Pulmonary Complications of Bone Marrow Transplantation

Ayman O. Soubani, MD; Kenneth B. Miller, MD; and Paul M. Hassoun, MD

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BMT=bone marrow transplantation; BO=bronchiolitis obliterans; CMV=cytomegalovirus; DAH=diffuse alveolar hemorrhage; DCO=diffusing capacity of carbon monoxide; GVHD=graft-vs-host disease; HHV-6=human herpes virus-6; HSV=herpes simplex virus; IPS=idiopathic pneumonia syndrome; PAP=pulmonary alveolar proteinosis; PCP=Pneumocystis carinii pneumonia; PFT=pulmonary function test; RSV=respiratory syncytial virus; TBI=total body irradiation; TLC=total lung capacity

Keywords: bone marrow; complications; pulmonary; transplant

The first successful allogeneic bone marrow transplantation (BMT) was performed in the late 1960s. Since then, BMT has been used with increasing frequency for the treatment of malignant and nonmalignant hematologic diseases, solid tumors, and metabolic and genetic diseases. It is estimated that in 1993, approximately 15,000 cases of allogeneic and autologous BMTs were carried out worldwide.1 BMT is a standard therapy for aplastic anemia, acute leukemias, chronic myelogenous leukemia, non-Hodgkin’s lymphoma, and Hodgkin’s disease with long-term disease-free survival exceeding 60%.2,3 Also encouraging results are noted in the role of BMT in the management of hemoglobinopathies, immunodeficiency disorders, myelodysplastic syndrome, multiple myeloma, and testicular and breast cancers.2

Pulmonary complications, which occur in 40 to 60% of patients who receive BMTs, account for meaningful morbidity and mortality.3-5 Multiple factors are thought to contribute to pulmonary complications, including the type and duration of immunologic defects produced by the underlying disease and therapy, the development of graft-vs-host disease (GVHD), and the conditioning regimens employed.5,6 The spectrum of pulmonary complications includes infectious and noninfectious conditions. These are classified as early or late depending on whether they occur before or after 100 days posttransplantation (Fig 1). Their relative frequency varies according to the type of BMT (ie, autologous vs allogeneic) (Table 1). For practical purposes, pulmonary complications of stem-cell transfection (the newest form of BMT) are similar to those related to autologous BMT.

PULMONARY EDEMA

Pulmonary edema is one of the earliest complications following BMT. Although the exact incidence is not known, it is not uncommon.5 The onset is usually rapid and occurs in the second or third week posttransplantation with dyspnea, weight gain, and bibasilar crackles on physical examination, and reduced arterial oxygen tension. Chest radiographic abnormalities include vascular redistribution and diffusely increased interstitial markings. Pleural effusions are occasionally detected. Some patients may require temporary mechanical ventilation.9

The etiology of pulmonary edema may be due to increased capillary hydrostatic pressure (cardiogenic type), increased pulmonary capillary permeability (noncardiogenic type), or a combination of both. Large volumes of fluids infused to minimize the toxicity of conditioning regimens, antibiotics, blood products, and total parenteral nutrition combined with cardiac and renal dysfunction from previous chemotherapeutic and immunosuppressive agents such as doxorubicin (Adriamycin), cyclophosphamide, cisplatin, and cyclosporine contribute to cardiogenic pulmonary edema. Echocardiography usually reveals a dilated heart with poor left ventricular function. However, lung injury from conditioning regimens that include cyclophosphamide and total body irradiation (TBI) combined with septic episodes are possible causes for increased pulmonary capillary permeability and noncardiogenic pulmonary edema.6,9 Prophylactic intervention consisting of careful clinical examination, close monitoring of weight changes, and appropriate use of diuretic therapy with the earliest signs of fluid overload lead to a reduction in the incidence of pulmonary edema following BMT.9

IDIOPATHIC PNEUMONIA SYNDROME

Idiopathic pneumonia syndrome (IPS) is defined as diffuse lung injury occurring after BMT for which an infectious etiology is not identified. Histologically, there is an interstitial mononuclear infiltrate associated with diffuse alveolar damage. The incidence of IPS

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after allogeneic BMT is approximately 12%. The median time of onset of IPS is 42 to 49 days after BMT; however, there is an early peak in the first 14 days followed by a lower but consistent incidence through the following 80 days. Risk factors for developing IPS include a low Karnofsky score prior to transplantation, high dose of TBI (>1,200 rad), and the presence of GVHD. Patients usually present with dyspnea, fever, nonproductive cough, hypoxemia, and diffuse radiographic infiltrates. The overall in-hospital mortality in patients who develop IPS is 71%; however, only 32% die from progressive respiratory failure while most die from recurrent respiratory failure after initial improvement or from other causes like viral and fungal infections without resolution of the IPS. Crawford and Hackman indicated that 44% of patients demonstrated resolution of IPS. Seemingly paradoxical, patients who received total fractionated TBI in excess of 1,200 rad and patients with evidence of acute GVHD (grade 2) had better prognosis.

