11. Supportive care in bone marrow transplantation: pulmonary complications

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Pulmonary complications after marrow transplantation

Incidence and significance

Overall, 40% to 60% of patients develop pulmonary disease at some time after marrow transplantation, and 24% to 40% require intensive care [1,2]. Characteristics such as increased HLA disparity with the donor source, high-dose conditioning regimens, active malignancy, and advanced age of the patient are associated with increased incidence of complications [3,4]. The incidence among patients who receive total body irradiation (TBI) for conditioning is higher than that of patients who receive only chemotherapy. Pneumonia as a clinical syndrome is the leading infectious cause of death, and until recently, Cytomegalovirus (CMV) was the most common cause of fatal pulmonary infection [5]. The incidence of some pulmonary infections, such as Pneumocystis carinii and perhaps bacterial pneumonia, has decreased due to the routine use of prophylactic antimicrobial agents. However, diffuse 'idiopathic' pulmonary injury continues, with mortality rate exceeding 60%. Newer understanding of idiopathic lung injury has led to the delineation of the recently coined 'idiopathic pneumonia syndrome' [6].

Significant pulmonary dysfunction persists or develops in some long-term survivors months and even years after successful marrow transplantation. Airflow obstructive defects occur in at least 10% of patients with chronic GVHD and have been seen, albeit rarely, in recipients of autologous marrow [7–9]. Obliterative bronchiolitis is the most commonly identified obstructing lesion and may progress to profound respiratory insufficiency and death [7]. Progressive restrictive lung disease may be seen as a complication of transplantation occurring years after the procedure. Little is currently known about the incidence and risks of these long-term processes.

Temporal sequence of pulmonary disease syndromes

Specific complications tend to occur within well-defined periods that correspond to the state of immune reconstitution [10]. These complications may be

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grouped according to the time of presentation relative to the day of marrow transplantation [11]. The groupings are based in part on the fact that chronic GVHD occurs approximately at or beyond day 100 after allogeneic transplant, delimiting a 'late' from an 'early' period.

Complications within the first 30 days are dominated by regimen-related toxicities. A period of pancytopenia is the rule, although administration of hematopoietic colony stimulating factors may shorten the duration [12]. Pulmonary edema syndromes due to excess fluid administration have been reported in up to half of marrow transplantation recipients, but should be expected less frequently with appropriate attention to fluid management [13]. Also, congestive heart failure due to cardiotoxic chemotherapy, adult respiratory distress syndrome (ARDS) due to chemoradiotherapy injury or sepsis, and pulmonary hemorrhage in the presence of thrombocytopenia contribute to diffuse infiltrates. These patients frequently suffer from multiorgan disease with regimen-related toxicities or, among allogeneic marrow recipients, grade II–IV (moderate-severe) acute GVHD. Severe oral mucositis is common and may result in recurrent aspiration of oral secretions. Secondary infection of the denuded oral mucosa with Herpes simplex virus (HSV) or Gram-negative bacilli may delay healing and increase the risk of pneumonia. During this period, diffuse pulmonary infiltrates rarely are infectious, and opportunistic infections are not prevalent [14].

During days 30 to 100–150, granulocyte number and function usually have returned to normal, but defects in humoral and cell-mediated immunity persist. Both opportunistic and idiopathic pneumonias occur in this period. Historically, viral pneumonias, especially CMV, were the most frequent causes for diffuse pulmonary infiltrates. More recently, the advent of effective prophylaxis and early treatment strategies has markedly decreased the incidence of CMV and HSV pneumonia [15–17].

Impact of transplant techniques (PBSCs, growth factors)

The primary differences in pulmonary complications between autologous and allogeneic marrow transplantation are the incidence of infections and late airflow obstructive defects. Viral pneumonia is significantly less common among autologous marrow recipients, presumably due to less suppression of cytotoxic T lymphocytes (CTLs) from graft-versus-host disease and its treatment and prophylaxis. CMV pneumonia occurs in 4% or less of autologous recipients [18]. Additionally, invasive fungal disease after the initial period of neutropenia appears less common for similar reasons [19].

Idiopathic lung injury, associated with chemoirradiation or sepsis syndrome, occurs after both autologous and allogeneic marrow transplantation with similar frequency. We have recently shown that there is no statistical difference in the incidence of idiopathic injury within the first four months: 7.6% for allogeneic and 5.7% for autologous [20].

The use of alternative hematopoietic precursor sources, such as mobilized

peripheral blood stem cells, and cytokines, such as hematopoietic cell colony stimulating factors, have shortened the time to engraftment [12]. The shorter period of neutropenia would be expected to decrease the incidence of pulmonary complications through several avenues. First, marrow recipients should be at reduced risk of opportunistic infections due both to the improved granulocyte numbers and to the shortened duration of hospitalization. Second, improved platelet counts should decrease hemorrhage associated with lung injury.

However, the risks for lung injury associated with chemoirradiation therapy may be unchanged by the hematopoietic precursor source. Idiopathic lung injury remains a danger. At present, few data exist to convincingly demonstrate that the incidence of pulmonary complications is lower with the newer transplant techniques. It is likely that opportunistic infections will decrease but idiopathic injury will be unchanged, similar to the experience with autologous marrow transplantation.

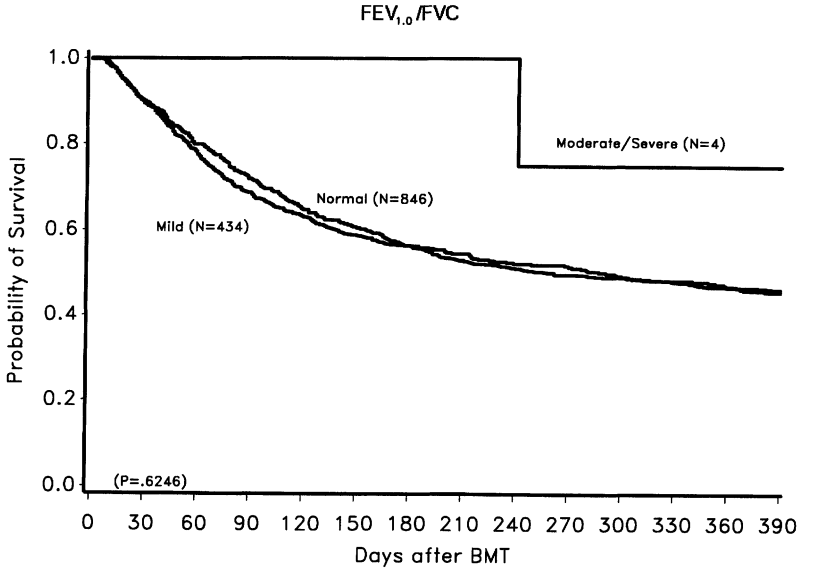
Surveillance for pulmonary complications

Pulmonary function testing

Pretransplant. Pulmonary function testing (PFT) is a standard part of the pretransplant evaluation at many centers. The results form baseline data for comparison with later testing and have been used as an indication to exclude a candidate from transplant. Abnormalities in the measures of airflow, lung volume, and diffusing capacity have been associated with increased risk of pulmonary complications after transplant [21,22].

