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Clin Chest Med 25 (2004) 189–201

CLINICS
IN CHEST
MEDICINE

Pulmonary complications in bone marrow transplantation: a practical approach to diagnosis and treatment

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Hematopoietic stem cell transplantation (HSCT) has become the standard technique of bone marrow transplantation (BMT); nearly 20,000 procedures were performed in North America during 1998 [1]. The donor source may be the patient (autologous), a sibling or unrelated person (allogeneic), an identical twin (syngeneic), or a genetically-unrelated umbilical cord blood sample [2]. Although syngeneic grafts do not develop graft-versus-host disease (GVHD) and have lower treatment-related mortality compared with allogeneic transplants, the advantages are often counterbalanced by a greater risk of malignant relapse. Thus, overall mortality is similar for syngeneic and allogeneic BMT.

The process of HSCT involves three stages: (1) conditioning of the recipient, (2) infusion of hematopoietic stem cells, and (3) engraftment. Conditioning may involve cytoreductive therapy with or without total body irradiation (TBI). For solid tumors, high-dose cytoreductive chemotherapy may be used in an attempt to achieve complete tumor ablation. Some chemotherapeutic agents (eg, cyclophosphamide and busulfan) are direct pulmonary toxins that can lead to the development of drug-induced lung injury and interstitial pneumonitis [3]. TBI also may be used during the conditioning phase to prevent the relapse of the primary disease and graft failure. Dose-related, radiation-induced lung injury is reflected by a reduction in diffusing capacity of the lung [4]. Furthermore, the combination of high-dose chemotherapy and TBI synergistically increases the incidence and the severity of pulmonary complications [5]. In fact, idiopathic pneumonia syndrome (IPS) may be a direct consequence of radiation- and chemotherapy-induced lung injury [6].

The hematopoietic stem cells can be collected from bone marrow, peripheral blood, placenta, or umbilical cord blood (Table 1). Peripheral blood has become the preferred source of stem cells for autologous recipients because it eliminates the need for general anesthesia that is associated with bone marrow aspiration. Hematopoietic stem cells that are harvested from the patient's peripheral blood after treatment with granulocyte colony–stimulating factor (G-CSF) or granulocyte-macrophage colony–stimulating factor (GM-CSF) are being used increasingly in autologous recipients. For allogeneic HSCT, techniques, such as removal of T lymphocytes from the donor graft, have lowered the incidence of GVHD. Nonetheless, recipients are still prone to development of cytomegalovirus (CMV) infection, invasive fungal infections, and Epstein-Barr virus–associated posttransplantation lymphoproliferative disease. More recently, hematopoietic stem cells from placental or umbilical cord blood were used to perform allogeneic transplants. This technique also is associated with a lower incidence of graft rejection and GVHD [7].

Engraftment is defined as an absolute neutrophil count that is greater than 0.5×10^9/L and a sustained platelet count that is greater than 20×10^9/L that lasts for three consecutive days without transfusions. This

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0272-5231/04/$ – see front matter
doi:10.1016/S0272-5231(03)00121-7

Table 1
Sources of bone marrow transplantation

Bone marrow stem cells	Peripheral blood stem cells	Umbilical cord stem cells
Autologous or allogeneic	Autologous or allogeneic	Allogeneic
General anesthesia required for harvest	No general anesthesia required for harvest	Cannulation of placental vessels for harvest
Slower engraftment	G-CSF priming with leukapheresis required	Better immune tolerance with HLA incompatibility
Comparable risk of infection, mortality, and relapse with peripheral blood stem cells	Thrombocytopenia, splenic rupture, and cerebrovascular events can occur after harvest	Readily available and decreased wait time for BMT
Lower risk of chronic GVHD, better patient quality-of-life	Contains more total cells	Lower risk of transmissible infection (ie, CMV)
	Faster engraftment	Reduced number of stem cells in harvest
	Increased risk of chronic GVHD	May increase the risk of malignancy relapse

Abbreviations: CMV, cytomegalovirus; G-CSF, granulocyte colony–stimulating factor.

typically occurs 3 weeks after HSCT. Although engraftment usually signifies the restoration of the phagocytic function of leukocytes, immune system dysfunction persists for months after engraftment. Abnormal CD4:CD8 cell count ratios and immunoglobulin deficiencies are examples of this dysfunction among HSCT recipients. In addition, agents for prophylaxis against GVHD (eg, methotrexate and cyclosporine) also contribute to the immunosuppressed condition of patients who have undergone allogeneic transplants and may cause drug-induced pulmonary disease.

Pulmonary complications encompass various noninfectious conditions, including pulmonary edema, diffuse alveolar hemorrhage (DAH), IPS, bronchiolitis obliterans (BO), and cryptogenic organizing pneumonia (COP) [5,8–10]. Nonetheless, infections remain a leading cause of mortality in recipients of allogeneic transplants and are a major cause of morbidity among recipients of autologous transplants. Furthermore, pulmonary complications and respiratory failure occur more often with allogeneic, than with autologous bone marrow or peripheral stem cell, transplants. This may be due to the effects of GVHD, as well as the intense immunosuppressive therapy that is used to prevent it.