The diagnosis of IPS is usually one of exclusion; however, a recent National Heart, Lung, and Blood Institute workshop suggested the following criteria for diagnosis: symptoms and signs of pneumonia and evidence of abnormal pulmonary physiology such as worsening alveolar to arterial oxygen gradient and new or increased restrictive pulmonary function test abnormality, with evidence of widespread alveolar injury, including multilobar infiltrates on routine chest radiograph or CT scan; and absence of active lower respiratory tract infection. Appropriate evaluation includes BAL that shows no bacterial or nonbacterial pathogens, transbronchial biopsy if the condition of the patient permits, and a second confirmatory normal test.

**Table 1—Relative Frequency of Pulmonary Complications in Autologous vs Allogeneic BMT**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Autologous</th>
<th>Allogeneic</th>
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<tbody>
<tr>
<td><strong>Infectious</strong></td>
<td></td>
<td></td>
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<tr>
<td>Bacterial</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>Fungal</td>
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<td>+++</td>
</tr>
<tr>
<td><em>P. carinii</em></td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>CMV</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Other viruses¹</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Noninfectious</strong></td>
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<tr>
<td>Pulmonary edema</td>
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<tr>
<td>DAH</td>
<td>++</td>
<td>++</td>
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<tr>
<td>IPS</td>
<td>+</td>
<td>+++</td>
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<tr>
<td>BO</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Impaired PFT results</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>GVHD</td>
<td>±</td>
<td>+++</td>
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</tbody>
</table>

*Symbols: +++=common; ++=less common; ++=rare; ±=exceedingly rare.

¹See text.
result for infection performed 2 to 14 days after the initial procedure.

There is no specific therapy for IPS, and corticosteroids have no proved efficacy. The severity of IPS is reduced in patients receiving cyclosporine or IV immunoglobulin prophylaxis for GVHD. These observations support an immunopathologic mechanism for this disease.\(^{14}\)

**Diffuse Alveolar Hemorrhage**

This is a form of noninfectious pneumonia that has been described after both autologous and allogeneic BMT. It has been reported in 21% of recipients of autologous bone marrow.\(^ {15}\) The syndrome is characterized by the sudden onset of progressive dyspnea, nonproductive cough, fever, and hypoxemia. Hemoptysis is rare. Chest radiograph shows diffuse consolidation usually involving more than one lobe, and BAL characteristically reveals a progressively bloodier return of the lavage fluid (Fig 2). No opportunistic organisms are identified. The syndrome usually occurs around the 12th day (ranging between 7 and 40 days) after transplantation.\(^ {15}\) Risk factors for development of diffuse alveolar hemorrhage (DAH) include the following: age older than 40 years, solid malignancy, receiving TBI, severe mucositis, renal insufficiency, and WBC recovery. There is no significant association between DAH and prolonged prothrombin time and partial thromboplastin time or thrombocytopenia.\(^ {15}\)

Interestingly, DAH most frequently occurs at the time of engraftment and not during the nadir of bone marrow suppression. It is believed that the syndrome results from inflammation caused by influx of neutrophils to the lungs. In addition, airway inflammation in patients with Hodgkin’s disease prior to conditioning for BMT predicted the development of DAH and death after transplantation.\(^ {16}\) The in-hospital mortality associated with DAH ranges between 50% and 80%.\(^ {6,15}\)

It is important to detect DAH early because the administration of high doses of corticosteroids to patients with DAH may favorably alter the natural history of this syndrome.\(^ {17,18}\) A recent report showed that high-dose corticosteroids given to BMT recipients with DAH improved total survival and survival to hospital discharge and decreased the development of subsequent respiratory failure.\(^ {19}\) The dose of corticosteroids was greater than 30 mg of methylprednisolone or its equivalent, generally in the form of 125 to 250 mg of methylprednisolone every 6 h, given for the first 4 to 5 days and subsequently tapered, based on clinical improvement, over 2 to 4 weeks.

**Bacterial Infections**

Bacterial infections are common early complications of BMT and correlate with the period of granulocytopenia before marrow engraftment. The routine use of prophylactic antibiotics and the early empiric treatment with broad-spectrum antibiotics make the diagnosis of bacterial pneumonia difficult; however, recent studies estimated the incidence of bacterial pneumonia in the early posttransplantation period to be 20 to 50%.\(^ {13}\) Gram-negative organisms presumably from the GI tract or oral mucosa are the predominant group of bacteria; however, the risk of Gram-positive infections with organisms like Streptococcus and Staphylococcus has increased with the widespread use of indwelling central lines. In addition, the presence of oral mucositis requiring frequent use of narcotic analgesics may predispose to aspiration and infection with Gram-positive and anaerobic organisms.\(^ {6}\) *Legionella pneumophila* was reported to be the cause of an outbreak of severe nosocomial pneumonia with high mortality after BMT.\(^ {20}\)

**Viral Infections**

*Cytomegalovirus*  

Cytomegalovirus (CMV) pneumonia is an important infection during the first 6 months following BMT. It usually occurs 6 to 12 weeks posttransplantation and involves 10 to 40% of marrow recipients. The fatality rate of CMV pneumonia is 85%.\(^ {1}\) CMV infection results from reactivation of latent endogenous virus as a result of profound immunosuppression in 70% of CMV-seropositive BMT recipients. Alternatively, acquisition of the virus from the infusion of “CMV-seropositive” marrow or blood products from seropositive donors has resulted in CMV infection in approximately 36% of CMV-seronegative BMT recipients.\(^ {21}\)