Abnormal pretransplant PFT results are predictive of mortality [23]. After other clinical characteristics associated with death after transplantation (age, relapsed malignancy, HLA-mismatched graft, etc.) have been accounted for, restrictive lung defect (decreased total lung capacity), hypoxemia, and reduced diffusing capacity are associated with statistically increased risk of death, especially within the first few months after transplant (figure 1). In this study, the risks associated with these PFT results were applicable to autologous as well as allogeneic marrow recipients, suggesting that the risks predicted mortality due to treatment-related toxicities. Surprisingly, hypoxemia and reduced diffusing capacity were independently associated with death, each carrying risk. It was initially assumed that these two physiologically linked measurements would provide similar information regarding mortality risk. However, reduced diffusing capacity appears to predict death by means other than respiratory failure. It is likely that reduced diffusing capacity is associated with an increased risk of fatal hepatic veno-occlusive disease (data unpublished). Systemic endothelial injury due to previous chemotherapy may account for both the diffusing capacity abnormalities and fatal liver failure.

While pretransplant PFT results are statistically associated with complica-



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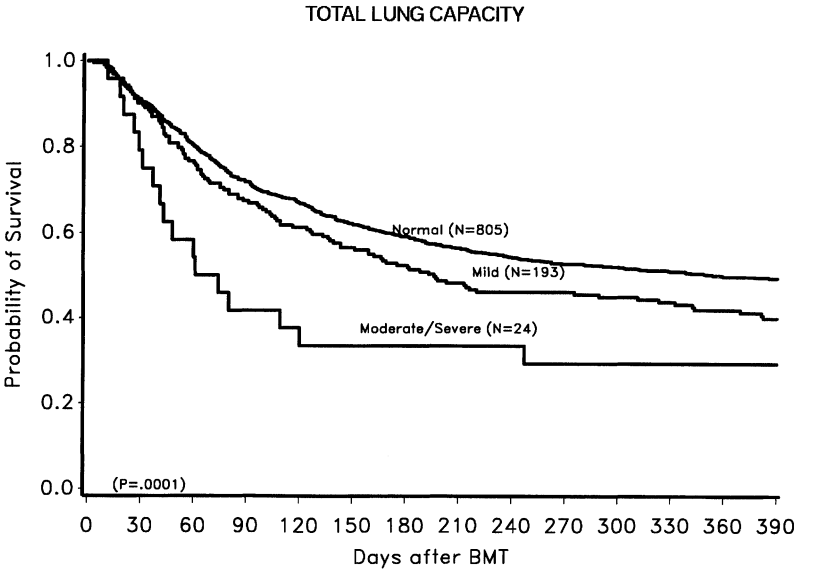

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Figure 1. Kaplan–Meier survival plots for marrow recipients with normal, mild abnormalities or moderate-severe abnormalities in PFT before marrow transplantation. Log-rank *p*-values are indicated in parentheses. **(A)** FEV_1/FVC; normal ≥80%, mild <80% and ≥60%, moderate/severe <60%. **(B)** Total lung capacity (TLC); normal ≥80% of predicted, mild <80% and ≥60% of predicted, moderate/sever <60% of predicted. **(C)** Diffusing capacity (D_LCO_{sb}); normal ≥80% of predicted, mild <80% and ≥60% of predicted, moderate/severe <60% of predicted. **(D)** Alveolar-arterial pO_2 gradient ($P(A\text{-}a)O_2$); normal ≤20 mmHg, mild >20 mmHg and ≤30 mmHg, moderate/severe >30 mmHg. (From Crawford SW, Fisher L. Predictive value of pulmonary function tests before marrow transplantation. Chest 101:1257–64, 1992, with permission.)