Specific pulmonary complications tend to occur within well-defined periods that correspond with the state of immune reconstitution after the marrow transplant (Fig. 1; Table 2) [8]. Pulmonary edema, DAH, and GVHD may be exceptions and do not always occur within a defined time period after BMT. Nevertheless, it is useful to divide the posttransplant period into three phases: phase 1 (the first 30 days); phase 2 (Days 31 to 100); and phase 3 (more than 100 days after the transplant). This temporally-based diagnostic scheme enables clinicians to appropriately assess and manage a wide spectrum of different

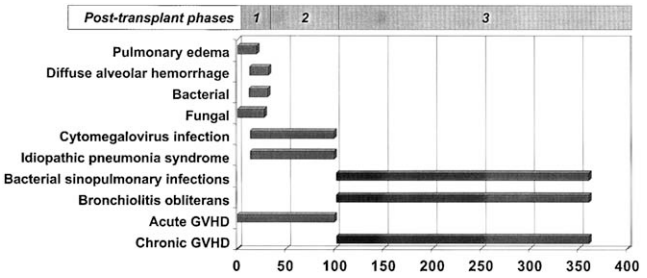

Fig. 1. Temporal patterns of major pulmonary complications after bone marrow transplantation. Most pulmonary complications occur in the early phases after bone marrow transplantation. If survival to later phases is achieved, chronic pulmonary complications, such as bronchiolitis obliterans predominate. (*Modified from* Krowka MJ, Rosenow EC, Hoagland HC. Pulmonary complications of bone marrow transplantation. Chest 1985;109(4):237–46; with permission.)

Table 2
Pulmonary complications in bone marrow transplantation

Complications	Days after BMT	Incidence	Pulmonary infiltrates
Pulmonary edema	1–30	Unknown	Diffuse
DAH	1–30	5%	Diffuse
Bacterial pneumonia	1–30	20–50%	Focal
Aspergillus	1–30	20%	Focal
HSV	1–30	5–7%	Diffuse
CMV	31–100	10–40%	Diffuse
IPS	31–100	10–17%	Diffuse
PCP	31–100	<1%	Diffuse
COP	≥31	1–2%	Diffuse
Chronic GVHD	>100	20–45%	No infiltrates
BO	>100	6–10%	No infiltrates
DPTS	>100	Unknown	Diffuse
RLD	>100	<20%	No infiltrates
PAP	>100	<5%	Diffuse
Vasculopathy	>100	<5%	No infiltrates

Abbreviations: DPTS, delayed pulmonary toxicity syndrome; HSV, herpes simplex virus; PAP, pulmonary alveolar proteinosis; PCP, *Pneumocystis carinii* pneumonia; RLD, restrictive lung disease.

pulmonary complications that occur within defined periods after transplantation.

Posttransplant phase 1 (Days 1–30)

Phase 1 precedes engraftment and is characterized by prolonged neutropenia with disruption of mucosal barriers as a direct result of the conditioning regimen. Our timeline reflects a shortened neutropenic period because of our routine use of hematopoietic colony–stimulating factors [11]. Cytopenia is less severe in autologous transplants than in allogeneic transplants. Despite the increased risk of various bacterial, fungal, and viral infections during phase 1, noninfectious complications, such as pulmonary edema and DAH, also may occur. In addition, the development of mucositis can cause severe dysphagia, odynophagia, and upper airway inflammation that leads to aspiration of blood or secretions or the development of laryngeal edema [12].

Pulmonary edema

Pulmonary edema typically occurs in the second or third week after the transplant [9]. Patients usually complain of dyspnea and have typical clinical findings that include weight gain, bilateral pulmonary rales, and hypoxemia. Chest radiographic abnormalities include bilateral interstitial infiltrates with or without pleural effusions. Pulmonary edema may be due to increased capillary hydrostatic pressure or increased pulmonary capillary permeability. High-dose anthracycline and platinum chemotherapy may play a role by impairing renal and cardiac function. Additionally, hypoalbuminemia may exacerbate extravascular lung water. Empiric diuresis is often indicated to prevent the development of respiratory insufficiency.

Diffuse alveolar hemorrhage

DAH is a form of noninfectious pneumonitis that is characterized by the sudden onset of dyspnea, nonproductive cough, fever, and hypoxemia [5]; hemoptysis is rare. Most episodes of DAH occur around Day 12 after BMT. Overall, DAH has been reported in 5% of all BMTs [13]. Recipients of autologous transplants are at higher risk than recipients of allogeneic transplants. Chest radiograph abnormalities usually precede the clinical diagnosis. The infiltrates are usually bilateral, interstitial, and centrally predominant. DAH is typically diagnosed with bronchoalveolar lavage (BAL). The diagnosis of DAH is considered when successive aliquots of BAL fluid become increasingly hemorrhagic; the diagnosis is established if all cytologic, pathologic, and microbiologic studies exclude the presence of pulmonary infection. The diagnostic yield of BAL for DAH may vary among institutions because of differences in patient selection and bronchoscopic technique. Furthermore, because of the patchy nature of DAH, serial bronchoscopies may be necessary before a diagnosis is established.

Risk factors for the development of DAH include intensive conditioning chemotherapy, TBI, and age older than 40 years. Unlike alveolar hemorrhage in other settings, DAH after BMT is not significantly associated with prolonged prothrombin or partial thromboplastin time or with thrombocytopenia. Pathologic examination shows that DAH is characterized by diffuse alveolar damage, alveolar desquamation, and hyaline membrane formation. Epithelial injury at the time of neutrophil recovery may play a role in the pathophysiology. On the basis of the available literature, we use corticosteroids for treatment [14]; however, the reported in-hospital mortality rate that is associated with DAH is high (80%).