Several risk factors are associated with the develop-
ment of CMV pneumonia following BMT, including the following: seropositive recipients; older patients; conditioning regimens containing TBI, CMV excretion, and viremia; T-cell depletion for GVHD prophylaxis; and moderate to severe acute GVHD. In a review of 545 BMT recipients, Meyers et al found that among seronegative recipients, positive serologic test results of the marrow donor and use of granulocyte transusions from seropositive donors increased the relative rate for CMV infection by 2.3 and 2.5, respectively. Among both seropositive and seronegative recipients, older age, transplant for acute nonlymphocytic leukemia, and GVHD increased the risk for CMV infection. The authors also found that CMV pneumonia occurred in 91 (16.7%) of 545 patients with a mortality rate of 84.6%. Among the seronegative patients, CMV viremia and acute GVHD were the most significant risk factors for subsequent CMV pneumonia with relative rate of 2.6 and 2.5, respectively.

The common clinical features of CMV pneumonia are fever, nonproductive cough, dyspnea, and hypoxemia with diffuse interstitial infiltrates on chest radiograph. Histologically, the diagnosis is confirmed by finding pulmonary macrophages containing the typical inclusion bodies. Also, the diagnosis can be made by indirect immunofluorescence with monoclonal antibodies to early antigen of CMV applied to BAL specimen centrifuged into tissue culture monolayers. This technique allows diagnosis within 16 h with a reported sensitivity of 96% and specificity of 100% when compared with open lung biopsy. The reliability of the detection of CMV in BAL fluid as an indicator of infection has been controversial because it is possible to isolate the virus in the absence of active disease. However, 50% of asymptomatic seropositive allogeneic transplant recipients for whom CMV was isolated from BAL eventually developed CMV pneumonia. These data suggest that although detection of CMV does not prove active infection, it does define a population at risk for the development of CMV pneumonia.

Early diagnosis of CMV pneumonia is a major determinant of survival since recent studies demonstrated that the combination of ganciclovir and high-dose immunoglobulin in the treatment of CMV pneumonia in patients with BMT is associated with improved survival. However, relapse occurs in nearly one third of the patients. Furthermore, if respiratory failure due to CMV pneumonia has occurred, therapy with ganciclovir and high-dose immunoglobulin is usually not successful. Another approach is based on the observation that recovering the virus from the blood is highly predictive of developing CMV pneumonia. This led some investigators to advocate weekly screening for viremia following transplantation using cultures, polymerase chain reaction, and immunofluorescence staining, allowing early treatment with ganciclovir and high-dose immunoglobulin. The preferred approach to the management of CMV pneumonia is prophylaxis: including the use of seronegative or filtered blood products to seronegative recipients, high-dose acyclovir prophylaxis for CMV-seropositive patients at the time of transplantation, the routine use of ganciclovir prophylaxis, passive immunization with human immunoglobulins, and improving GVHD treatment and prophylaxis.

**Herpes Simplex Virus**

The most common early infection following BMT is caused by herpes simplex virus (HSV), usually in the form of gingivostomatitis. A rare but severe type of HSV infection is HSV pneumonia, which usually occurs in the setting of mucocutaneous disease. HSV pneumonia develops by contiguous spread from oropharynx to the trachea, resulting in focal or multifocal infiltrates. However, the disease may result in diffuse pneumonia in the setting of viremia.

**Human Herpes Virus-6**

This is a recently described herpes virus that is epidemiologically and biologically similar to CMV. It is the cause of exanthem subitum (roseola) in children. The virus has been isolated from respiratory tract secretions of BMT recipients with interstitial pneumonitis. A recent study evaluated the association between human herpes virus-6 (HHV-6) infection and idiopathic interstitial pneumonia in BMT recipients in whom thorough analysis failed to identify fungi, bacteria, or other viruses as the cause of their pneumonia. Quantitative polymerase chain reaction was used to detect the level of HHV-6 DNA in the lung tissues of 15 BMT recipients as compared to 15 immunocompetent patients without pneumonitis and 6 fetuses. Six of the 15 BMT recipients had levels of HHV-6 DNA in lung tissue that were 10 to 500 times higher than the control subjects. Increased HHV-6 DNA levels correlated with increased severity of GVHD and the presence of idiopathic pneumonitis in these patients; however, there was a decreased risk of death from pneumonitis compared to BMT recipients with lower levels. HHV-6 serum antibody titers alone did not predict the levels of HHV-6 DNA in the lung tissues, but there was a direct correlation between HHV-6 DNA levels and the change in HHV-6 antibody titer between pretransplantation samples and those obtained at the time of open lung biopsy. In conclusion, HHV-6 infection is a potential cause of idiopathic pneumonitis; however, its presence may carry a favorable outcome.
Respiratory Syncytial Virus and Parainfluenza Virus