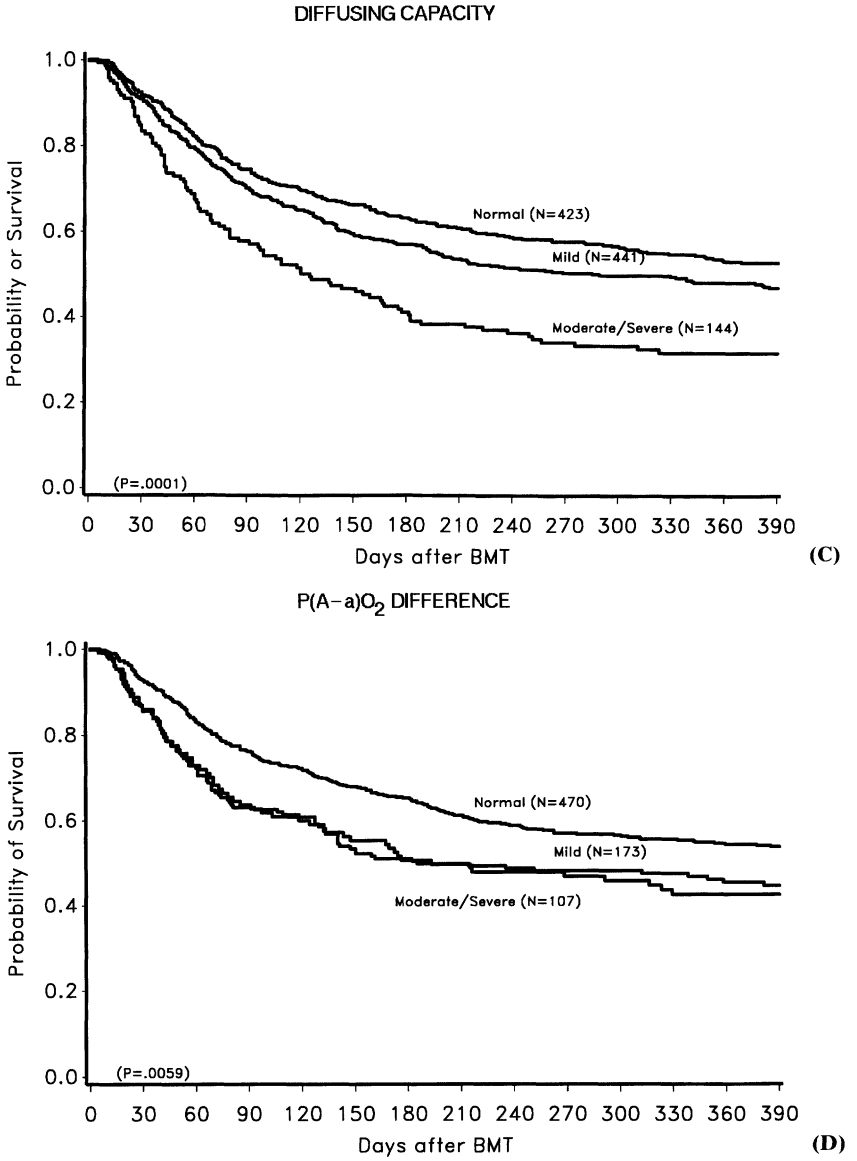
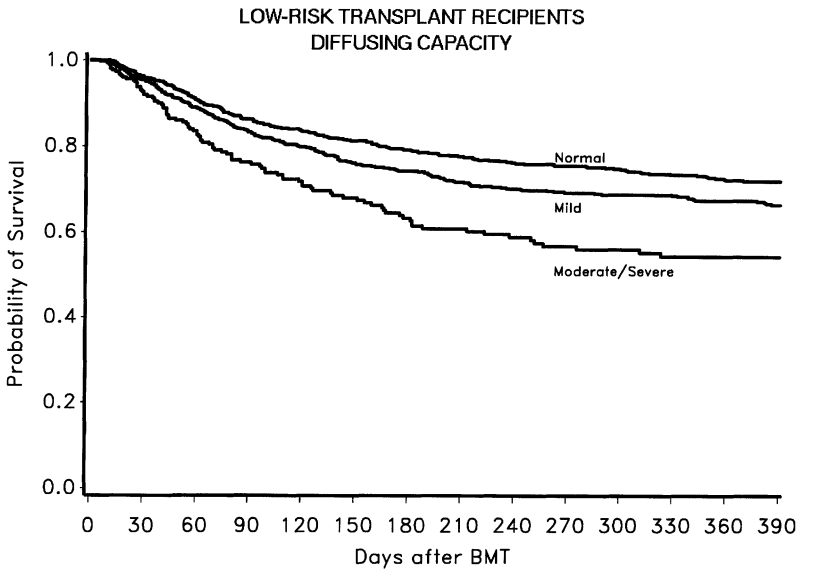


Figure 1 (continued)

tions and death, there are no absolute values for these tests that predict these outcomes with specificity (figure 2). On average, a total lung capacity or diffusing capacity value (corrected for hemoglobin content) below the lower limits of normal may be associate with a 20% decrease in the probability of survival. Such information should not be used as an absolute contraindication



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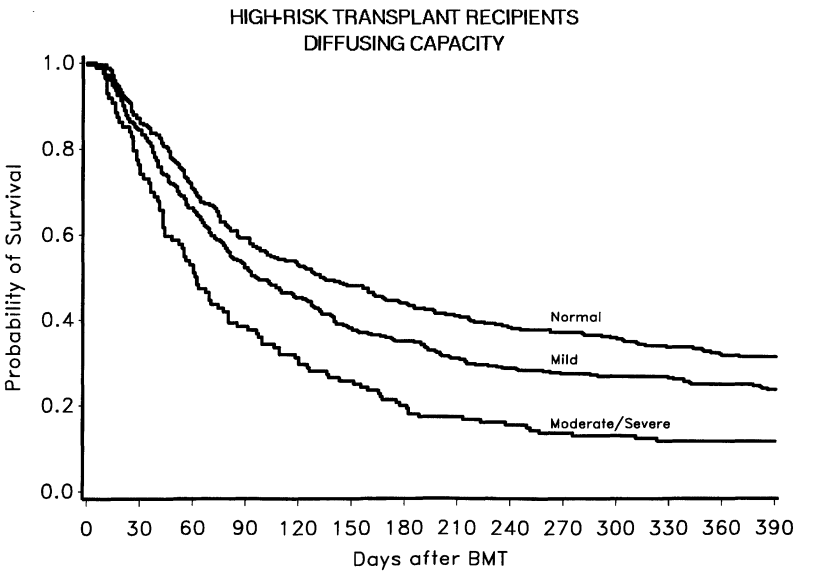

(B)

Figure 2. Kaplan–Meier survival plots estimated from the Cox proportional hazards regression model for 'low-risk' patients compared to those for 'high-risk' patients for various degrees of D_LCO_{sb} abnormality. **(A)** 'Low-risk' patients were less than 21 years old with malignancy in remission and received HLA-identical marrow grafts. **(B)** 'High-risk' patients were more than 21 years old with malignancy in relapse and received HLA-nonidentical marrow grafts. (From Crawford SW, Fisher L. Predictive value of pulmonary function tests before marrow transplantation. Chest 101:1257–64, 1992, with permission.)

to transplantation, but rather in combination with other known risks for transplant-related mortality to fully assess the risks.

Posttransplant. There are both acute and long-term decrements in pulmonary function after intensive chemotherapy and irradiation as utilized in marrow transplantation [24–33]. Reductions in lung volumes, diffusing capacity, and exercise tolerance were documented after treatment for leukemia in children as well and were thought largely secondary to chemotherapy [34]. PFT abnormalities have been reported to include declines in lung volumes, gas diffusion, and airflow. Reductions in lung volumes and diffusing capacity are common 'early' (i.e., months) after marrow transplant. The declines in lung volumes may be at least partially reversible within two years after transplantation, while the low diffusing capacity reportedly persists for several years. Development of airflow obstruction has been seen in approximately 10% of allogeneic marrow recipients in the presence of chronic graft-versus-host disease (GVHD) and most often is related to obliterative bronchiolitis [7,8,35].

Few reports have examined abnormalities in other PFT results for association with increased mortality. Badier et al. noted that both relapse of malignancy and overall mortality were correlated with falls in lung volumes and diffusion one year after marrow transplantation [33].