Engraftment syndrome

Engraftment syndrome is a noninfectious pulmonary complication that is temporally defined by its

occurrence during recovery from neutropenia. It has been described in autologous BMT and peripheral stem cell transplantation [15]. The clinical features typically included fever, pulmonary infiltrates, skin rash, and hypoxia. The median time of onset was 7 days after BMT, with a median duration of 11 days. The lower incidence of engraftment syndrome in recipients of BMT who have sepsis supports the noninfectious nature of this syndrome. The criteria for diagnosis include: (1) onset of symptoms within 5 days after attaining an absolute neutrophil count that is greater than 0.5×10^9/L, (2) temperature greater than 38.3°C, (3) skin rash similar to that in acute GVHD, (4) pulmonary infiltrates on a plain chest radiograph, (5) normal cardiac function, (6) oxyhemoglobin saturation less than 90%, and (7) negative cultures from blood and BAL [15,16]. Treatment is primarily supportive; some patients receive empiric corticosteroid therapy. In one series, corticosteroids resulted in the prompt resolution of the fever and hypoxia [15]. The data suggest that this syndrome may be self-limiting; the prognosis of these patients may be better than that of recipients of BMTs who have other types of respiratory insufficiency [15,16].

Bacterial, fungal, and viral infections

Bacteremia is a common complication during the neutropenic phase and frequently contributes to the development of bacterial pneumonia. Mucositis and the use of opiates and sedatives may predispose to aspiration of secretions that contain various bacterial and fungal pathogens. Corticosteroid therapy that is used to treat acute GVHD further increases the risk of opportunistic infection.

Empiric treatment with antibiotics for neutropenic fever and appropriate antibiotic prophylaxis (particularly trimethoprim-sulfamethoxazole for *Pneumocystis* pneumonia) have reduced the risk of opportunistic infections and the rate of respiratory failure from pneumonia [17,18]. The prophylactic use of fluconazole, itraconazole, and low-dose amphotericin B also has lowered the incidence of invasive candidiasis. The efficacy of prophylaxis with oral itraconazole or low-dose amphotericin B in invasive aspergillosis also was proven in several studies [19,20]. Antiviral prophylaxis also has been effective in lowering infection rates. Table 3 lists the agents that we use as routine prophylaxis. In addition, the use of high-efficiency particulate air filtration reduces ambient *Aspergillus* spore counts and may prevent infection.

Despite early antimicrobial treatment, many respiratory infections occur in recipients of BMT. Invasive aspergillosis was reported in up to 20% of recipients of BMT [9]. The onset of *Aspergillus* infection occurs in a bimodal distribution, with the first peak at a median of 16 days and the second peak at a median of 96 days after BMT [21]. Risk factors include transplant from allogeneic donor, older age, male sex, summer season, transplantation outside of laminar flow rooms, construction in the vicinity of the hospital (ie, demolition of buildings), acute GVHD, and corticosteroid therapy. The clinical features of invasive pulmonary aspergillosis include fever, dyspnea, dry cough, wheezing, pleuritic chest pain, and hemoptysis. Localized infiltrates that are nodular or cavitary on CT of the chest are likely to be *Aspergillus* infection. A "halo" sign (produced by perinodular hemorrhage) on chest CT is also suggestive. Antigenemia and polymerase chain reaction (PCR) assays have been evaluated for early diagnosis, but their use may not improve patient outcome [22,23]. Definitive diagnosis is established through demonstration of tissue invasion. The presence of *Aspergillus* spp in the BAL culture should be considered evidence of invasive disease and warrants immediate therapy [24].

Treatment of aspergillosis is usually with intravenous (IV) amphotericin B, at a dose of 0.5 to 1.0 mg/kg/day [17]. When the disease is stabilized and the patient is afebrile, maintenance therapy with itraconazole can be used to prevent reactivation. Surgical resection of localized disease may be required for complete eradication [25]. Newer antifungal agents are undergoing clinical trials and may

Table 3
Agents used for prophylactic treatment in recipients of bone marrow transplants

Organism	Prophylaxis	Proven efficacy?
Gram-negative bacteria	Fluoroquinolones	Probable[a]
Candida	Fluconazole	Yes
Aspergillus	Amphotericin B	Yes
	Itraconazole	Yes
Herpes simplex virus	Acyclovir	Yes[b]
Cytomegalovirus	Acyclovir	Yes
	Ganciclovir	Yes
Pneumocystis carinii	TMP-SMX	Yes
	Aerosolized pentamidine	Probable

Abbreviation: TMP-SMX, trimethoprim-sulfamethoxazole.

[a] Reduces bacteremia but not infection-related fatality rates; therefore, not recommended for asymptomatic, afebrile, neutropenic recipients.

[b] For seropositive recipients only.

give rise to promising alternatives to amphotericin B in the treatment of invasive aspergillosis. Voriconazole, a second-generation triazole, was recently evaluated in a randomized multi-center trial [26]. Although voriconazole did not meet the predefined criteria for noninferiority compared with liposomal amphotericin B, it proved to be superior in the prevention of breakthrough infections and had a better toxicity profile. Caspofungin acetate is a new type of antifungal agent that inhibits glucan synthesis, also with an improved toxicity profile [27]. The United States Food and Drug Administration recently approved caspofungin for treatment in patients who have refractory invasive aspergillosis or in patients who cannot tolerate first-line antifungal therapy [27]. Despite appropriate therapy, the mortality rate remains high.

