared to three (50%) of the six patients treated with higher doses, and six (55%) of the 11 patients treated with lower doses ( $P = 0.8462$ ). Multiple logistic regression analysis showed that allogeneic stem cell transplant (OR = 22.05, 95% CI 2.53 – 192.48;  $P = 0.0051$ ) and late onset DAH (OR = 12.71, 95% CI 1.36 – 119.01;  $P = 0.0259$ ) were independently associated with increased mortality. Being on corticosteroid at the onset of DAH was not independently associated with mortality (OR = 5.74, 95% CI 0.49 – 66.61;  $P = 0.1625$ ). Two of the 11 patients (18%) who did not

receive mechanical ventilation compared to 21 of the 37 patients (57%) who received mechanical ventilation died in the hospital ( $P = 0.0386$ ). Among the 36 patients in whom corticosteroid therapy was initiated for DAH, no significant difference was found in the timing of the initial corticosteroid therapy: corticosteroid therapy was started at a median of 0.5 (range from  $-3$  to  $4$ ) days after BAL in survivors and median of 0 (range from  $-2$  to  $4$ ) days in non-survivors ( $P = 0.4854$ ).

## **Discussion**

In this study of 48 HSCT recipients with DAH, we found a hospital mortality rate lower than that previously reported in the literature. We confirmed that DAH occurs during the early post-transplant period in most patients and showed that autologous transplant and early onset DAH are associated with a favorable prognosis. We confirmed that hemosiderin-laden macrophages in the BAL fluid and the macroscopic appearance of BAL return complement each other in the diagnosis of DAH. Despite the use of corticosteroid therapy in almost all patients, there were variations in the dose and duration of treatment.

The development of DAH in HSCT recipients is associated with high morbidity and mortality. Previous studies have shown that most HSCT recipients with DAH require mechanical ventilator support (5, 7-10). In the present study, 85% of the patients required admission to the intensive care unit and the majority received mechanical ventilator support. The mortality rate of DAH in HSCT recipients is very high, with reported ranges

between 64% and 100% (Table 3) (2, 4, 5, 8, 10-13). In those requiring mechanical ventilation, the reported mortality rates range between 81% and 100% (2, 5, 8, 10). Although the initial presentation of DAH in HSCT recipients may be respiratory failure, the two most commonly reported causes of death are multiple organ failure and sepsis (5, 12). Respiratory failure with active pulmonary hemorrhage has been reported to be responsible for less than 15% of the deaths (12). However, in the present study, the overall mortality was lower than previously reported and respiratory failure was responsible for most of the deaths. Variations in patient mix and recent improvements in clinical practices of infectious diseases, critical care medicine and bone marrow transplantation may explain the differences in mortality rate and the causes of death between the present and previous studies.

Compared to 48% in our study, 83% of the patients received allogeneic transplant in the study by Lewis et al (5). Peripheral blood stem cell source was used in 67% of our patients compared to none of the patients in the studies by Robins and Metcalf (4, 12). In the studies by Robins and Metcalf, none of the patients had leukemia or myelodysplastic syndrome, and about one-third had solid tumors (4, 12). In our study, 65% of the patients had leukemia or myelodysplastic syndrome, and only 2% had solid tumor. In the last few years, there have been newer developments that help in the prevention, early diagnosis and treatment of infectious complications, especially cytomegalovirus infection. We have also been using noninvasive ventilation and lung protective strategies, which have been shown to improve outcome, in providing ventilator support to these patients. Changes in conditioning regimen, the more frequent use of autologous transplant and peripheral

blood stem cell source, and the early diagnosis of DAH and initiation of corticosteroid therapy may also have contributed to the improved outcome in the present study.

Autologous transplant and early onset DAH were associated with good outcome in this study. The prognostic significance of the transplant type and source of stem cell in HSCT recipients with DAH has not been well described. Earlier studies of DAH consisted mostly of autologous HSCT recipients (4, 12). In the current study, we had an almost equal number of autologous and allogeneic HSCT recipients. The survival advantage of the autologous group is not surprising since allogeneic transplant recipients are prone to multiple other complications, including graft versus host disease. In the present study, we did not find statistically significant difference in stem cell source between survivors and non-survivors. There is limited information in the literature addressing the prognostic importance of peripheral blood stem cell source in critically ill HSCT recipients. In one study of critically ill HSCT recipients admitted to the intensive care unit, there was no significant difference in mortality between the two stem cell source groups (14). We found that early onset DAH is associated with a favorable prognosis. The association with neutrophil engraftment and the good response to corticosteroid therapy may account for the favorable prognosis in early onset DAH. We also noted that only one of the eight patients who were receiving corticosteroid at the onset of DAH survived. However, since these patients had underlying conditions such as graft versus host disease and were more likely to have late onset DAH, the corticosteroid therapy was not found to be an independent risk factor for mortality.

Because DAH in HSCT recipients is considered to be an inflammatory response to various insults, and based on retrospective studies, systemic corticosteroids are used to treat DAH (7, 12, 15). However the dose and duration of treatment are not well defined. In a retrospective study, Metcalf et al have shown improved survival in HSCT recipients treated with methylprednisolone at a daily dose of > 30 mg (12). They used methylprednisolone 125 to 250 mg every 6 hours for the first 4 to 5 days and then tapered over 2 to 4 weeks (12). In the present study, an initial daily methylprednisolone dose of 1 g for three days was used in the majority of the patients with gradual tapering over a period of about three weeks. However, there were wide variations in our practice stressing the need for prospective studies to determine the ideal dose and duration.