In order to investigate the clinical significance of declines in pulmonary function early after marrow transplantation, we recently reviewed prospective, nonrandomized PFT results of all 960 marrow recipients who performed PFT between days 60 and 120 after marrow transplantation over an eight-year period for association with nonrelapse mortality [36]. At three months after transplantation, the mean values for total lung capacity (TLC) and diffusing capacity decreased, and restrictive ventilatory defects (TLC < 80% of predicted) were noted in 34% of the cohort. Airflow rates (FEV_1/FVC) were unchanged. A restrictive lung defect at three months after transplant or a significant decline (≥15%) in TLC from baseline despite remaining within the normal range were associated with a twofold increased risk of nonrelapse mortality. Neither airflow obstruction nor impairment in diffusing capacity were associated with an increased risk (figure 3). Abnormalities of the TLC at three months after transplant were associated with death with respiratory failure, but not with an increased risk of chronic GVHD.

These data support an increase in the nonrelapse mortality rate associated with either the presence of a restrictive defect three months after marrow transplantation or a significant decline in lung volume compared to baseline. This effect is most pronounced more than one year after marrow transplant and appears to be due to an increase in the rate of death with respiratory failure, not chronic GVHD. On the basis of these results, we routinely evaluate lung function three months and then yearly after marrow transplantation.

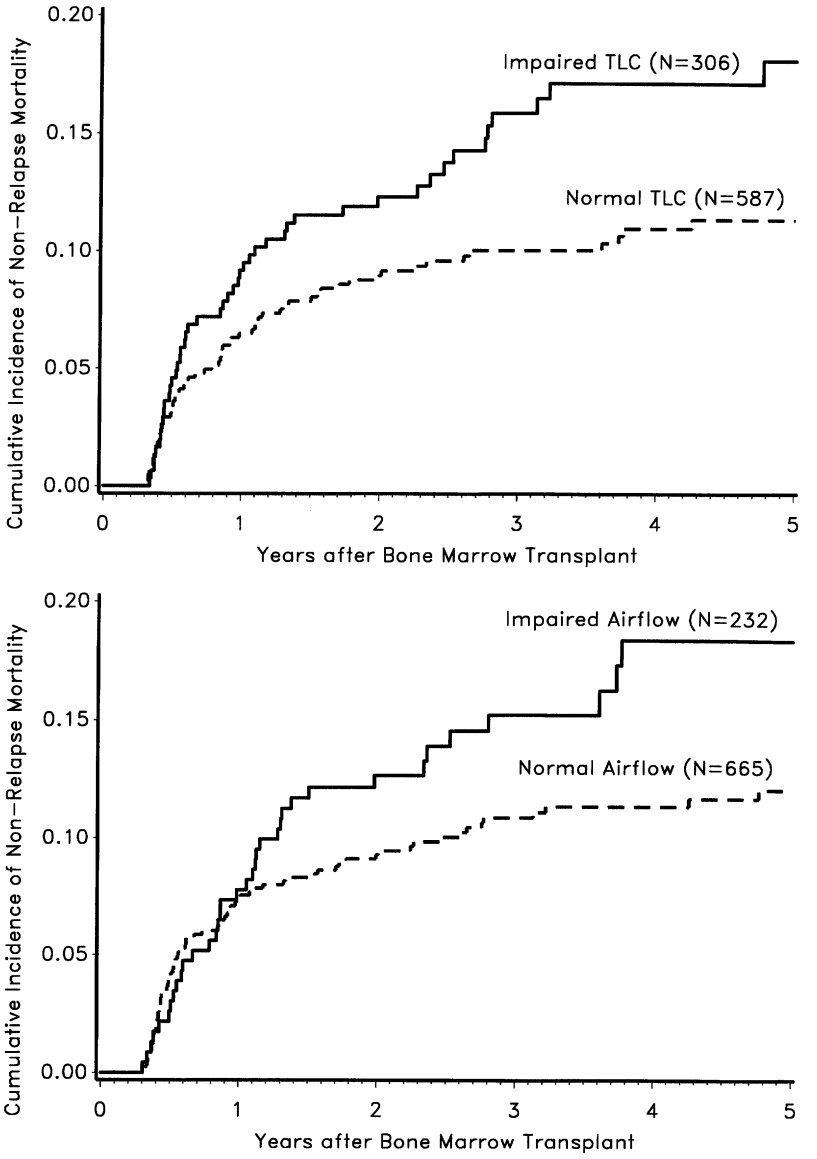

Figure 3. Estimates of the cumulative probabilities of nonrelapse death as functions of pulmonary function test results three months after marrow transplantation. **(A)** total lung capacity ($p = 0.004$, logrank); **(B)** FEV_1/FVC ($p = 0.08$, logrank); and **(C)** diffusing capacity ($p > 0.05$, logrank). In each plot, the solid curve corresponds to marrow recipients with pulmonary function test result impairment and the dashed curve to those with normal pulmonary function test results. (From Crawford SW, Pepe M, Lin D, Benedetti F, Deeg HJ. Abnormalities of pulmonary function tests after marrow transplantation predict non-relapse mortality. Am J Respir Crit Care Med 152:690–695, 1995, with permission.)

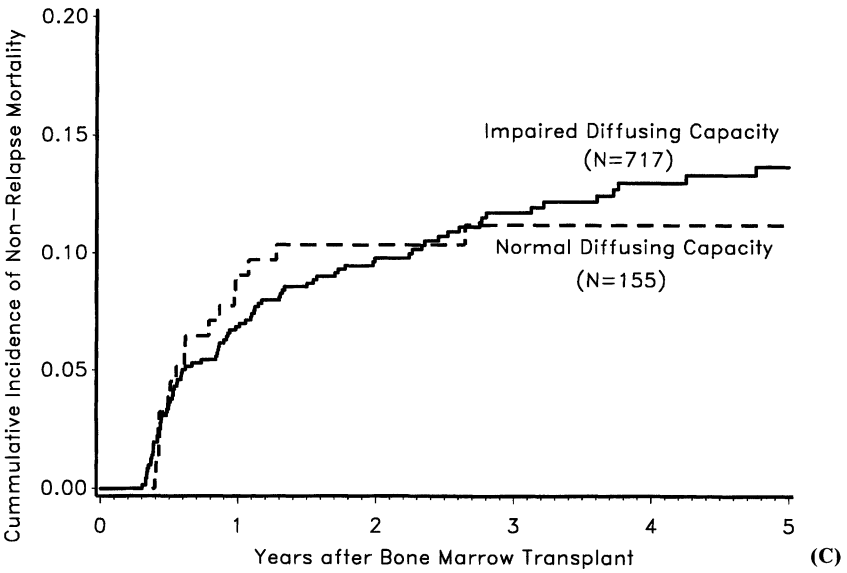

Figure 3 (continued)

Radiographs. Attention to radiographic abnormalities of the chest is crucial to avoid unnecessary complications. Focal abnormalities frequently represent opportunistic infection in neutropenic hosts and those with malignancy, even in the absence of symptoms. In our experience, focal lesions evident on chest radiography in patients with recent chemotherapy or hematological malignancy were infectious in over 80% of cases. Stanford investigators noted that focal lung lesions in patients with non-Hodgkin's and Hodgkin's lymphoma are most often parenchymal lymphoma [37,38]. However, fungal pneumonia may present after chemotherapy and be indistinguishable radiographically from malignancy [39]. Additionally, tuberculosis after transplantation most often occurs in patients with evidence of prior parenchymal lung disease [40].