Herpes simplex pneumonitis

The most common early infection after BMT is caused by the herpes simplex virus (HSV) and is usually due to endogenous reactivation. The incidence of pulmonary involvement is estimated to be 5% to 7% [8]. HSV is excreted by 80% of seropositive patients who have not had acyclovir prophylaxis [5]. A BAL specimen alone may not be diagnostic for HSV pneumonitis; evidence of tissue invasion is often required to confirm the diagnosis [5]. Most patients who have HSV pneumonitis have obvious mucocutaneous involvement that precedes the lung involvement. In addition, herpetic tracheitis or esophagitis is commonly associated with herpetic pneumonitis. Focal infiltrates may occur as a result of direct spread from the oropharynx, whereas diffuse infiltrates likely occur as a result of viremia. IV administration of acyclovir is the current therapy of choice; oral administration is used as effective prophylaxis.

Posttransplant phase 2 (Days 31–100)

Neutropenia usually resolves by the second month after BMT, but humoral and cell-mediated immunity are still impaired during phase 2. The period of highest risk of infection is between the depression of native or passively transferred immunity and the establishment of the immunoactive transplanted cells. Immunity conferred by the transplant may take up to 100 days to become effective and is impaired by GVHD. During this phase, patients who have pulmonary complications usually present with dyspnea, hypoxemia, and bilateral interstitial infiltrates. Viral infections, such as CMV, respiratory syncytial virus, influenza, and parainfluenza predominate. *Pneumocystis carinii* pneumonia (PCP) also may occur during phase 2, although it is rare in patients who receive adequate prophylaxis. After infectious causes are excluded, IPS becomes the working diagnosis by default.

Cytomegalovirus pneumonitis

CMV pneumonitis usually occurs 6 to 12 weeks after BMT and affects 10% to 40% of patients [9,28]. Ninety percent of CMV pneumonitis cases occur within the first 100 days after BMT. Prophylactic therapy with ganciclovir may be followed by late-onset CMV disease after prophylaxis is discontinued. Risk factors include acute GVHD, older age (a relative risk of 1.4 per decade), conditioning with TBI, allogeneic BMT, administration of antithymocyte globulin, and previous CMV exposure [28]. Recipients of autologous BMT are less likely to be infected because they are less immunosuppressed than recipients of allogeneic BMT. Active infection can occur from reactivation of endogenous virus, reinfection from the donor graft, or transfusion of blood products from seropositive donors. Clinicians have adopted the practice of filtering blood products from seropositive donors to remove CMV-infected leukocytes and prevent CMV transmission.

The common clinical features of CMV pneumonitis include fever, dry cough, dyspnea, and hypoxemia with diffuse interstitial infiltrates on chest radiographs. The diagnosis can be made by indirect immunofluorescence with monoclonal antibodies to CMV antigen in a BAL specimen that is applied on tissue culture monolayers [29]. This technique allows diagnosis within 16 hours and was 96% sensitive and 100% specific compared with open lung biopsy (OLB). Diagnostic methodology has improved over the last 20 years. Tests, such as rapid shell vial centrifugation cultures, CMV antigenemia assay, and PCR to detect CMV DNA, have changed prophylactic and therapeutic treatment strategies for CMV infection. Shell viral centrifugation cultures have been used since 1984; this test can be used to detect CMV in tissue, blood, urine, throat, marrow, and BAL specimens [30]. Although this method has a high positive predictive value for subsequent disease after BMT, patients who are infected with CMV without preceding viremia cannot be detected with this test [31]. This test has limited value in monitoring the response to treatment because results become negative 2 to 3 weeks after initiation of antiviral agents, regardless of clinical outcome [32,33].

CMV antigenemia assay is more sensitive than shell viral centrifugation cultures and can be used to

monitor progress of antiviral treatment [30]. When immunofluorescence culture techniques are used with this assay, it can diagnose CMV infection up to 10 days before the onset of clinical disease [32]. Although this assay offers distinct advantages, the techniques that are used in its performance need to be standardized. Like the CMV antigenemia assay, PCR screening is more sensitive in detecting CMV infection before the onset of disease [34]. It also can be used to monitor CMV clearance from blood. The PCR test can be performed with plasma rather than with peripheral blood leukocytes. This technique is particularly useful during neutropenia because the number of leukocytes per slide is too low to allow CMV antigenemia testing. One study demonstrated a negative predictive value of 97% with the use of PCR in serial plasma specimens from patients who had undergone allogeneic BMT [35]. Despite these advantages, its specificity and positive predictive value are low [34,36].

Prophylactic therapy with acyclovir or ganciclovir is effective in preventing CMV infection, although administration of the latter is associated with neutropenia [33,37]. A survival benefit has not been demonstrated consistently. Instead of routine prophylaxis for CMV disease, an alternative strategy involves the use of pre-emptive therapy that is based on PCR or CMV antigenemia assay results. A negative PCR for CMV DNA is highly predictive of absence of disease and may allow for the more targeted use of ganciclovir prophylaxis [38]. In high-risk patients, the use of pre-emptive or prophylactic therapy led to a delay in the appearance of CMV disease, sometimes 3 to 4 months after BMT.

The use of IV immunoglobulin for prophylaxis of CMV disease remains controversial. Currently, IV immunoglobulin prophylaxis is not routinely recommended for recipients of BMT [1]. The restrictive use of CMV-negative blood products in seronegative patients reduces the incidence of CMV infections. Early diagnosis is crucial; several studies demonstrated a survival advantage of early combined therapy with ganciclovir and immunoglobulin [28]. If respiratory failure occurs before initiation of therapy, survival is unlikely. Even with early administration of therapy, relapses occur in nearly one-third of treated patients.