Although these viruses may cause interstitial pneumonia after BMT, they are not routinely looked for; thus, their significance may be underestimated. A recent study examined the incidence and clinical course of parainfluenza virus infection in 1,253 BMT recipients who had manifestations of a viral disease or fever without apparent cause. Twenty-seven patients (2.2%) had parainfluenza demonstrated by viral cultures. Eight patients had only upper respiratory tract involvement, 8 had symptoms of upper and lower respiratory tract involvement, and 11 had only lower respiratory tract involvement. Respiratory failure developed in 6 of the 19 patients with lower respiratory tract infection and all 6 died. The clinical picture of parainfluenza virus infection is similar to respiratory syncytial virus (RSV) infection with symptoms of coryza and sinusitis, and lower respiratory tract involvement characterized by bronchiolitis and pneumonia. Unlike RSV, parainfluenza virus infection is not seasonal and may develop at any time during the year. The diagnosis of parainfluenza infection may be elusive when appropriate specimens are obtained for culture. Most of the cases of parainfluenza infection are self-limited; however, in some patients, the pneumonia is severe and occasionally fatal. Aerosolized ribavirin has been used for the treatment of both RSV and parainfluenza pneumonia with variable results.

Fungal Infections

Fungi have been found to be the cause of pneumonia in 12 to 45% of patients after BMT. Most cases are diagnosed in the first 30 days posttransplantation. Because the antemortem diagnosis of fungal infections in BMT recipients is extremely difficult, systemic antifungal therapy is routinely used in the neutropenic patient with persistent fever despite 3 to 5 days of broad-spectrum antibiotics. The organisms causing the earliest invasive fungal infection are Candida species, but they are rarely the sole cause of pneumonia. Candida is a frequent cause of fungemia and the portal of entry is thought to be the GI tract or indwelling catheters.

Aspergillus is the most common fungus associated with pneumonia after BMT and has been variably reported in 0 to 20% of transplants. In general, risk factors predisposing to Aspergillus infection include prolonged granulocytopenia, broad-spectrum antibiotics, disruption of mucosa, and treatment with corticosteroids. The clinical features of invasive pulmonary aspergillosis include fever, dyspnea, dry cough, wheezes, pleuritic chest pain, and sometimes hemoptysis. The presence of concomitant sinusitis is suggestive of aspergillosis. The radiographic picture is variable and ranges from diffuse to local infiltrates and cavitation (Fig 3).

Mortality from Aspergillus pneumonia in BMT recipients is exceedingly high, reaching 85% or more. This may be due in part to the delay in establishing the diagnosis and initiating treatment. Although demonstration of tissue invasion is required to confirm the diagnosis, the presence of Aspergillus species in sputum or BAL culture should be considered evidence of invasive disease until proved otherwise and warrants institution of therapy.

Amphotericin B (doses of 0.5 to 1.5 mg/kg/d) is the most effective antifungal treatment against Aspergillus; however, its efficacy in the treatment of invasive pulmonary aspergillosis after BMT has been disappointing. As a result, prophylaxis is considered the most effective way in treating aspergillosis. Because the risk of infection is related to the number of Aspergillus spores in the air, the use of high-frequency particulate air filters and laminar air-flow rooms are effective in preventing Aspergillus infection. Oral or IV “low-dose” amphotericin B (0.1 to 0.25 mg/kg/d) or the use of “aerosolized” amphotericin B is well tolerated by BMT patients and is commonly used prophylactically with variable efficacy. Recent reports suggest that fluconazole (400 mg/d) was effective in decreasing the incidence of systemic fungal infection following BMT. Granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor may be used to shorten the granulocytopenic period, hence decreasing the risk of Aspergillus infection.

Pneumocystis carinii Pneumonia

The implementation of prophylaxis with trimetho-
prim/sulfamethoxazole has resulted in significant reduction in the incidence of *Pneumocystis carinii* pneumonia (PCP) in BMT recipients. PCP is found in less than 10% of bone marrow recipients, usually in those who cannot take trimethoprim/sulfamethoxazole or pentamidine prophylaxis. The median time of onset of PCP is 2 months posttransplantation. The yield from BAL of *P carinii* in BMT recipients is probably less than the 90% reported with HIV-infected patients. This is most likely due to the lower pathogen burden and the tendency for *P carinii* to be primarily localized in the interstitium during the early phases of the disease. Transbronchial biopsy, in addition to BAL, is likely to increase the sensitivity of bronchoscopic diagnosis of *P carinii* in such patients. The response to treatment is good if instituted early. Prophylaxis against PCP should be continued indefinitely in patients with active GVHD.

**Bronchiolitis Obliterans**

The development of obstructive airway disease as a result of bronchiolitis obliterans (BO) is an important problem after BMT. BO was first described in 1982 as a late complication of allogeneic BMT; however, it has been described rarely after autologous transplant. The incidence of BO has been reported to be between 2% and 13%, and patients with depressed immunoglobulin level posttransplantation and those with chronic GVHD are at an increased risk.