Suspicion of focal lesions on chest radiography should prompt aggressive diagnostic evaluation before transplantation. Computerized tomographic examination may help localize and anatomically define the lesion(s). Depending upon the number, size, and location of the lesions, diagnostic procedures are warranted for treatment planning. Bronchoscopy, percutaneous needle aspiration, and/or lung resection should generally follow radiographic identification.

Predictors of mortality with respiratory failure

Predicting respiratory failure

It can be predicted which patients are at risk to require mechanical ventilatory support. The risk factors present at time of transplantation for subsequent

respiratory failure are receipt of an HLA-nonidentical donor marrow, active phase of malignancy, and older age (>21 years) [41]. The incidence of respiratory failure increases from 10% to 13% with none of these risk factors to over 50% when all three are present.

It is important that transplant units and patients have adequate information to assess the risks associated with marrow transplantation. Such information is crucial to discussions of advanced-care directives and cost containment. Given the difficulty in assessing medical futility in the marrow transplant recipient with respiratory failure, autonomous decisions by the patient should be followed [42]. Advanced-care directives should be obtained prior to marrow transplantation from marrow recipients at risk for respiratory failure, and the estimated risk of complications should be used in counseling before marrow transplantation.

Predicting outcome

Studies of intensive care for respiratory failure of patients with cancer [43–45], hematological malignancies [46,47], and marrow transplantation have reported low survival rates. In reports from our center, the University of Minnesota, and others, approximately 3% of marrow recipients receiving mechanical ventilation survived to six months after transplantation [1,48–51]. Recent studies of pediatric marrow transplant recipients find the same poor prognosis as noted among adults [52]. In addition, intensive care for marrow recipients with respiratory failure utilizes inordinate medical resources. In a study of 50 patients by Denardo et al., nonsurvivors of respiratory failure utilized the vast majority of blood products administered in the intensive care unit [51].

The results of these studies can be viewed in various ways. The low incidence of long-term survivors can be taken to mean that 'the prognosis is uniformly grim.' Such a conclusion may imply that medical intervention would be futile. However, given the controversy surrounding the meaning of medical futility, a low probability of survival alone may not be a valid argument for withholding mechanical ventilation from the marrow transplant recipient.

Another view of the data would be that long-term survival is possible. The decision regarding continued treatment should be made by the patient (or surrogate) on the basis of the probabilities and likely burdens imposed by the treatment. Given the relatively young age of many of the marrow transplant recipients and the prospects for long-term survival, optimism may be an appropriate view to take of the data. Early identification of patients destined to die despite life support, without compromising the chances of potential survivors, is clearly needed.

In recent work at the Fred Hutchinson Cancer Research Center, we have identified specific predictors of nonsurvival in mechanically ventilated marrow transplant recipients [53]. A nested case–control study of all survivors ($n = 53$) and a cohort of matched nonsurvivors ($n = 106$) were selected from

Table 1. Estimated probability of survival after mechanical ventilation in marrow transplant recipients

Clinical condition during support	Estimated survival[a] (95% CI)
Severe lung injury[b]	1.3% (0.5, 3.0)
Hepatic–renal dysfunction[c]	2.0% (0.1, 4.0)
Hypotension[d]	0.5% (0.06, 1.7)
Severe lung injury and Hepatic–renal dysfunction or Hypotension	0% (0, 2.0)

[a] Survival defined as alive 30 days after extubation and discharge from hospital.
[b] $F_1O_2 > 0.6$ or PEEP > 5 cm H_2O after initial 24 hours of support.
[c] Bilirubin > 4 mg/dl and creatinine > 2 mg/dL.
[d] Requirement of more than four hours of vasopressor support of more than 5 ug/kg/min of dopamine.

all mechanically ventilated marrow transplant recipients (n = 865) from January 1980 to July 1992. Patients mechanically ventilated less than 24 hours after a procedure or after a second marrow transplant were excluded. Survival was defined as alive 30 days after extubation and discharge from hospital.

Survival was statistically associated with younger age, lower APACHE III score, and a shorter time from transplant to intubation, but these measures lacked sensitivity for clinical use. However, there were *no* survivors among an estimated 398 patients who had severe lung injury ($F_1O_2 > 0.6$ or PEEP > 5 cm H_2O) who also required more than four hours of vasopressor support or had sustained combined hepatic and renal insufficiency (table 1). Using these factors, an accurate prediction of death could be made within four days of mechanical ventilation in 90% of nonsurvivors. Over the last five years of the review, there was a statistically significant improvement in survival rates (from 5% to 16%) ($p = 0.008$) that was not explained by a change in patient age, the intubation rate or timing, or the percentage of HLA-nonidentical allogeneic transplants.

These data appear to conflict with those presented by Faber–Langendoen et al., where among 191 marrow recipients requiring mechanical ventilation, age over 40 years and respiratory failure within 90 days of transplant were generally associated with fatality [48]. The bases for the differences in the data are unclear. The Fred Hutchinson Cancer Research Center data were largely confined to several months after transplant, while the University of Minnesota experience included patients several years after transplant. Regional differences in patient care may also contribute. Regardless, the Faber-Langendoen et al. report does not dispute that severe multiorgan failure with mechanical ventilation after marrow transplantation is highly fatal.

We concluded that severe lung injury combined with hemodynamic insta-

bility or hepatic–renal insufficiency are sensitive and highly specific predictors of nonsurvival in mechanically ventilated marrow transplant recipients. These overwhelmingly negative results in the largest cohort assembled — nearly equal in size to the total published experience — justify a standard of care for certain mechanically ventilated bone marrow transplant patients that restricts prolonged intensive care. We use such information to counsel patients and families to the expected outcomes of such situations, and will withdraw life-support on the basis of these data.