Pneumocystis carinii pneumonia

Before the introduction of chemoprophylaxis, PCP occurred in 5% to 15% of recipients of BMT [8]. The diagnosis is generally made by BAL. Mortality can be as high as 37% after pneumonitis is evident. The role of corticosteroids in the treatment of recipients of BMT who have PCP and respiratory failure is not as well-defined as in patients who have HIV. The advent of chemoprophylaxis with trimethoprim-sulfamethoxazole resulted in a significant reduction in the incidence of PCP in patients who are undergoing BMT [17]. All patients who undergo BMT at Mayo Clinic receive this prophylactic therapy. Our experience suggests that prophylaxis has virtually eliminated PCP in this group. Prophylaxis should be administered from engraftment until 6 months after BMT [1]. In patients who receive additional immunosuppressive therapy or who have chronic GVHD, it may be necessary to extend the prophylaxis beyond 6 months [1]. Pentamidine can be used in patients who are intolerant of trimethoprim-sulfamethoxazole but is less effective [39].

Idiopathic pneumonia syndrome

Pneumonia develops in 40% to 60% of patients after allogeneic BMT. In 30% to 45% of patients who have nonbacterial pneumonia, no infectious agent can be identified [40]. A National Institutes of Health (NIH) workshop addressed the issues of definitions and diagnostic criteria for IPS after BMT [6]. IPS is defined as "evidence of widespread alveolar injury in the absence of active lower respiratory tract infection after BMT" [41]. The usual clinical features include the presence of diffuse pulmonary infiltrates, fever, dyspnea, and hypoxemia [6]. The median onset time from transplant is approximately 45 days [6]. The clinical course is variable but the pneumonia may resolve in a minority of the patients. The NIH criteria are used to make the diagnosis (Box 1). Bronchoscopy with BAL is required to exclude infection.

IPS is estimated to occur in 10% to 17% of patients who undergo allogeneic BMT. The pathogenesis is not well defined, but the probability of disease increases with the number of risk factors, which include allogeneic BMT, high-dose TBI, increasing

Box 1. New diagnostic criteria for idiopathic pneumonia syndrome

Symptoms and signs of pneumonia
Hypoxemia or restrictive pulmonary tests
Bilateral pulmonary infiltrates
Absence of infection (negative BAL)

age, chronic myelogenous leukemia, previous splenectomy, and GVHD. The pulmonary infiltrates are likely the result of cumulative tissue toxicity from chemotherapy or radiotherapy. The pathology involves interstitial infiltration with mononuclear cells, especially lymphocytes. The systemic activation of inflammatory cytokines, lung injury from leukoagglutination, cell-mediated immune injury secondary to GVHD, and radiation or drug-induced lung toxicity are potential contributing factors.

No proven efficacious treatment exists for IPS after BMT, although corticosteroids were reported to be helpful in patients who received autologous BMT [42]. It was recently reported that etanercept, a tumor necrosis factor−α binding protein, that is used in combination with methylprednisolone, improved pulmonary function within the first week in three pediatric patients who received allogeneic BMT and had IPS [43]. We have observed clinical improvement in a limited number of adult patients. Overall mortality from IPS is estimated to be approximately 70% to 90% [12,42]. Subsequent infection and multi-organ failure contribute to the poor outcome. Patients who have IPS who require mechanical ventilation are unlikely to survive [41].

Posttransplant phase 3 (Day 100+)

The third posttransplant phase is marked by the appearance of chronic GVHD, a primary determinant of the frequency and nature of pulmonary complications. CMV and fungal infections also may occur and may be related to the early termination of prophylactic therapy or prolonged immunosuppression from treatment of chronic GVHD. Noninfectious pulmonary complications during this phase consist of restrictive and obstructive airway diseases: BO, COP, and delayed pulmonary toxicity syndrome [10,44]. One retrospective study discovered late-onset noninfectious pulmonary complications in 18 (10%) of 179 patients who had undergone BMT [44]. The only significant variables that were associated with late-onset noninfectious pulmonary complications were chronic GVHD and complications of GVHD prophylactic therapy (ie, cyclosporine and prednisone).

Bronchiolitis obliterans

Chronic expiratory airflow obstruction is reported to occur in 6% to 10% of recipients of allogeneic BMT [8,45], mostly in long-term survivors who have chronic GVHD. This condition is usually secondary to BO. The cause is unknown. A strong association with chronic GVHD suggests an immunologic mechanism that induces bronchial epithelial injury. Nonetheless, the pathogenesis is likely to be multifactorial. For example, low immunoglobulin levels and prolonged administration of methotrexate have been linked to BO. Furthermore, prophylactic regimens for GVHD directly injure the bronchial epithelium.