The etiology of BO remains unclear. Several postulated causes include viral infection, autoimmune process directed against the bronchial tree, and damage of small airways secondary to GVHD. Clinically BO develops anytime after the third month post-BMT. Initially symptoms often resemble those of upper respiratory tract infection and may be mistakenly treated as such. In other patients, BO is detected by gradual deterioration of results of pulmonary function tests (PFTs) with nonreversible airflow obstruction at mid to low lung volumes (FEV<sub>1</sub>/FVC with evidence of air trapping. Diffusing capacity is usually reduced, and occasionally there is a restrictive ventilatory component combined with reduction in exercise capacity. Then the patients usually develop dyspnea with persistent cough, expiratory wheezes, inspiratory rales, and hyperinflation on chest radiograph without infiltrates. Some authors suggest increasing the immuno-suppressive therapy (like high-dose methylprednisolone sodium succinate [Solu-Medrol] and cyclosporine) to treat this disorder; however, it is not clear if this has any impact on the evolution of this disease, and common symptoms progress to fatal respiratory failure with an overall mortality of 65% at 3 years posttransplantation.

The diagnosis of BO is based on the appropriate clinical picture and results of PFTs. It is confirmed histologically by open lung biopsy specimen; however, this is not always necessary and bronchoscopy with transbronchial biopsy may be adequate to establish the diagnosis and/or exclude an infectious etiology. Some investigators have proposed that findings of high-resolution CT scan that include peripheral bronchiolitis, patchy areas of consolidation with decreased peripheral vascular markings, and examination of BAL lymphocytes may be helpful in making the diagnosis of BO.

**Graft-vs-Host Disease**

GVHD is thought to result from an immune reaction mediated by donor T lymphocytes that recognize the recipient’s tissue as foreign. The mortality is associated with the grade of GVHD and can be as high as 50% in severe GVHD. In the first 100 days following BMT, acute GVHD develops in 25 to 75% of patients and primarily affects the skin, liver, and GI tract. Pulmonary complications of acute GVHD are minimal. Some authors considered lymphocytic bronchitis to be a pulmonary manifestation of acute GVHD. This condition is characterized pathologically by monomorphic lymphocytic infiltration of the bronchial mucosa with reduction of ciliated and goblet cells and submucosal gland necrosis. Clinically the patients develop cough with recurrent bronchitis and bronchopneumonia. However, subsequent studies failed to show a relationship between lymphocytic bronchitis and acute GVHD and, therefore, the former entity appears to be a nonspecific response to the effects of chemotherapy, irradiation, and infection.

Chronic GVHD occurs in 20 to 45% of patients surviving 6 months beyond transplantation, with approximately 65% of these cases being preceded by acute GVHD. The disorder usually presents as multorgan autoimmune disease with rash, oral and ophthalmic sicca syndrome, hepatic damage, malabsorption, polyserositis, immunodeficiency, and opportunistic infections. Pulmonary involvement in chronic GVHD is common and ranges from sinopulmonary infections due to encapsulated bacteria, Aspergillus, and *P carinii*, chronic aspiration, sinopulmonary sicca syndrome with chronic bronchitis, progressive obstructive airway disease, BO, and late-onset lymphoid interstitial pneumonia.

**Impaired Results of PFTs**

Obstructive airway disease defined as FEV<sub>1</sub>/FVC less than 70% and FEV<sub>1</sub> less than 80% of predicted is emerging as an important complication of BMT, seen in up to 17% of patients without prior evidence of airflow limitation. The disorder is associated with higher mortality and is usually manifested symptomatically from 6 to 12 months posttransplantation. The clinical...
picture usually consists of cough, dyspnea, and wheezing with a normal chest radiograph. In a small subset of patients, the disorder may be rapidly progressive leading to respiratory failure and death.57

The Seattle group identified chronic GVHD (which was present in 69% of patients with obstructive airway disease) and prolonged methotrexate treatment as highly significant risk factors for the development of airflow obstruction. Other risk factors included decreased IgG and IgA levels, increased age, male gender, lower FEV₁/FVC before transplantation, and the lack of HLA matching graft. There was no significant association with the underlying disease, dose of conditioning irradiation, or the development of acute GVHD.49,58,59

In addition, mild to moderate restrictive lung disease with reduction in diffusing capacity may complicate BMT. This disorder is found in approximately 20% of patients studied 12 months posttransplantation.60,61 Most patients present with dyspnea, cough, chest tightness, and fever; however, some patients are asymptomatic and the defect is detected only by PFT. The etiology of this problem is multifactorial and includes the toxic effects of chemotherapy and irradiation, recurrent pulmonary infections, generalized muscle weakness, and chronic GVHD leading to scleroderma-like skin changes resulting in chest wall restriction.62 The course of restrictive lung disease is usually stable and a minority of the patients improve.63

The value of pretransplantation PFTs is not well established. Commonly they are used as baseline for future studies; however, a number of studies have indicated that pretransplantation PFTs have a predictive value in the outcome following BMT. Crawford and Fisher64 studied the association between PFTs performed before BMT and mortality following transplantation in 1,297 patients. They found that abnormalities in total lung capacity (TLC), diffusing capacity of carbon monoxide (DCO), and alveolar-arterial oxygen gradient were significantly associated with the use of mechanical ventilation and death following transplantation. When each of these variables was added to a multivariate relative risk analysis, DCO (<80% of predicted) and alveolar-arterial oxygen gradient (>20 mm Hg) were found to be independent risk factors for death. However, the data showed that the risk associated with abnormal PFT results is less than that associated with other recognized risk factors such as older age, relapse status, and HLA mismatching. The authors concluded that pretransplantation PFTs should be used in assessing fully the risks to BMT recipients, but should not be used as absolute exclusion criteria for transplantation.