Noninfectious lung disease

Idiopathic pneumonia syndrome

Incidence and epidemiology. While 40% to 60% of patients develop pneumonia after allogeneic marrow transplantation, no infectious etiology is identified in 30% to 45% of cases with nonbacterial pneumonia [3,54]. These episodes are referred to as idiopathic pneumonias (or idiopathic interstitial pneumonias) to indicate the lack of documented infection and uncertainty regarding the precise etiologies. Several studies have reported the incidence of idiopathic pneumonia to be 11% to 17% after allogeneic marrow transplantation, with a median onset of 39 to 52 days and associated mortality rates of 60% to 70% [3,4,55].

The risk factors associated with idiopathic pneumonia in most studies were transplantation for malignancy and age greater than 20 years. Suggested etiologies for the apparently noninfectious lung injury after marrow transplantation have included chemoirradiation damage [55–57], occult Cytomegalovirus infection [58], and a graft-verus-host reaction [59].

Clinical presentation and course. The usual clinical presentation of 'interstitial pneumonia' is described as diffuse radiographic infiltrates, fever, dyspnea, and hypoxemia [3,4]. However, this presentation also describes viral pneumonia. There is no apparent distinction in presentation for idiopathic processes. The diagnosis of idiopathic pneumonia is one of exclusion of infection. Large studies of pneumonia after marrow transplantation by Meyers et al. [3] and Wingard et al. [4] therefore have required examination of lung tissue either from lung biopsy or autopsy for the diagnosis.

A recent description of the clinical course of idiopathic pneumonia diagnosed by lung biopsy is found in a review of 41 allogeneic marrow transplant recipients with an open lung biopsy between 1983 and 1988 that did not reveal infection [60]. The onset of pneumonia was 11 to 143 days after transplant (mean = 35), and 93% of cases displayed diffuse pulmonary infiltrates. Overall in-hospital mortality was 71% ($n = 29$). The case-fatality rate was 59% ($n = 24$). Thirteen patients (32%) died with progressive respiratory failure. The other 11 fatalities (27%) died either with recurrent respiratory failure after initial

Table 2. Definition of idiopathic pneumonia syndrome

1) Evidence of widespread alveolar injury: • multilobar infiltrates on chest radiograph or computed tomography • symptoms and signs of pneumonia • evidence of abnormal physiology
and
2) Absence of active lower respiratory tract infection, documented by • negative bronchoalveolar lavage, lung biopsy, or autopsy with examination of stains and cultures for bacteria, fungi, and viruses, including cytomegalovirus (CMV) centrifugation culture, cytology for viral inclusions and Pneumocystis carinii, and immunofluorescence monoclonal antibody staining for CMV, respiratory syncytial virus, influenza virus, parainfluenza virus, and adenovirus

improvement (n = 7) or due to nonpulmonary causes without resolution of pneumonia (n = 4). Infection was a major complication and was present at autopsy in 11 of 16 cases (69%). Six of 12 patients discharged from the hospital died within one year, most commonly with relapse of malignancy.

On the basis of this review of lung biopsies, the overall mortality of idiopathic pneumonia after allogeneic marrow transplantation is high, but less than one third of patients die of progressive respiratory failure, and infection is commonly associated with death despite a previous negative lung biopsy.

Definition of IPS. The results of a recent National Institutes of Health workshop addressed the issues of definitions and diagnostic criteria for idiopathic pneumonia after marrow transplantation [6]. That workshop recommended that the process be referred to as 'idiopathic pneumonia syndrome' (IPS) to reflect the diversity of clinical presentations and likely multifactorial etiologies of the apparently noninfectious diffuse lung injuries. IPS was defined as 'evidence of widespread alveolar injury in the absence of active lower respiratory tract infection' after marrow transplantation (table 2). Bronchoalveolar lavage, rather than lung biopsy, was recommended as the primary diagnostic approach.

At the Fred Hutchinson Cancer Research Center, we sought to determine whether this newly defined IPS occurs with the same incidence or with the same risk factors as described in the past for idiopathic pneumonia. Ready access to minimally invasive and highly sensitive diagnostic techniques (such as bronchoalveolar lavage and centrifugation viral culture) may have increased the recognition (and thus the reported incidence) of lung injury [61]. In addition, it is probable that the spectrum of lung injury in marrow recipients has changed over time, with modification in infection prophylaxis, methods and intensity of cytoreduction, and immune suppression.

Among 1165 consecutive marrow recipients from 1988 to 1991, IPS was documented in 85 marrow recipients by bronchoalveolar lavage (n = 68), open lung biopsy (n = 3), or autopsy (n = 14). The incidence estimate for IPS within 120 days of transplantation was 7.7%. Median time to onset was 21 days (mean 34 ± 30). Similar to previous studies, hospital mortality was 79%. Fifty-three

transplant recipients (62%) died with progressive respiratory failure. IPS resolved in 22 patients (26%), and 18 (21%) survived to discharge. Mechanical ventilation was required by 59 marrow recipients (69%) within a median of two days of onset of infiltrates, and two (3%) of these patients survived to discharge. Pulmonary infection (predominantly fungal) was noted in 7 of 25 (28%) marrow recipients who had an autopsy. Potential risk factors for IPS were assessed in univariate and multivariate logistic regression analyses. Although the difference in incidence was not significantly different between autologous (5.7%) and allogeneic marrow recipients (7.6%), risks were identified only for the latter, namely, malignancy other than leukemia and grade 4 graft-versus-host disease. No factors were associated with recovery.

Based on this recent study, the incidence of IPS appears lower, the onset earlier, and the risk factors changed from those previously reported for idiopathic pneumonia. The major risks appear to be regimen-related toxicity and multiorgan dysfunction associated with alloreactive processes.

Pulmonary hemorrhage

Epidemiology, clinical presentation, and course. Robbins et al. described a syndrome of diffuse pulmonary infiltrates, fever, hypoxemia, thrombocytopenia, and renal insufficiency occurring within the first few weeks after autologous marrow transplantation for solid tumors [62]. The hallmark of the syndrome was progressively bloodier return from bronchoalveolar lavage (BAL) and the absence of infection in the lungs. This diffuse alveolar hemorrhage (DAH) syndrome was associated with a very high mortality — over 90%. DAH appeared unrelated to the platelet count, but correlated with increased requirements for platelet transfusion.