The onset of obstructive pulmonary disease is generally in posttransplant phase 3 but ranges from 3 to 24 months after BMT [5]. Patients generally present with progressive dyspnea, wheezing, and nonproductive cough. Fever is unusual and the chest radiograph is usually normal [45]. Hyperinflation may be seen on chest radiography. Airflow obstruction is the hallmark of BO. A reduction in the ratio of forced expiratory volume in 1 second to forced vital capacity (FEV_1:FVC) is more prevalent among patients who have chronic GVHD; FEV_1 is predictive of the course of the disease [45]. A decrease in FEV_1 to less than 80% of the predicted value and an FEV_1:FVC ratio of less than 70% are suggestive. This finding, coupled with the lack of bronchodilator response of FEV_1, is usually sufficient to make the diagnosis of BO. Although OLB is required to demonstrate histologic confirmation of BO, we do not recommend routine biopsies. Bronchoscopy with transbronchial lung biopsy is not helpful. High-resolution CT may be useful in establishing the diagnosis of BO without OLB. A mosaic pattern of lung attenuation (possibly due to regional airway obstruction) and bronchiectasis may be seen on high-resolution CT. Air trapping on expiratory high-resolution CT images may be a sensitive indicator of BO and may correlate with the decrease of FEV_1 [46].

Treatment is based on anecdotal reports and experience. It generally involves increased immunosuppression with prednisone followed by cyclosporine or azathioprine. Experience with BO in recipients of heart-lung transplants suggests that the addition of azathioprine to cyclosporine may slow progression. Unfortunately, BO is often progressive and unresponsive to therapy. A rapid onset of obstructive disease and severe obstruction (FEV_1<45%) are associated with a poor outcome [45]. If the onset is gradual, the obstruction may stabilize in as many as 50% of patients. Respiratory tract infections are common and pneumothoraces also may occur. The mortality rate is high and aggressive treatment is important.

Delayed pulmonary toxicity syndrome

Patients who receive autologous transplants that involve high-dose chemotherapy may develop pulmonary toxicity months to years after the transplan-

tation procedure [47]. Patients present with dyspnea, cough, and fever. Interstitial infiltrates are present on chest radiographs. Patients respond to corticosteroid therapy and have a good prognosis, which seems to distinguish this syndrome from IPS.

Cryptogenic organizing pneumonia

Patients who have bilateral pulmonary infiltrates and restrictive physiology may have COP, formerly known as "bronchiolitis obliterans with organizing pneumonitis," as the predominant pathology [10]. This condition is pathologically and functionally distinct from BO. BO presents with an obstructive pattern on pulmonary function tests; COP is restrictive and is characterized by the presence of patchy pulmonary infiltrates on chest radiography. In contrast, BO typically shows clear lung fields. The pathology of both is marked by proliferative bronchiolitis; however, COP affects distal airways and is associated with an inflammatory alveolar-filling process. Risk factors for COP include allogeneic BMT and GVHD. COP can be treated with corticosteroids, but infections must be excluded first. Corticosteroid treatment achieves resolution in approximately two thirds of patients who have idiopathic COP. Recipients of BMT also have an excellent response. The response to treatment further distinguishes COP from BO [44].

Miscellaneous pulmonary complications

Miscellaneous causes of pulmonary physiology disease include restrictive lung disease, pulmonary vasculopathy, pleural disease, and pulmonary alveolar proteinosis. Restrictive lung disease occurs in up to 20% of patients who undergo BMT, is rarely symptomatic, and generally improves over the ensuing years. Treatment is not required. Pulmonary veno-occlusive disease may occur 3 to 4 months after BMT and is caused by venous thrombosis. Diagnosis may require right-sided heart catheterization with a pulmonary angiogram that reveals increased pulmonary artery pressure with normal wedge pressure. Pleural effusions also may occur and rarely require evaluation unless unilateral. Causes of effusions include pulmonary edema, focal infection, and pulmonary embolism or infarction. Secondary pulmonary alveolar proteinosis may occur after BMT, especially in myeloid diseases [48]. The expectoration of gelatinous material is suggestive but the diagnosis generally is made by bronchoscopy. The BAL fluid reveals a thick, milky effluent of lipoproteinaceous material that stains positive by periodic acid–Schiff. Treatment is generally supportive but whole-lung lavage may be required. GM-CSF may offer another potential therapeutic option [49]. Other causes of pulmonary infiltrates include transfusion-related lung injury and leukemic infiltrates.

Diagnostic considerations

Radiology

The evaluation of recipients of BMT who have pulmonary complications should be based on the timing of the complication and the appearance of infiltrates on chest radiographs. Localized infiltrates are likely to be caused by bacterial and fungal pathogens, whereas diffuse infiltrates are more likely to be viral. Nodules or cavitary lesions are more likely to be due to *Aspergillus* infection or septic emboli. CT scanning of the chest is a useful tool and may provide a basis for changes in management [50]. Chest CT scanning can help to establish the location and the extent of pulmonary infiltrates, thereby facilitating tissue sampling with bronchoscopy or lung biopsy. The chest CT may be particularly important in the evaluation of fungal infections, GVHD, radiation pneumonitis, and BO.

Bronchoscopy with bronchoalveolar lavage

Fiberoptic bronchoscopy with BAL is the procedure of choice to evaluate pulmonary infiltrates in recipients of BMT. BAL can be safely performed, even in patients who have severe thrombocytopenia [51]. The diagnostic yield for PCP and bacterial pneumonia seems to be as great in patients who have undergone allogeneic BMT as in patients who have HIV infection [52]. Rapid centrifugation with shell vial culture seems to be a specific method of detecting CMV infection [29]. PCR detection of viral DNA or RNA may further enhance diagnostic yield. Although BAL is useful in detecting the presence of infections, negative results do not exclude fungal infections, such as aspergillosis [52]. Transbronchial biopsy does not seem to improve diagnostic yield in recipients of BMT who have diffuse infiltrates and we do not use it routinely. Furthermore, transbronchial biopsy may be unsafe to perform in severely thrombocytopenic patients.