Although the onset of DAH is usually within the first 30 days following HSCT (2, 4, 5, 7, 15), late onset DAH is not uncommon (6). In the present study, 42% of the DAH was late onset. Similar to previous studies, dyspnea was the most common symptom and fever and cough were present in the majority of our patients (2, 4, 7, 15, 16). Hemoptysis is rare in HSCT recipients with DAH, limited to very few case reports (2, 16). None of the 29 patients had hemoptysis in the study by Robbins et al (4). Fifteen percent of the patients had hemoptysis in our study.

There are similarities and differences in the pathogenesis and diagnostic criteria between idiopathic pneumonia syndrome, periengraftment syndrome and DAH (3). The diagnosis of DAH in HSCT recipients is often made by progressively bloodier returns or increased

number of hemosiderin-laden macrophages in BAL fluid (4). Our study showed that these two criteria complement each other in the diagnosis of DAH. However, these diagnostic criteria have some weaknesses. The appearance of the BAL return introduces an element of subjectivity and bloodier returns can be due to the presence of blood in the distal airways even if the source is not alveolar. Despite the appearance of bloodier BAL return, the hemosiderin-laden macrophages were elevated above the diagnostic threshold level only in the minority of our patients. Following acute alveolar hemorrhage, it may take 48 to 72 hours for hemosiderin-laden alveolar macrophages to appear in BAL fluid, partly explaining this low diagnostic sensitivity (17). Moreover, the small number of alveolar macrophages in the immediate post-transplant period may not be adequate enough to correctly estimate the percentage of hemosiderin-laden alveolar macrophages in BAL fluid.

The present study has several limitations. It was a retrospective study limited to a single medical center with a small sample size. The small sample size has resulted in unstable logistic regression model with wide 95% CI of the odds ratios. The study included patients with underlying diagnoses predominantly of hematologic malignancies. Because of our referral pattern, almost all of our patients were Caucasians. Since measurement of hemosiderin-laden macrophages was not part of the routine protocol, DAH may have been under-diagnosed. However, it is difficult to determine the impact of such under-diagnosis on outcome. Despite its limitations, our study showed a higher survival rate of HSCT recipients with DAH compared to previous studies. We also noted that early onset DAH and autologous transplant are favorable prognostic indicators. Future studies should

address the differences in pathogenesis between early and late onset DAH as well as between autologous and allogeneic HSCT recipients with DAH. We also need prospective clinical trials to determine the optimal dosage and duration of corticosteroid therapy.

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**Table 1: Characteristics of 48 hematopoietic stem cell transplant recipients with diffuse alveolar hemorrhage**

Characteristics

Age, years 47.7 ± 12.0

Gender

Male 29 (60%)

Female 19 (40%)

Race

White 44 (92%)

Hispanic 1 (2%)

Asian 2 (4%)

Black 1 (2%)

Indications for HSCT

Hematologic malignancy

Acute myeloid leukemia 11 (23%)

Multiple myeloma 10 (21%)

Non-Hodgkin lymphoma 8 (17%)

Acute lymphocytic leukemia 4 (8%)

Chronic myeloid leukemia 3 (6%)

Myelodysplastic syndrome 3 (6%)

Hodgkin lymphoma 3 (6%)

Others

Amyloidosis 3 (6%)

Breast cancer	1 (2%)
Paroxysmal nocturnal hemoglobinuria	1 (2%)
POEMS syndrome	1 (2%)
Type of transplanted stem cell	
Autologous	25 (52%)
Allogeneic	23 (48%)
Source of stem cell	
Peripheral blood	32 (67%)
Bone marrow	16 (33%)

POEMS = Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin disorders

**Table 2: Differences between survivor and non-survivor hematopoietic stem cell transplant recipients with diffuse alveolar hemorrhage**

<u>Characteristics</u>	<u>Survivors</u>	<u>Non-survivors</u>	<u>P-value</u>
	N = 25	N = 23	
Age	47.4 ± 12.9	48.1 ± 11.3	0.8460
Gender			0.5142
Male	14 (56%)	15 (65%)	
Female	11 (44%)	8 (35%)	
Race			0.2320
White	24 (96%)	20 (87%)	
Asian	0	2 (9%)	
Black	1 (4%)	0	
Hispanic	0	1 (4%)	
Type of transplanted stem cell			0.0040
Autologous	18 (72%)	7 (30%)	
Allogeneic	7 (28%)	16 (70%)	
Source of stem cell			0.8381
Peripheral blood	17 (68%)	15 (65%)	
Bone marrow	8 (32%)	8 (35%)	
Timing of diffuse alveolar hemorrhage			0.0096
Early	19 (76%)	9 (39%)	
Late	6 (24%)	14 (61%)	

**Table 3: Hospital mortality of hematopoietic stem cell transplant recipients with diffuse alveolar hemorrhage**

<u>Study</u>	<u>Number</u>	<u>Death (%)</u>
Witte (13)	39	30 (77)
Lewis (5)	23	17 (74)
Robbins (4)	29	23 (79)
Jules-Elysee (2)	10	10 (100)
Huaranga (8)	26	21 (81)
Metcalf (12)	65	49 (75)
Sisson (10)	14	9 (64)
Present study	48	23 (48)
Total	254	182 (72)