Initially seen in 29% of the patients at the University of Nebraska, the incidence of the syndrome declined significantly, to less than 7%, presumably due to alterations in either patient selection or transplant conditioning regimens. Among marrow recipients with lymphoma at the Memorial Sloan Kettering Cancer Center, the reported incidence was 8% [63]. All centers reporting the syndrome note mortality rates over 67%.

Recent European studies of alveolar hemorrhage suggest that the finding of blood in BAL fluid may not represent a specific syndrome. DeLassence et al. reported that among a cohort of 194 immunosuppressed patients undergoing bronchoalveolar lavage, detection of alveolar bleeding by the presence of alveolar siderophages did not correlate with specific lung pathology, presence of infection, or clinical outcome [64]. Siderophages did correlate with uremia, thrombocytopenia, coagulopathies, and a long history of tobacco smoking. This quantitative measure of alveolar bleeding circumvents the subjective nature of recognizing 'progressively bloodier' BAL. The correlations support a contention that alveolar blood is a *sign* of disease, and not a specific diagnostic category. Spanish investigators noted that there was poor correlation between the presence of blood in the lungs at autopsy and BAL results during

life in patients after allogeneic marrow transplant or hematological malignancy, further questioning the specificity of the BAL findings as representing a specific syndrome [65].

Pathogenesis and pathology. All cases of DAH that have come to autopsy have demonstrated diffuse alveolar damage, alveolar desquamation, and hyaline membrane formation, typical of ARDS. Because the incidence of the syndrome tended to correlate with the recovery of circulating granulocytes in affected patients, the Nebraska investigators proposed that neutrophilic inflammation played a pathogenic role [66]. Supporting this contention, visual evidence of airway inflammation (ascertained by a bronchitis index) before transplant was associated with the syndrome.

The timing and pathology of the syndrome suggest that chemoradiation injury to multiple organs is central. It remains unclear whether the hemorrhage is a key element to the pathogenesis and outcome, or merely an expected consequence of diffuse lung injury in the presence of a coagulopathy.

Treatment. There are no controlled studies of the treatment of DAH. Retrospective data from Nebraska and anecdotal reports of four cases from Stanford suggest that high-dose corticosteroids may improve the survival rates [67,68]. Doses of methylprednisolone ranging from greater than 30 mg/day to 1 gram/day have been associated with survival. Metcalf et al. reported mortality rates improved from more than 90% to 67% with the routine addition of corticosteroids in the treatment plan [67]. Clouding the interpretation of this finding was the simultaneous declining incidence of the syndrome at the authors' center, suggesting that unidentified factors influencing the course and severity of the disease may have been altered as well.

Airflow obstruction and bronchiolitis

Epidemiology. Several centers report that 6% to 10% of allogeneic marrow recipients develop chronic airflow obstruction. Most of these cases are among long-term survivors with chronic GVHD. Schultz et al. recently reported a higher incidence in children transplanted at the center in Vancouver, Canada [69]. It is unclear whether this represents a regional difference or an age-related effect.

In 70% of the reported cases, the histology of the lungs was obliterative bronchiolitis [7]. The obliterative bronchiolitis lesions in the lungs of marrow transplantation recipients are occasionally, but not invariably, accompanied by interstitial infiltrates of mononuclear cells. However, interstitial fibrosis and bronchitis, without obliteration, have also been noted among patients with airflow obstructive physiology. Recently, airflow obstruction with obliterative bronchiolitis has been reported in two patients after autologous marrow transplantation [9]. On the basis of these findings, new onset airflow obstruction is

the hallmark of this problem, not the presence of obliterative bronchiolitic lesions.

Pathogenesis. The etiology of obliterative bronchiolitis after marrow transplantation is unknown. Those causes recognized in otherwise normal hosts, such as recurrent aspiration, viral infection with influenza, adenovirus or measles, and bacterial or mycoplasma infection, have not been found consistently in marrow recipients with obliterative bronchiolitis. Immunological mechanisms inducing bronchial epithelial injury are suggested by the strong association between chronic GVHD and the development of obliterative bronchiolitis [7,8,70]. Factors associated with the increased risk of GVHD, such as increasing age and HLA-nonidentical marrow grafts, are not independent risk factors for the development of obliterative bronchiolitis. The lung epithelium may be the target of immune mediated injury in chronic GVHD through the expression of Ia antigens and subsequent activation of donor cytotoxic T cells. The reported association with the administration of methotrexate also raises the possibility of direct drug-related injury to the pulmonary bronchial epithelium [8]. Also, there is a higher incidence of decreased levels of IgG among patients with obliterative bronchiolitis than that seen in other marrow recipients [70]. This hypogammaglobulinemia may be a manifestation of the immunological lesion responsible for the airway disease or merely may be related to the presence of chronic GVHD [71].

Airflow obstruction is occasionally seen within 100 days of transplant. Histology is available for fewer of these cases, and the defect is possibly related to airway infection. This early presentation is often associated with acute GVHD.

Clinical presentation and course of disease. Typical manifestations of airflow obstruction due to obliterative bronchiolitis after marrow transplantation are insidious progression of tachypnea, dyspnea on exertion, and dry, nonproductive cough. Fever is not common [35]. Physical findings may be minimal. Scattered expiratory wheezing and occasionally diffuse inspiratory crackles may be heard, but chest auscultation is sometimes normal. The chest radiograph is commonly interpreted as normal; however, recent studies reveal that almost all affected children have typical abnormalities noted on high-resolution chest CT scans [72].

The diagnosis of airflow obstruction is made among marrow transplantation recipients by routine pulmonary function testing When the presentation is more than 150 days after marrow transplantation, evidence of chronic GVHD is usually present, although the condition may occur at any time after transplantation.

The syndrome is often progressive and results in death due to respiratory failure. A more rapid onset and faster rate of progression is associated with worse outcome [35]. Control of chronic GVHD with increased immunosuppression may achieve stabilization of the airway disease. Patients with

gradual declines in airflow tend to have more benign courses. Marrow recipients with the onset of airflow obstruction beyond 150 days after transplantation tend to have a more gradual decline in lung function. Airflow may stabilize in 50% of these patients. Reversal of the obstruction is reported in only 8% of cases [7].