The relation between posttransplantation PFT results and mortality was recently examined in a review of a prospective study.65 A total of 906 BMT recipients underwent PFTs approximately 3 months following transplantation. The results were compared with pretransplantation values. Restrictive ventilatory defects (TLC <80% of predicted) were noted in 32% of the patients and 24% experienced a significant decrease (≥15%) in TLC compared with pretransplant values. Diffusing capacity was abnormally low in 81% of patients 3 months posttransplantation and declined by more than 15% compared with baseline in 52% of the patients. Only 10% of the patients had a significant worsening in airflow (≥5% decline in FEV₁/FVC) 3 months following transplantation compared with baseline. A restrictive ventilatory defect or a reduction in TLC more than 15% from baseline, even when it remained within the normal range, was associated with a twofold increase in the risk of nonrelapse mortality. However, there was no increased risk of nonrelapse mortality with airflow obstruction or impairment in DCO. The increase in nonrelapse mortality was most pronounced more than 1 year following transplantation and appeared to result from increased rate of death associated with respiratory failure and not chronic GVHD.

It is recommended to obtain baseline PFT results before BMT and repeat testing 80 to 100 days and 1 year (or earlier if clinically indicated) posttransplantation. Those patients who show abnormalities should be evaluated for possible pulmonary infection, reversible airway disease, BO, and chronic GVHD.

Late Infection

It has been reported that 28% of patients experience three or more infections after 6 months following BMT, usually in the setting of chronic GVHD.26 The most frequent are sinopulmonary bacterial infections. It is believed that chronic GVHD leads to damage of the airways, impaired production of secretory IgA, and splenic dysfunction.54 Streptococcus pneumoniae and other Gram-positive organisms are the most common pathogens; however, Haemophilus and Pseudomonas are important considerations in patients who develop obstructive airway disease following BMT. Some investigators recommend routine prophylaxis with penicillin or trimethoprim/sulfamethoxazole to decrease the incidence of these late bacterial infections.5

Late viral infections include cutaneous varicella-zoster virus infection, which is the most common and affects as many as 40 to 50% of BMT recipients.3,61 Pulmonary involvement may be part of the systemic dissemination of varicella-zoster infection. The earlier use of acyclovir therapy may limit the systemic spread.1 CMV pneumonia is less common during this period.26

Fungal infections, particularly oropharyngeal candidiasis, are commonly seen in patients suffering from chronic GVHD. Also, the prolonged use of corticosteroids in the treatment of other BMT complications
predisposes to Aspergillus and *P. carinii*.

**MISCELLANEOUS**

_Airway problems_ are among the earliest after bone marrow transplantation and are related to toxicity of conditioning regimens that lead to severe mucositis, which may be complicated by aspiration of blood and secretions or development of laryngeal edema, which may require intubation to maintain airway patency.⁶,⁷⁶

_Mediastinal emphysema_ has been described after BMT and correlated with the development of IPS and the use of high-dose radiation during conditioning. There are no serious consequences to this problem and none of the described patients needed to be intubated.⁶

_Pulmonary vascular complications_ in the form of endothelial swelling with arteriolar, venular, and capillary thrombi have been described after BMT; however, their clinical significance is not clear.⁷ Also, pulmonary embolization of bone and fat fragments may occur during the infusion of donor’s marrow and may lead to transient hypoxia.⁸ Another unusual vascular complication of BMT is pulmonary venoocclusive disease, which may lead to pulmonary hypertension and right-sided heart failure; treatment with high-dose corticosteroids was effective in some cases.⁶⁵

_Chemotherapy and irradiation_ used in conditioning regimens have potential pulmonary toxic reactions. Chemotherapeutic agents such as cyclophosphamide, busulfan, and cytarabine (cytosine arabinoside) have been implicated in pulmonary damage that may be dose-related or appear at any time. Also, TBI damage is dose-related and presents within the first 90 days after radiation exposure.⁶ The clinical picture of chemotherapeutic and TBI pulmonary toxic reactions is usually identical and starts with fever, cough, dyspnea with hypoxemia, and diffuse interstitial infiltrates. Characteristically there is significant reduction in diffusing capacity accompanied by reduced lung volumes.³ In addition, methotrexate predisposes to interstitial pneumonitis and eosinophilic pneumonia.³⁶⁰

_Secondary malignancies_ are increased after BMT. A recent report showed that 35 of 2,246 patients developed secondary neoplasms (16 non-Hodgkin’s lymphoma, 6 leukemia, and 13 solid tumors) a median of 1 year (range, 0.1 to 13.9 years) posttransplantation.⁷⁰ This incidence is seven times that of primary cancer in the general population. TBI, acute GVHD, and antithymocytes globulins increased the likelihood of secondary malignancy, while chronic GVHD did not appear to be associated with secondary neoplasms.⁶¹⁷⁰

The chest could be a primary or metastatic site of these secondary malignancies.