Even if BAL establishes a specific diagnosis, the impact on patient outcome remains unclear. In a retrospective review, bronchoscopic results led to changes in treatment in 41% of patients [51]. Despite

the isolation of an organism and appropriate therapeutic changes, the survival of patients who had a diagnostic bronchoscopy did not differ from those in whom no pathogen was isolated. If patients who were mechanically ventilated were excluded from the analysis, the survival difference was still statistically insignificant. Our experience at the Mayo Clinic in Jacksonville, Florida indicates a 60% yield of BAL in recipients of BMT who have pulmonary infiltrates. Nonetheless, 30-day and 1-year survival do not seem to be improved by a positive BAL. A second review of an 8-year experience found that bronchoscopy with BAL had little impact on overall survival [53]. Although bronchoscopy is useful in establishing a diagnosis of pulmonary infiltrates in patients who received BMT, the results may not influence outcome.

Open lung biopsy

When results of BAL are negative, surgical lung biopsy (either by way of thoracotomy or video-assisted thoracoscopy) may be diagnostic [54]. Even in severely immunosuppressed patients, the morbidity and mortality that are associated with this technique seem to be acceptable, especially when the biopsy is performed thoracoscopically. Unfortunately, the yield of OLB in patients who have a negative BAL is low in our experience. Furthermore, caution should be exercised in discounting fungal disease on the basis of a negative OLB. When postmortem examinations are used for confirmation, the false-negative rate for diagnosis of fungal infections with OLB is as high as 20% [54]. This may be due to the nonhomogeneous distribution of filamentous fungi and necrotic hemorrhagic tissue destruction. If focal infiltrates are found to be fungal, resection may be curative [25]. In patients who have a history of lymphoma, OLB may be necessary to diagnose recurrence of a focal infiltrate. In patients who have diffuse infiltrates, OLB is generally reserved for occasions when BAL is either nondiagnostic or technically impossible [52].

Regardless of the diagnostic technique, the outcome for patients who have severe respiratory insufficiency is poor. Clinicians must take care not to compromise further the patient's status unless the risk-benefit ratio is favorable. The patient's preoperative respiratory status before OLB may, therefore, influence decision making. One study that compared the outcomes of 18 OLBs in 41 immunocompromised patients noted that the preoperative need for mechanical ventilation was associated with early postoperative mortality [55].

Pulmonary function tests as a measure of risk

Pulmonary function testing provides useful information for the prediction of pulmonary complications in recipients of BMT. Clinicians may use the results to guide decisions about the conditioning regimen. For example, in a patient who has a pre-existing abnormal pulmonary function, it may be prudent to avoid therapies with direct pulmonary toxicity. Abnormalities in gas exchange and diffusing capacity have been associated with increased risk of death after BMT [56]. Decreased total lung capacity, diffusing capacity for carbon monoxide (DCO), and a high alveolar-arterial oxygen gradient correlate with increased risk of respiratory failure after BMT. The risk of pulmonary complications that is attributable to abnormal pulmonary function is lower than that associated with other factors, such as age and HLA antigen mismatching. The clinician must assess the collective risk to determine the best therapeutic option in individual recipients of BMT.

Long-term outcome

Pulmonary complications have been reported to lead to respiratory failure in up to 23% of recipients of BMT [57,58]. Review of our experience at Mayo Clinic in Jacksonville, Florida suggests that approximately 15% of patients develop respiratory failure. Age greater than 21 years, allogeneic BMT, and active phase of malignancy are known risk factors that predispose to the development of respiratory failure. The long-term outcome for recipients of BMT who have respiratory failure is usually dismal; less than 25% of patients who receive ventilatory support survive to extubation [57]. Many patients who are extubated require reintubation, with few subsequently surviving. In the largest published patient series, only 4% survived to hospital discharge [57]. Six-month survival is 5% or less and the rates have not improved over the last 15 years. Long-term survival is even more unlikely in patients who required prolonged (>15 days) ventilation [58].

Noninvasive ventilation may offer an alternative management strategy in patients who have respiratory insufficiency. A recent study reported the usefulness of noninvasive ventilation in immunosuppressed patients who presented with pulmonary infiltrates, fever, and acute hypoxemic respiratory failure [59]. In this prospective, randomized trial of 52 patients, which included 17 patients who had undergone BMT, the rates of complications and mortality were reduced in the group who received noninvasive