Treatment. There are no prospective studies of the treatment of new onset airflow obstruction after marrow transplantation. Obstructive airflow in the presence of chronic GVHD is managed primarily by controlling the GVHD with increased immunosuppression. Airflow obstruction has improved in some patients with increased immunosuppression [73]. Experience with obliterative bronchiolitis among the recipients of heart–lung transplant suggests that the addition of azathioprine (1.0–1.5 mg/kg/day) to cyclosporine may be effective in arresting the decline in airflow in these patients [74]. In addition, aerosolized bronchodilator treatment for symptomatic patients is appropriate. Early and aggressive antibiotic treatment for any potential lower respiratory infection should be initiated. Prophylactic trimethaprim-sulfamethoxazole (or other form of anti-Pneumocystis prevention) should be continued for the duration of immune suppression. Routine intravenous replacement of immunoglobulin for those with low class or subclass levels is usual [75].

Similar immunosuppressive management is recommended for airflow obstruction that develops early in the transplant course in the absence of chronic GVHD. Evaluation for possible airway infection by respiratory viruses or fungus should be undertaken in rapidly developing obstruction, especially in the presence of acute GVHD.

Early recognition and treatment may improve outcome. Therefore, routine spirometry after marrow transplantation among patients with chronic GVHD is encouraged to detect the insidious onset of this process.

Diagnostic approaches

Bronchoscopy

Fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) is the procedure of choice to evaluate diffuse infiltrates after marrow transplantation (table 3). Rapid virological and microbiological detection methods permit sensitive and specific detection of viral as well as bacterial and Pneumocystis carinii infections. Fluorescent antibody staining with monclonals has increased sensitivity over cytology alone [76]. Rapid centrifugation (shell vial) culture appears to be an even more sensitive method of detecting viral infection [77]. PCR detection of viral nucleic acids may further increase the sensitive of detection.

BAL is safe in marrow transplantation recipients and may be performed in profoundly thrombocytopenic patients with little risk of bleeding or infection,

Table 3. Routine laboratory evaluation of bronchoalveolar lavage specimens in marrow and stem cell transplant recipients

Pathology[a]
Wright–Giemsa stain
Papanicolaou stain
Silver stain
Modified Jimenez stain (or other suitable for detecting Legionella)
Consider in exceptional setting: Monoclonal fluorescent antibody stain for Pneumocystis
Microbiology
Stains:
Gram
Wet mount KOH or calcofluor white
Modified acid-fast
Fluorescent antibody stain for Legionella
Culture:
Bacterial (aerobic), semiquantitative method
Fungal
Legionella (chocolate yeast extract)
Acid fast
Virology
Fluorescent antibody stains:[b]
CMV
HSV
RSV, parainfluenza and influenza viruses pooled antibodies[c,d]
Culture (rapid centrifugation technique preferred):[e]
CMV
HSV
Adenovirus
RSV, parainfluenza and influenza viruses (in appropriate clinical setting)

[a] Studies usually reviewed by a pathologist.

[b] Studies may be performed in a virology or pathology laboratory.

[c] Separate studies for each virus should be performed if the study with pooled antibodies is positive.

[d] Fluorescent antibody stains may be supplemented or replaced by enzyme-immunoassays (EIAs) as available.

[e] If accessible. Culture may be replaced with fluorescent antibody stains or EIAs alone if culture facilities are unavailable.

even when performed via the transnasal route [78]. Although BAL can document the presence of viral and bacterial infection, negative results do not exclude the presence of fungal infection nor confirm the diagnosis of idiopathic pneumonia. The use of additional invasive procedures must be individualized on the basis of the likelihood of undiagnosed treatable infection. The yield in Pneumocystis carinii infection is unclear; however, we have never confirmed the presence of the organism by any other means after BAL failed to detect an infection. Transbronchial lung biopsy does not appear to improve the diagnostic yield in marrow recipients with diffuse infiltrates [79], is not specific for idiopathic processes [80,81], and may be unsafe in thrombocytopenic patients.

Video-assisted thorascopic surgery

Most reports note that thoracotomy may be undertaken with acceptable morbidity and mortality, even in severely immunosuppressed patients, as long as the platelet count is adequate (usually >50,000/mm^3) [82–84]. Open lung biopsy has the highest probability of rendering a specific diagnosis of the procedures available and had been the mainstay of diagnosis for diffuse pulmonary infiltrates prior to the advent of rapid and sensitive virological diagnostic techniques applied to bronchoscopy specimens.

The morbidity of lung biopsy may be diminished in the hands of a surgeon who is skilled in the use of a thoracoscope. Thorascopically directed biopsy permits diagnostic tissue to be obtained without a formal thoracotomy incision. In most patients, the postoperative recovery is faster with less incisional pain [85,86]. Access to thorascopic lung biopsy has increased our willingness to subject marrow transplant recipients to surgery. One limitation to the procedure is the requirement for bilateral bronchial intubation to permit deflation of the involved lung. Patients with little pulmonary reserve or severe bilateral disease may tolerate this procedure poorly.

Thorascopic lung biopsy also has a role in the diagnosis and management of focal lung lesions, especially those close to the pleural surface. Surgical resection of a focal fungal lesion may be curative while also diagnostic. Caution must be exercised, however, in discounting fungal disease on the basis of a negative open lung biopsy. Despite the relatively large tissue specimen that can be sampled, the diagnosis may not be evident in the pathological examination. Invasive filamentous fungi, by their focal nature and accompanying large degree of tissue infarction and hemorrhage, may not be seen in as many as 20% of cases in which they are present. Therefore, it is difficult to withdraw or withhold empirical antifungal therapy in the neutropenic patient despite "negative" results.

Conclusions

The number of transplant procedures continues to increase as the indications expand and the sources of donor stem cells enlarge. More patients are at risk for complications and require supportive care. To a large extent, support for these patients is similar to that for others receiving intensive induction chemotherapy regimens. Distinctions include the severe degree of immune suppression, the predictable rate and pattern of reconstitution of immunity that follows transplantation, and the presence of GVH reactions among allogeneic recipients.

Increasingly, we are able to predict with more precision patients at risk for complications. Among the tools are pulmonary function tests, both before and after transplantation. In addition, the prognosis for patients with respiratory

failure is clearer. The dilemma of identifying those patients who will not survive is being unravelled.

Diagnostic and treatment procedures clearly can be undertaken in these patients with acceptable risks. Bronchoalveolar lavage and thorascopic lung biopsy yield results in patients previously thought to be at high risk for such procedures. Further analyses will continue to define situations where these modalities produce the highest yields, as well as the limitations of such approaches.

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