_Secondary pulmonary alveolar proteinosis (PAP)_ has been recently described as a potential cause of reversible respiratory failure following BMT.⁷¹ Ten pa-

tients with immunosuppressive illnesses, including three with BMT, were reported to have PAP. The diagnosis was based on the identification of periodic acid-Schiff-positive proteinaceous material from BAL with characteristic ultrastructural pattern demonstrated by electronic microscopy. Data obtained from sequential BAL in these patients showed that at least four, including one BMT recipient, had reversible disease that coincided with recovery from neutropenia. Although rare, PAP should be considered when a BMT recipient presents with diffuse pulmonary disease, because this entity can be diagnosed accurately by BAL and has potential for spontaneous reversibility.

**MECHANICAL VENTILATION**

Although mechanical ventilation is technically not a complication but a therapy for respiratory failure after BMT, it is included herein as a reflection of severity of pulmonary complication posttransplantation. The incidence of ventilatory support after BMT ranges between 12% and 21%.⁷²,⁷³ Although 27% of patients may survive the initial episode of ventilatory support, the overall mortality is exceedingly high, reaching 95% in most studies.⁷²-⁷⁴ Pretransplantation factors that are significantly correlated with the need for ventilatory support posttransplantation include increased age, disease in relapse at the time of transplantation, conditioning with high-dose TBI, and receiving HLA nonidentical marrow. However, several factors did not demonstrate an association with mechanical ventilation, like pretransplantation pulmonary dysfunction by PFT and immunosuppression with methotrexate. Survival after ventilatory support was not found to be correlated with any pretransplantation or posttransplantation factors.⁷⁵

**DIAGNOSTIC APPROACH**

The initial approach to the evaluation of a bone marrow recipient with respiratory symptoms and/or pulmonary infiltrates is different from that of a normal host with community-acquired pneumonia. Patients’ conditions can deteriorate rapidly and therefore a prompt and systematic diagnostic workup, with the occasional need for invasive procedures, is imperative.⁷⁵

The _history and physical examination_ are important tools in localizing the problem and identifying extrapulmonary signs and symptoms that may be helpful in determining the etiology of the pulmonary infiltrates. The history should also focus on the time of onset of symptoms following transplantation: prior viral exposures, including CMV status of the patient and donor, and the presence of GVHD. In addition, initial evaluation should include obtaining the patient’s weight and comparing it with previous measurement.

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Chest radiography is the primary tool for screening pulmonary complications of BMT. To our knowledge, there are no well-designed studies to evaluate the sensitivity and specificity of the chest radiograph in BMT recipients with pulmonary symptoms; however, it is widely accepted that the initial radiographic pattern of pulmonary infiltrates helps in narrowing the differential diagnosis and directing further management.  

Although it is not unusual to have overlap and atypical presentations, assessment of the chest radiographic findings is helpful in the approach to pulmonary complications of BMT. For example, while segmental or lobar consolidation suggests an infectious process such as bacterial or fungal pneumonia, nodules or cavitary lesions, however, are more likely to be due to Aspergillus infection and septic emboli. A diffuse pattern on the chest radiograph may be due to PCP, CMV pneumonia, pulmonary edema, DAH, IPS, or drug or radiation-induced pulmonary toxic reactions. The presence of mediastinal lymphadenopathy raises the suspicion of recurrence of the underlying disease process.

Another radiographic clue is the rate at which pulmonary infiltrates develop. For example, pulmonary processes that progress rapidly over 24 h suggest bacterial pneumonia, pulmonary edema, and DAH. Conversely, pulmonary infiltrates that evolve over a longer period of time are likely to be due to Aspergillus, P. carinii, CMV, or IPS.

Chest CT scan is helpful in the evaluation of pulmonary disease in a BMT recipient. A prospective study showed that high-resolution CT was helpful in establishing the location and extent of the pulmonary process. It facilitated tissue sampling (ie, bronchoscopy, open lung biopsy), prompted change in management, and added confidence to the clinical diagnosis. CT is especially helpful in patients with normal chest radiograph or those showing nonspecific changes. Another study indicated that CT demonstrated diagnostically relevant findings that were not apparent on the plain radiograph in 57% of cases. CT is particularly useful during the evaluation of fungal infections, PCP, radiation pneumonitis, GVHD, BO, and recurrence of lymphoma.

BAL is an important tool in investigating pulmonary infiltrates in a BMT recipient, especially when the infiltrates are infectious in origin. BAL is very helpful in the diagnosis of PCP, CMV pneumonia, tuberculosis, and some fungal infections. DAH can be diagnosed satisfactorily in almost all patients by BAL. A review of the National Institutes of Health experience on the efficacy of BAL in 327 immunocompromised patients with pulmonary infiltrates showed the procedure to be diagnostic in 55%, nondiagnostic in 45%, and leading to false-negative results in 22%. A recent study evaluated the role of bronchoscopy with BAL in the evaluation of 27 BMT recipients referred for evaluation of pulmonary infiltrates. The procedure was diagnostic in 20 (74%). In 17 cases (67%), an infectious etiology was identified. The use of bronchoscopy significantly influenced subsequent management with a positive change in therapy being instituted in 17 of the 27 cases (63%).