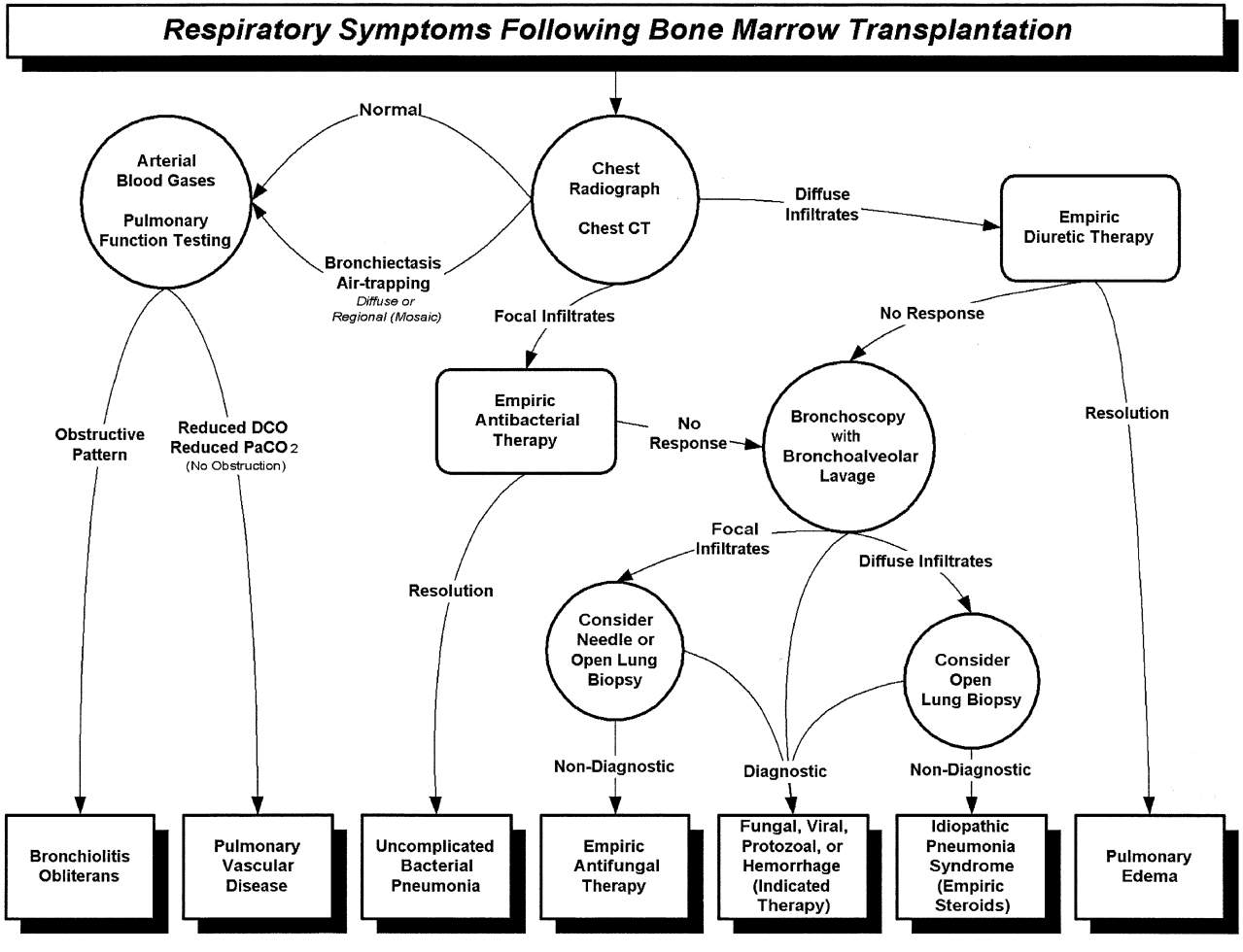

Fig. 2. Algorithmic approach to diagnosis of common respiratory complications after bone marrow transplantation. Temporal consideration of likely disease processes is not shown but can be additionally helpful.

ventilation compared with standard therapy. The noninvasive ventilation was given for at least 45 minutes and was alternated every 3 hours with periods of spontaneous breathing.

Because of the poor outcome that is associated with respiratory failure, recipients of BMT and their families should be provided with adequate information to assess the risks that are associated with BMT before the procedure. End-of-life discussions with patients before transplantation are emotionally challenging but may lead to advanced-care directives and clarification of the resuscitative status.

An algorithmic approach to management of pulmonary complications

Several diagnostic factors must be considered in treating patients who have respiratory complaints after BMT. Decisions are dependent on the timing of symptoms and the clinical presentation. To assist the clinician, various algorithms have been proposed [9]. Fig. 2 outlines our approach to pulmonary symptoms in recipients of BMT. This algorithm recognizes that a definitive diagnosis is not possible in many cases and emphasizes a management approach. It is applicable to pulmonary complications during any of the posttransplant phases. Consideration of the likelihood of the different complications in the different posttransplant phases enables the clinician to optimize the care of the patient.

One of the earliest distinguishing features is the radiographic appearance of the pulmonary infiltrates. Because information that is obtainable from plain radiographs may be insufficient for the evaluation of pulmonary infiltrates, a chest CT is an important diagnostic adjunct. This is especially important when considering diffuse parenchymal disease, which may be occult on the plain radiograph. Our algorithm emphasizes the role of empiric treatments, whether antimicrobial therapy or diuresis. Some experts may consider empiric therapy controversial. If the patient does not respond to empiric therapy, BAL may give further therapeutic guidance by identifying a specific cause. Bronchoscopy with BAL does not decrease mortality; therefore, we do not recommend repeating this test if the initial study is negative. If an OLB is required, a video-assisted thoracoscopic approach should be considered first. We believe this algorithm offers a reasonable and practical approach toward the management of pulmonary symptoms in patients who have undergone BMT.

In conclusion, pulmonary complications are common in the setting of BMT. Many are specific to BMT and tend to occur during identifiable periods after transplantation. The spectrum of pulmonary complications has been influenced by recent changes in transplantation technique and prophylactic therapy for various infections. Ultimately, improvement in the management of pulmonary complications rests on more precise immunomodulation. In the interim, clinicians are dependent on traditional diagnostic methods and empiric therapy. Future analyses should help to define situations in which these methods can produce the highest diagnostic yield and lead to improved management of these complications.

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