Transbronchial biopsy will modestly increase the sensitivity of BAL in the diagnosis of infection. Also, it can help diagnosing drug-induced lung damage in 40 to 65%. The Seattle group found that transbronchial biopsy lacked the desired sensitivity in investigating 24 cases of diffuse pneumonia after BMT; diagnostic material was obtained in 14 samples (58%). Five tissue samples were inadequate and five yielded false-negative results. The best results were with idiopathic pneumonia (10/13) and PCP (3/5), but this technique missed the diagnosis in all 5 cases of CMV pneumonia when compared with open lung biopsy. The experience of the National Institutes of Health on the diagnostic yield of transbronchial biopsy in 322 immunocompromised patients showed the procedure to be diagnostic in 29%. Nondiagnostic findings were found in 47% and negative results for any pathologic diagnosis in 24%.

Transthoracic needle aspirate under CT guidance is rarely used in the evaluation of pulmonary infiltrates following BMT. It has a sensitivity of 70% in focal lesions, with bacterial, fungal infections, and malignancy being the most common findings.

Open lung biopsy is considered the diagnostic standard in the evaluation of pulmonary infiltrates following BMT. Because of the large tissue sample obtained, the sensitivity and specificity of the procedure are greater than for any other procedure. The sensitivity of open lung biopsy ranges between 60% and 83%. The specificity when compared with autopsy findings is very high; however, Aspergillus infection may not be reliably excluded by open lung biopsy. In a review of 111 open lung biopsies on 109 BMT recipients, infection was found in 63% of patients with CMV being the causative agent in 90% of cases. The study also demonstrated a low incidence of infection (19%) in specimens obtained in the first 30 days posttransplantation.

The complications of invasive procedures should be taken into consideration when deciding on the next diagnostic step. Bronchoscopy with BAL is associated with minimal morbidity in BMT recipients. It can precipitate respiratory failure in 2% of cases, especially in unstable patients, minor bleeding in less than 1%, and postprocedural fever in 5 to 15%. Transbronchial biopsy increases the risk of major complications with significant bleeding in 3%, pneumothorax in 5%, and death in 0.2%. The complications of CT-guided transthoracic needle aspirate are pneumothorax in 12
to 15% and hemoptysis in 3 to 5%. Complications of open lung biopsy range from bleeding, pneumothorax, wound infection, and ventilator dependency and procedure-related mortality is less than 1%.  

The diagnostic approach of pulmonary disease following BMT depends on the following variables.

1. Temporal relation of the pulmonary infiltrates following transplantation: as mentioned above, pulmonary complications posttransplantation follow a predictable time pattern (Fig 1). Knowledge of this time sequence is an important diagnostic clue; however, it is also crucial to know that there is a degree of temporal overlap between the different conditions.

2. The severity of the patient’s illness and the rapidity with which it is progressing; if the patient’s condition is critical or progressing rapidly, the most appropriate approach is to start broad-spectrum empiric therapy, then to proceed directly to an invasive procedure.

3. The pattern of pulmonary infiltrates: in cases of diffuse pulmonary infiltrates, it is advised to start treatment with diuretics if indicated, then proceed to bronchoscopy and BAL before attempting biopsies. However, focal infiltrates are highly suggestive of an infectious etiology and treatment with broad-spectrum antibiotics should be instituted initially. In the absence of clinical response, biopsy by bronchoscopy with transbronchial biopsy or CT-guided transthoracic needle aspirate should be attempted. If the above procedures gave nondiagnostic results or were contraindicated because of severe hypoxemia or coagulopathy, then a decision has to be made between open lung biopsy or empiric treatment.

4. The presence of GVHD increases the need for immunosuppressive therapy following BMT. Patients are, therefore, susceptible to infections with encapsulated bacteria, P. carinii, and CMV. There is also an increased incidence of BO and obstructive and restrictive pulmonary diseases. These conditions should be considered when a BMT patient with GVHD presents with pulmonary symptoms.

5. It is important to know before deciding on an invasive procedure, especially open lung biopsy, whether such a procedure will change therapy or have an impact on survival. Most studies addressing this issue failed to show an improved survival in patients who underwent open lung biopsy for evaluation of pulmonary infiltrates following BMT; however, these were retrospective studies and the results may be explained by delay in performing the procedure or severity of the patient’s illness.

A diagnostic approach to the problem of pulmonary disease following BMT is suggested in Figure 4.

**Conclusion**

BMT is an effective and promising therapeutic tool for a number of conditions. It is, however, limited by the high incidence of complications, especially those related to the pulmonary system. Better selection of patients, the use of less toxic conditioning regimens, more effective prophylaxis and treatment of infections, improved treatment and prevention of GVHD, and more rapid recovery of the bone marrow will have a substantial impact on the morbidity associated with this form of therapy. Although the approach to the diagnosis of pulmonary disease following BMT will often

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**Figure 4. Approach to the pulmonary complications following BMT. CXR = chest radiograph; V/Q = ventilation/perfusion scan; TBB = transbronchial biopsy; FNA = fine-needle aspirate; OLB = open lung biopsy.**
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